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Original Research

Prophylactic Effectiveness of Coenzyme Q10 for Migraine in Adults: A Systematic Review and Meta-Analysis of Double-Blinded Randomized Clinical Trials

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Abstract

We aimed to evaluate the influence of coenzyme Q10 alone (CoQ10) or in association with other nutraceuticals (CoQ10+) on the frequency, severity, duration of migraine attacks, and quality of life. We conducted a meta-analysis and a network meta-analysis (NMA) according to PRISMA 2020. We searched PubMed, Web of Science, Google Scholar, and Europe PMC for eligible studies up to January 2024. We used R software for pooled outcomes. This meta-analysis was registered in PROSPERO (CRD42024499733). Five studies were included, with a total of 326 individuals with confirmed migraine. CoQ10/CoQ10+ was shown to be associated with significant improvement in migraine frequency per month, and migraine duration and severity. NMA indicated that CoQ10 combined with L-carnitine appeared to be more effective than CoQ10 on migraine frequency and severity (SMD= -0.99 [95% CI: -1,68 to -0,29]; SMD= -3.05 [95% CI: -4.05 to -2.04], respectively). CoQ10 associated with L-carnitine yielded the greatest significant decrease in migraine duration compared with placebo; NMA revealed no significant difference between CoQ10, CoQ10 with multivitamin, and CoQ10 with L-carnitine. Our findings suggest that for optimal effectiveness, the use of CoQ10/CoQ10+ should be prolonged for at least 3 months. Using CoQ10 had a significant effect on the improvement of the quality of life of patients with migraine. Our meta-analysis suggested a beneficial effect of CoQ10/CoQ10+ for reducing monthly migraine frequency, severity, and duration, notably when it was associated with L-carnitine. Additionally, CoQ10 significantly improved the quality of life.

Keywords: Coenzyme Q10; L-Carnitine; Migraine attack frequency; Migraine attack duration; Migraine attack severity; Quality of life

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Introduction

Migraine is a common neurologic disorder characterized by severe, unilateral and pulsating headaches, with or without aura, often accompanied by nausea, vomiting, and photophobia, affecting quality of life [1,2]. The worldwide prevalence is estimated at 1 billion people and it is considered the second most common cause of disability [1]. Recent studies revealed that mitochondrial dysfunction probably played a central role in migraine [3]. This includes disturbances in calcium homeostasis, increased free radical production, decreased mitochondrial membrane potential, and a decrease in oxidative phosphorylation [3]. Several studies have shown a positive effect of coenzyme Q10 alone (CoQ10) or in association with other nutraceuticals (CoQ10+) as a prophylactic integrative medicine in migraine attacks (MA) [4,5]. This natural supplement has no adverse effects on humans and has been shown to be well tolerated [4,5]. Given the conflicting results from various studies and the significant burden migraine pose on young adults, this meta-analysis is necessary to consolidate the evidence for CoQ10/CoQ10+ as treatments for migraine and help alleviate their impact. As the results of different studies have been conflicting, our aim was to evaluate the impact of CoQ10/CoQ10+ supplementation on the clinical aspects of migraine, including the severity, frequency, and duration of MA. In addition, we aimed to assess the quality of life of migraine patients using the Headache Impact Test-6 (HIT-6) and assess disability using the Migraine Disability Assessment (MIDAS) score. Also, to explore the role of CoQ10 alone compared with CoQ10 with L-carnitine through network meta-analysis (NMA). This meta-analysis presents a novel perspective on traditional medicine approaches to migraine treatment by showing the potential benefits of a three-month regimen of CoQ10 and L-carnitine. The findings indicate that this combination can effectively reduce the severity, frequency, and duration of MA, offering a promising complementary option for patient care.

Methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [6]. The clinical question was formulated according to the PICO framework (Table 1). This systematic review and meta-analysis was registered in PROSPERO (CRD42024499733).

Search strategy

We performed a literature search in PubMed, Google Scholar, Europe PMC, and Web of Science for suitable studies up to January 2024. We used keywords and MeSH (Medical Subject Heading) terms using the HeTOP website (Table 2). Two investigators searched independently for ongoing studies and unpublished trials using the International Clinical Trials Registry Platform (https://clinicaltrials.gov). Additional sources, including reference lists of reviews, were used to validate potentially eligible publications. Identified

Table 1. PICO framework

PICO framework	
Population	Adults (≥18 years) with confirmed migraine with or without aura
Intervention	Co-enzyme Q10 or Co-enzyme Q10 combined with additional nutraceuticals
Control	Placebo
Outcome	-Impact of Co-enzyme Q10 or Co-enzyme Q10 combined with additional nutraceuticals on episodic migraine (frequency, severity, duration of MA, and quality of life) -Indirectly evaluate the effectiveness of Coenzyme Q10 alone vs. Coenzyme Q10 combined with additional nutraceuticals in episodic migraine

Table 2. MeSH terms and keywords used for the literature search

	MeSH terms/keywords
Migraine	migraine* OR “migraine disease" OR headache OR “migraine headache"
Coenzyme Q10	(“co-enzyme Q10” OR Q10 OR “coenzyme Q10”, OR “Q10 deficiency” OR “coenzyme Q10 deficiency” OR “ubiquinol-10” OR ubiquinone)
Overall	(migraine* OR “migraine disease" OR headache OR “migraine headache") AND (“co-enzyme Q10” OR Q10 OR “coenzyme Q10”, OR “Q10 deficiency” OR “coenzyme Q10 deficiency” OR “ubiquinol-10” OR ubiquinone)

records were added to Mendeley to identify duplicates. The titles and abstracts and then the full-texts were independently checked for eligibility criteria by two researchers. In case of discrepancies, the two researchers discussed issues until a solution was found.

Eligibility criteria

We included all double-blind, randomized, controlled clinical trials that met the following criteria: (i) approved by national and/or regional regulatory authorities, (ii) written in English, (iii) conducted in adults (age ≥ 18 years) with confirmed migraine, (iv) compared CoQ10 with placebo, and (v) available data. We excluded studies conducted in pediatric populations (age < 18 years), open-label controlled trials, studies conducted in animals, or those that compared CoQ10 with treatments other than placebo.

Data extraction

Data extraction was performed independently by two investigators based on Microsoft Excel Office 16. The following information was retrieved: (a) First author's name, (b) publication date, (c) study design, (d) method of migraine confirmation, (e) the number of patients under CoQ10/CoQ10+, (f) number of patients under placebo, (g) follow-up period, (h) CoQ10/CoQ10+ dose per day, (i) age and sex of patients, (j) monthly migraine frequency (MA/month) in CoQ10/CoQ10+ and placebo groups, (k) migraine duration (hours) in CoQ10/CoQ10+ and placebo groups, (l) mean visual analog scale (VAS) scores of MA in CoQ10/CoQ10+ and placebo groups, (m) MIDAS scores in both groups, (n) HIT-6 scores in both groups, (o) mean differences and standard deviation (SD), and (p) headache diary results (HDR) in both CoQ10/CoQ10+ and placebo groups. The HDR was estimated using the following formula:

$$HDR = duration\ of\ headache \times frequency\ of\ headache$$

Quality assessment and bias risk

The quality of the included studies was assessed independently by two investigators using the second version of the Cochrane risk-of-bias tool for randomized controlled trials (ROB2) using the R software 4.4.1. Any disagreements were resolved by discussion between the two authors until a solution was found.

Data analysis

The data analysis was performed using the "meta" package in the R software version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) [7]. We estimated the pooled standardized weighted mean difference (SMD) and its standard deviation (SD) using the "metacont" function. We used the following equation to estimate the SD missing in the item data[8]:

$$SD_{change} = \sqrt{[(SD_{baseline}^2 + SD_{final}^2) - (2 \times 0.8 \times SD_{baseline} \times SD_{final})]}$$

Given the potentially high variability between studies, we opted for a random-effects model with inverse variance weighting rather than a fixed-effects model. The Cochran Q test (with a significance of p <0.1) and the I^2 statistic were used to assess heterogeneity. Heterogeneity was categorized as minimal (I^2 value, 0-25%), low (25-50%), moderate (50-75%), and high (>75%). In the case of substantial heterogeneity, a sensitivity analysis and subgroup analysis was performed. The significance for the pooled effect was set at p<0.05. In cases where p=0.05, the effect was considered statistically significant if the 95% confidence interval (CI) did not include 0. We performed NMA, using "netmeta" package, to compare placebo vs. CoQ10 and placebo vs. CoQ10+.

In the context of NMA, alongside evaluating homogeneity using the Cochran Q test, we also assessed the similarity and consistency of the indirect comparisons using the R software. The assessment of the similarity assumption for indirect comparison involved comparing the distribution of clinical variables at baseline (e.g., age, MA/month, migraine duration, and migraine severity) that could potentially act as effect modifiers. This was performed through visual inspection of scatter diagrams. Because there were fewer than 10 combined studies in each risk factor analysis, it remained unnecessary to study the bias risk using funnel plots or the Begg test and Egger test [9,10].

Evaluation of the quality of evidence for outcomes

We evaluated the quality of evidence of our outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering the risk of bias, inconsistency, indirectness, imprecision, and publication bias. The evidence was categorized as very low, low, moderate, or high quality based on these criteria [11]. Two independent investigators assessed the GRADE method for its outcomes.

Results

Study characteristics

Overall, screening for eligibility retrieved five studies including 326 patients with migraine [5,12-15]. Figure 1 illustrates our search protocol.

Table 3 presents the characteristics of the included studies. The age range spanned from 18 to 65 years. These participants were divided into two groups: the interventional group (IG) consisting of 163 patients who received CoQ10 or CoQ10+ and the placebo group (PG) comprising 163 individuals. In four studies, CoQ10/CoQ10+ was administered through capsules [12-15], and in one study, a CoQ10 liquid formulation with water-dispersed nanoparticles was used [5].

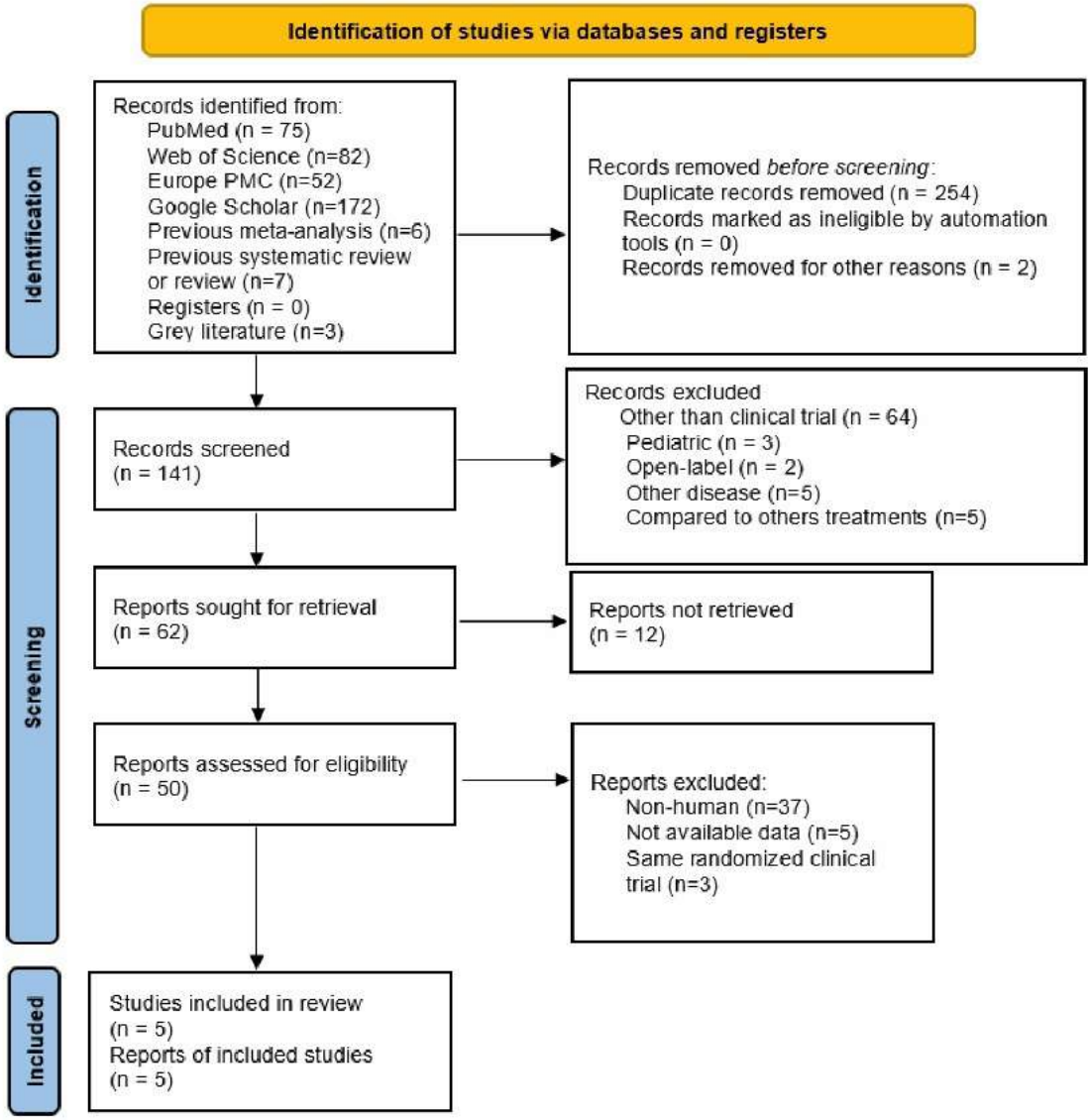

Figure 1. PRISMA flowchart of the study search

Quality assessment

Bias due to randomization was noted in the study conducted by Hajihashemi et al. (2019) [14]. Additionally, four studies exhibited bias stemming from missing data [5,13-15], and four other studies showed bias related to outcome measurements [12-15]. Overall, some concerns were identified in all included studies [5,12-15] (Figure 2A,B).

Monthly migraine frequency

Data for this outcome was available in four studies [5,13-15]. CoQ10/CoQ10+ significantly decreased the MA/month compared with the PG with high heterogeneity (Figure 3A). Sensitive analysis by excluding the study conducted by Hajihashemi et al. [14] reduced the heterogeneity (I^2=0%, p=0.69) and showed a significant positive outcome with CoQ10/CoQ10+ (SMD= -0.45 [95% CI: -0.76 to -0.14], p<0.01) (Figure 3B). This study was the source of heterogeneity based on a distinct low dosage (30 mg/day) [14]. GRADE evaluation showed moderate evidence (Table 4). Subgroup analysis according to treatment duration demonstrated a significant reduction in MA/month after 3 months with CoQ10/CoQ10+ compared with the PG (SMD = -0.49 [95% CI: -0.86 to -0.13], p<0.01) with insignificant heterogeneity (Figure 3C). Subgroup analysis according to the dosage of CoQ10/CoQ10+ revealed a significant reduction in MA/month with both 300 mg/day and 400 mg/day (95% CI: -0.44 [-0.87 to -0.02] vs. -0.45 [-0.9 to -0.0], respectively) (Figure 3D).

Through NMA, the estimated indirect effect showed that CoQ10 associated with L-carnitine was significantly more efficient compared with CoQ10 (SMD= -0.99 [95% CI: -1.68 to -0.29]) (Figure 3E). The Cochran Q test showed insignificant heterogeneity (I^2=0%, Cochran Q test=1.32; p=0.51).

Table 3. Characteristics of included studies

Studies	Origin	Study design	Age	Sex	Confirmation of migraine	CoQ10	Placebo	Severity evaluation	Dose/ Follow-up	CoQ10+
Sándor et al. (2005)[5]	Belgium	DBRCT	18-65 years	W: 100%	IHS	21	21	4-point VRS	100 mg*3/ day 4 months	None
Gaul et al. (2015)[12]	Germany	DBRCT	18-65 years	W: 86.6% M: 13.4%	IHS	55	57	3-point scale	150 mg*4/ day 2-3 months	Multivitamins and trace elements£
Dahri et al. (2017)[13]	Iran	DBRCT	18-50 years	W: 100%	IHS	39	38	VAS	200 mg*2/ day 3 months	None
Hajihashemi et al. (2019) [14]	Iran	DBRCT	20-40 years	Not available	IHS	24	26	VAS	30 mg/day 2 months	L-carnitine
Parohan et al. (2021)[15]	Iran	DBRCT	18-45 years	W: 73% M: 27%	IHS	24	21	VAS	100 mg*3/ day 2 months	None
Total	-	-	-	-	-	163	163	-	-	-

DBRCT, double-blind randomized control trials; W, women; M, male; CoQ10, Co-enzyme Q10; NOS, Newcastle-Ottawa Quality Assessment Scale; HIS, International Headache Society criteria; VAS, Visual Analog Scale; VRS, verbal rating scale; £, : 750 µg vitamin A, 200 mg vitamin C, 134 mg vitamin E, 5 mg thiamin, 20 mg niacin,5 mg vitamin B6, 6 µg vitamin B12, 400 µg folic acid, 5 µg vitamin D, 10 mg pantothenic acid, 165 µg biotin, 0.8 mg iron, 5 mg zinc, 2 mg manganese, 0.5 mg copper, 30 µg chromium, 60 µg molybdenum, 50 µg selenium, 5 mg bioflavonoides; CoQ10+, Additional nutraceuticals with CoQ10

Upon visual inspection of the scatter diagram for age and MA/month at baseline, no discernible differences were observed across studies (Figure 3F and 3G) [5,13-15].

Migraine duration

Migraine duration data were available in all included studies [5,12-15]. Compared with the PG, CoQ10/CoQ10+ demonstrated a significant decrease in the duration of migraines (SMD = -0.27 [95% CI: -0.46 to -0.08], $p<0.01$) with no significant heterogeneity (Figure 4A). The GRADE tool shows moderate evidence for this outcome (Table 4).

CoQ10/CoQ10+ significantly decreased the duration of MA after 3 months of treatment compared with a duration of less than 3 months (SMD= -0.29 [95% CI: -0.55 to -0.03] vs. SMD= -0.26 [95% CI: -0.56 to 0.04]) (Figure 4B). A dosage of 400 mg/day had a greater effect on the reduction of MA duration compared with 300 mg/day but did not reach significance (Figure 4C).

In NMA (Figure 4D), both CoQ10 and CoQ10 with multivitamins appeared to have similar effects compared with placebo with insignificant results on migraine duration. The combination of CoQ10 and L-carnitine displayed a statistically significant reduction in migraine duration compared with placebo. Although the indirect effect analysis suggests that CoQ10 with L-carnitine may be more effective in reducing migraine duration than CoQ10 and CoQ10 with multivitamins, this difference did not reach statistical significance (Figure 4D). The Cochran Q test showed insignificant heterogeneity (I^2=0%, Cochran Q test=0.21; p=0.97). Migraine duration for both the CoQ10 and CoQ10+ groups exhibited comparable ages and baseline migraine duration across the included studies (Figures 4E and 4F) [5,12-15].

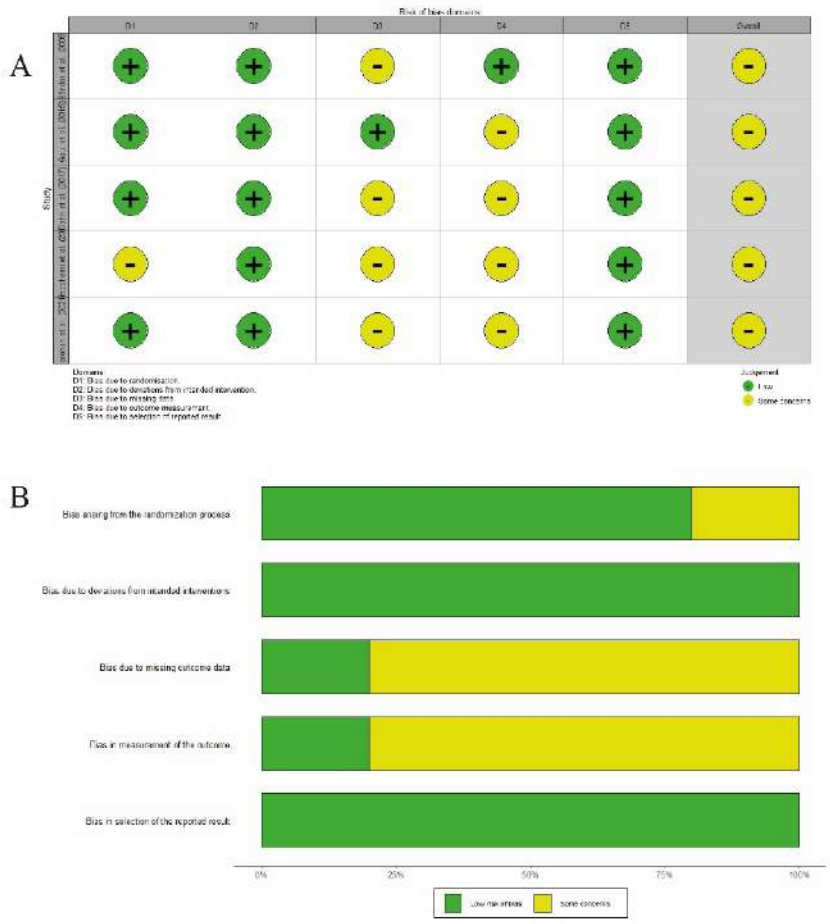

Figure 2. Quality assessment of the included studies. (A) Chart depicting the bias risk in the included studies. (B) Chart illustrating the summary of bias risk for the included studies.

Migraine severity

Migraine severity was evaluated using VAS scores in three studies [13-15]. CoQ10/CoQ10+ resulted in a significant reduction in VAS scores (SMD= -1.73 [95% CI: -3.26 to -0.21]), and the heterogeneity was significant (I^2=94%, p<0.01) (Figure 5A). Excluding the study of Hajihashemi et al. [14] revealed a significant positive impact of CoQ10/CoQ10+ on migraine severity (SMD= -0.77 [95% CI: -1.14 to -0.41], p<0.01) with insignificant heterogeneity (Figure 5B). Excluding this study contributed to reduced heterogeneity because it involved the use of CoQ10+, whereas the other studies analyzed this outcome solely on CoQ10. GRADE application demonstrated moderate evidence (Table 4).

Subgroup analysis according to the duration of treatment showed that CoQ10/CoQ10+ was significantly effective after a treatment period of 3 months (SMD = -0.72 [95% CI: -1.18 to -0.26]) (Figure 5C). Subgrouping based on the CoQ10/CoQ10+ dosage was not feasible in this study due to variations among the included trials, with one using 300 mg/day, another 400 mg/day, and a third using 30 mg/day in conjunction with L-carnitine.

NMA revealed that when compared with placebo, CoQ10 combined with L-carnitine better improved MA severity (Figure 5D). The estimated indirect effect showed that when compared with CoQ10, CoQ10 associated with L-carnitine was more effective (Figure 5D). The Cochran Q test showed significant heterogeneity (I^2= 97.1%, Cochran Q test= 34.62; p<0.01). The ages and VAS scores at baseline showed similarity across studies for migraine severity, as indicated by the scatter diagrams (Figure 5E and 5F, respectively) [13-15].

Headache diary results

The HDR was available in two studies [14,15]. Our meta-analysis indicated that CoQ10/CoQ10+ seemed

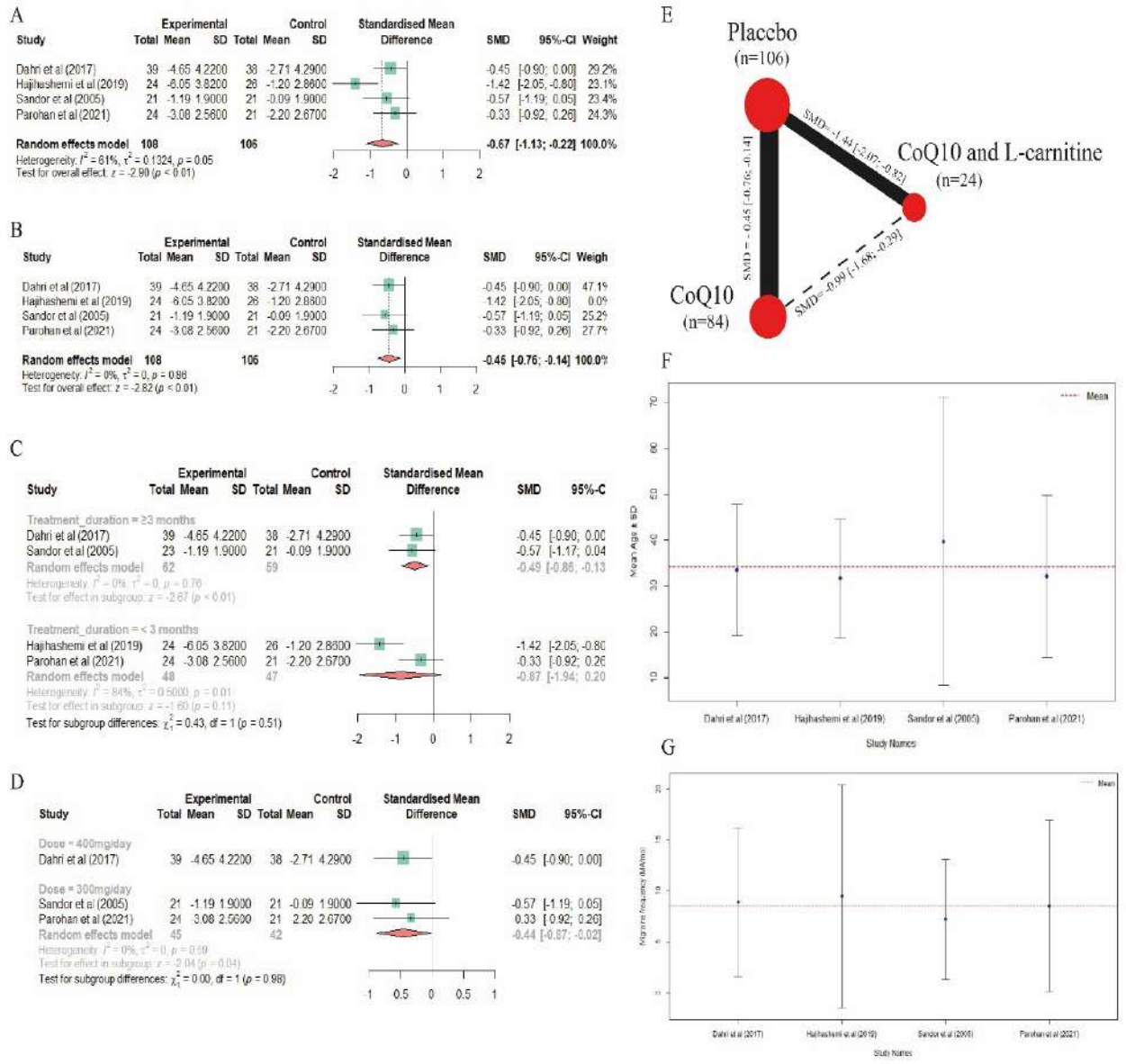

Figure 3. (A) Forest plot of the CoQ10/CoQ10+ impact on migraine frequency. (B) Forest plot of the CoQ10/CoQ10+ impact on migraine frequency after excluding the Hajihashemi et al. study. (C) Forest plot of the CoQ10/CoQ10+ impact on migraine frequency according to duration of supplementation. (D) Forest plot of the CoQ10/CoQ10+ impact on migraine frequency according to dosage of supplementation. Diamonds represent the combined effect size, horizontal lines indicate the confidence intervals, green squares represent the effect size in each study and the dashed, vertical line shows the null effect. (E) Network meta-analysis comparing the effectiveness of CoQ10 and placebo, and CoQ10+ and placebo with indirect effect between CoQ10 and CoQ10+ on migraine frequency. (F) Age scatter diagram for migraine frequency. (G) Baseline migraine frequency scatter diagram for migraine frequency. Each node represents a treatment, with its size reflecting the number of patients involved. Each line represents the direct comparisons between treatments, and the width of the line is proportional to the number of randomized controlled trials. Each dashed line represents the indirect effect model.

to have a positive effect on the HDR (SMD= -0.67 [95% CI: -1.41 to 0.07]; this result was not significant with significant heterogeneity (p=0.08) (Figure 6A).

Quality of life

Quality of life was evaluated using HIT-6 and MIDAS scores in two other studies that incorporated CoQ10 (without additional nutraceuticals) [13,15]. CoQ10 was associated with a significantly better improvement in HIT-6 scores (SMD= -0.82 [95% CI: -1.2 to -0.45], p<0.01) with low heterogeneity (I^2=0%, p=0.36) (Figure 6B). Additionally, MIDAS scores

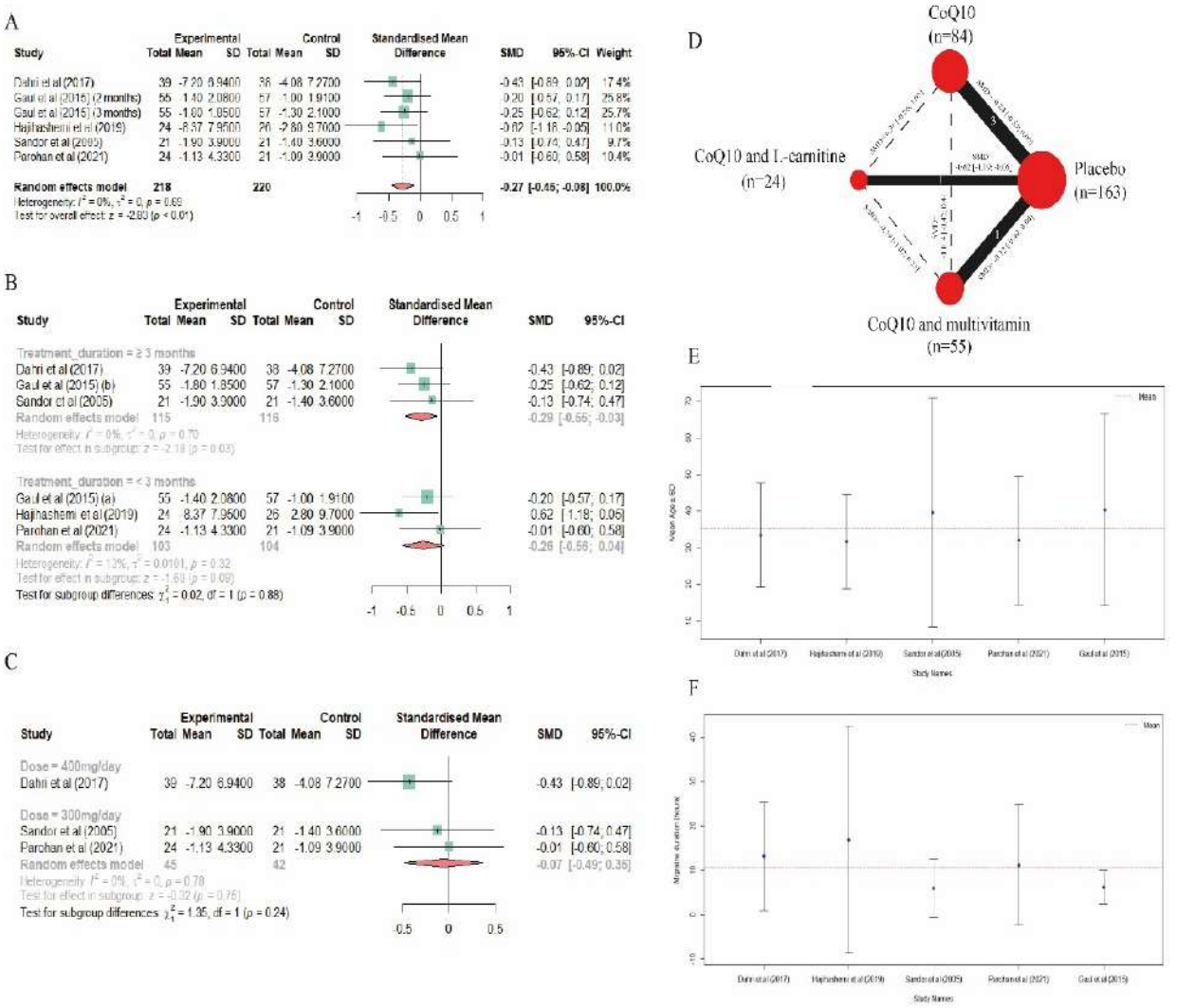

Figure 4. (A) Forest plot of the CoQ10/CoQ10+ impact on migraine attack duration. (B) Forest plot of the CoQ10/CoQ10+ impact on migraine attack duration according to duration of supplementation. (C) Forest plot of the CoQ10/CoQ10+ impact on migraine attack duration according to the dosage of supplementation. Diamonds represent the combined effect size, horizontal lines indicate the confidence intervals, green squares represent the effect size in each study and the dashed, vertical line shows the null effect. (D) Network meta-analysis comparing the effectiveness of CoQ10 and placebo, and CoQ10+ and placebo with indirect effect between CoQ10 and CoQ10+ on migraine duration. (E) Age scatter diagram for migraine duration. (F) Baseline migraine duration scatter diagram for migraine duration. Each node represents a treatment, with its size reflecting the number of patients involved. Each line represents the direct comparisons between treatments, and the width of the line is proportional to the number of randomized controlled trials. Each dashed line represents the indirect effect model.

were significantly reduced in IG compared with PG (SMD= -1.07 [95% CI: -1.59 to -0.54], p<0.01) with insignificant heterogeneity (I^2=45%, p<0.01) (Figure 6C). The effect of CoQ10 was assessed to have moderate evidence regarding both HIT-6 and MIDAS scores (Table 4).

Figure 6. Evaluation of CoQ10 impact on headache diary results and quality of life. (A) Forest plot of the CoQ10 impact on headache diary results. (B) Forest plot of the CoQ10 impact on HIT-6 score. (C) Forest plot of the CoQ10 impact on MIDAS score. Diamonds represent the combined effect size, horizontal lines indicate the confidence intervals, green squares represent the effect size in each study, and the dashed, vertical line shows the null effect. (D) Role of mitochondria in MAs and the target site of coenzyme Q10 as a supplement. Three microorganisms contribute to the development of MAs within mitochondria: dysfunction of adenosine triphosphate (ATP) production, resulting in energy deficiency; impairment of the electron transport chain (ETC); and disruption of calcium channels. These microorganisms prompt neuroinflam-

Table 4. Comparison between our meta-analysis and a previously published meta-analysis for the impact of Coenzyme Q10 or Coenzyme Q10+

Meta-analysis	Included studies	Method of statistical analysis	Population of study	MF	MS	MDu	QL
Zeng et al. (2019) [16]	Dahri et al. (2017) [13] Dahri et al. (2018) [17] Shoeibi et al. (2017) [18] Slater et al. (2011) [19] Rozen et al. (2002) [20]	RevMan 5.2	Children and adults	-	-	+	NS
Parohan et al. (2020) [21]	Dahri et al. (2018) [17] Sándor et al. (2005) [5] Shoeibi et al. (2017) [18] Slater et al. (2011) [19]	Stata 14	Children and adults	+	-	-	NS
Sazali et al. (2021) [4]	Sándor et al. (2005) [5] Gaul et al. (2015) [12] Dahri et al. (2017) [13] Dahri et al. (2018) [17] Nattagh-Eshtivani et al. (2018) [22] Hajihashemi et al. (2019) [14]	RevMan 5.2	Adults	+	-	+	NS
Our meta-analysis / Certainty of the evidence (GRADE)	Sándor et al. (2005) [5] Gaul et al. (2015) [12] Dahri et al. (2017) [13] Hajihashemi et al. (2019) [14] Parohan et al. (2021) [15]	Language R	Adults	+ Very low†§‡ Moderate*§	+ Very low†§‡ Moderate*§	+ Moderate§	+ Low§‡*** Low§‡***

*GRADE, Grading of Recommendations Assessment, Development and Evaluation; High certainty means we have strong confidence that the actual effect closely matches the estimated effect; Moderate certainty indicates a moderate level of confidence in the estimated effect, suggesting the true effect is likely close to the estimate but could differ significantly; Low certainty reflects limited confidence in the estimated effect, implying that the true effect may differ substantially from the estimate; Very low certainty indicates minimal confidence in the estimated effect, suggesting the true effect is likely to be substantially different from the estimate; MF, migraine frequency; MS, migraine severity; MDu, migraine duration; +, significant impact; -, insignificant impact; RevMa, review manager 5.2; MD, mean difference; QL, quality of life; NS, not studied; *, after excluding Hajihashemi et al. (2019) study; †, downgraded due to inconsistency; ‡, downgraded due to imprecision and large confidence interval; §, downgraded due to bias risk (some concerns); **, HIT-6 score; ***, MIDAS score*

mation, and generate reactive oxygen species (ROS) and oxidative stress, ultimately triggering MAs. Coenzyme Q10 specifically targets these three microorganisms as part of its mechanism of action. Therefore, it possesses anti-inflammatory properties. Additionally, it reduces neuronal hyperexcitability and alleviates the duration, severity, and frequency of MAs, thereby improving the overall quality of life.

Discussion

Our meta-analysis highlights the benefits of CoQ10/CoQ10+ in reducing MA/month, MA duration and severity, and improving quality of life. CoQ10 with L-carnitine was more effective than CoQ10 alone in decreasing MA/month and severity. For optimal results, CoQ10/CoQ10+ should be taken for at least 3 months. Our research represents the second meta-analysis conducted among adults in the migraine population. The previous meta-analysis was conducted by Sazali et al. (2021) [4]. Dahri et al. (2018)[17] and Nattagh-Eshtivani et al. (2018)[22] were excluded from our study because they relied on the same

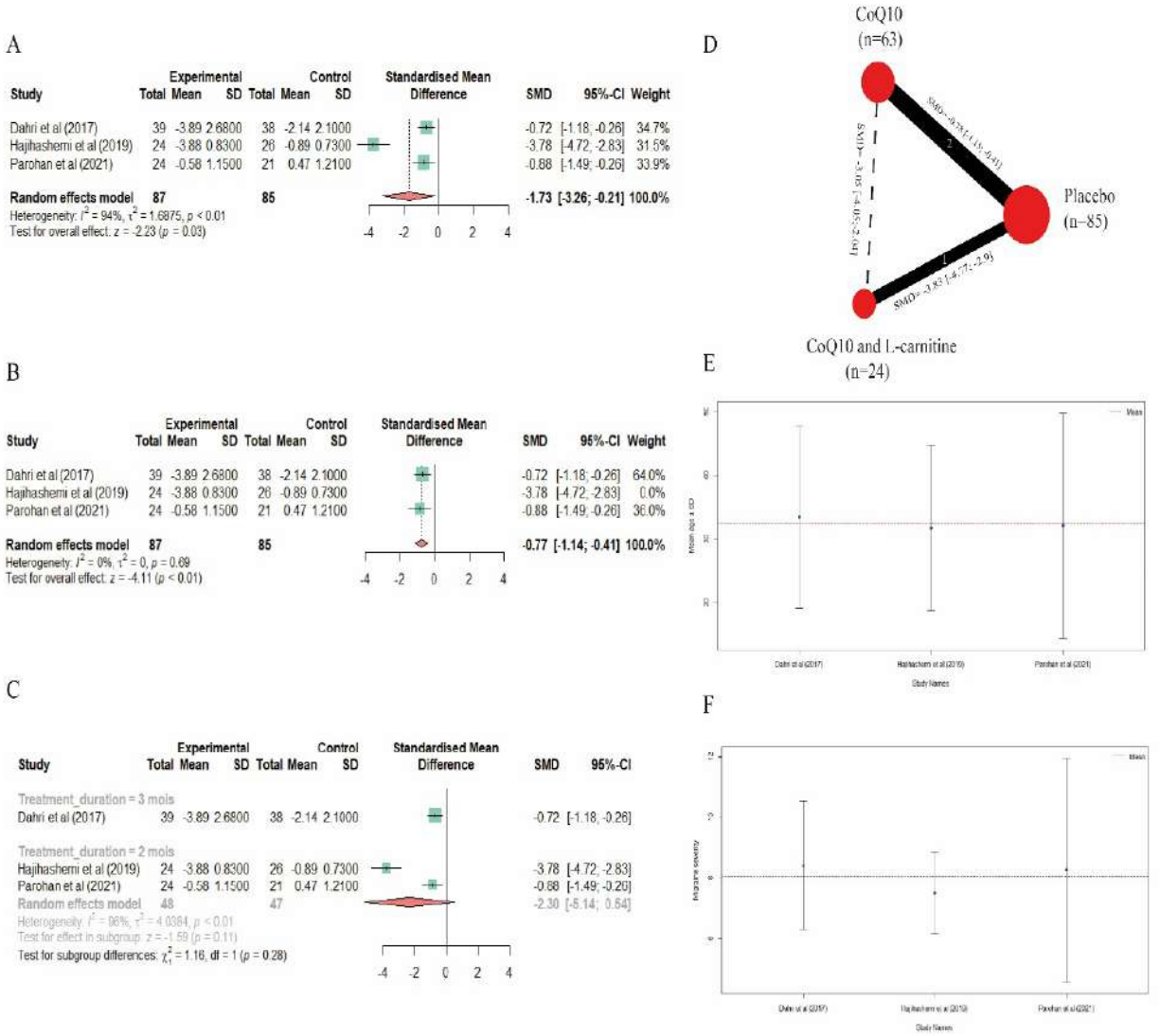

Figure 5. (A) Forest plot of the CoQ10/CoQ10+ impact on migraine attack severity. (B) Forest plot of the CoQ10/CoQ10+ impact on migraine attack severity frequency after excluding the Hajihashemi et al. study. (C) Forest plot of the CoQ10/CoQ10+ impact on migraine attack severity according to duration of supplementation. Diamonds represent the combined effect size, horizontal lines indicate the confidence intervals, green squares represent the effect size in each study, and the dashed, vertical line shows the null effect. (D) Network meta-analysis comparing the effectiveness of CoQ10 vs. placebo, and CoQ10+ vs. placebo with indirect effect between CoQ10 and CoQ10+ on migraine severity. (E) Age scatter diagram for migraine severity. (F) Baseline VAS scores scatter diagram for migraine severity. Each node represents a treatment, with its size reflecting the number of patients involved. Each line represents the direct comparisons between treatments, and the width of the line is proportional to the number of randomized controlled trials. Each dashed line represents the indirect effect model.

registry and participants as Dahri et al. (2017) [13]. We added a novel study conducted by Parohan et al. (2021) [15]. Two additional meta-analyses were conducted encompassing both children and adults (2020) [16,21]. Table 2 summarizes the variations in findings between our meta-analysis and the three mentioned meta-analyses [4,16,21]. We found a significant influence of CoQ10/CoQ10+ on MA severity, but Sazali et al. (2021) [4] observed no significant impact. In their study, the authors combined all included studies, with one using a 4-point verbal rating scale and the rest using VAS scores. In contrast, our studies exclusively included VAS evaluations.

CoQ10 is a nutraceutical categorized as a benzoquinone compound with vitamin-like proprieties [23]. It is a naturally produced element from tyrosine [23]. This nutrient constitutes a crucial element of the ETC, facilitating the transfer of electrons between com-

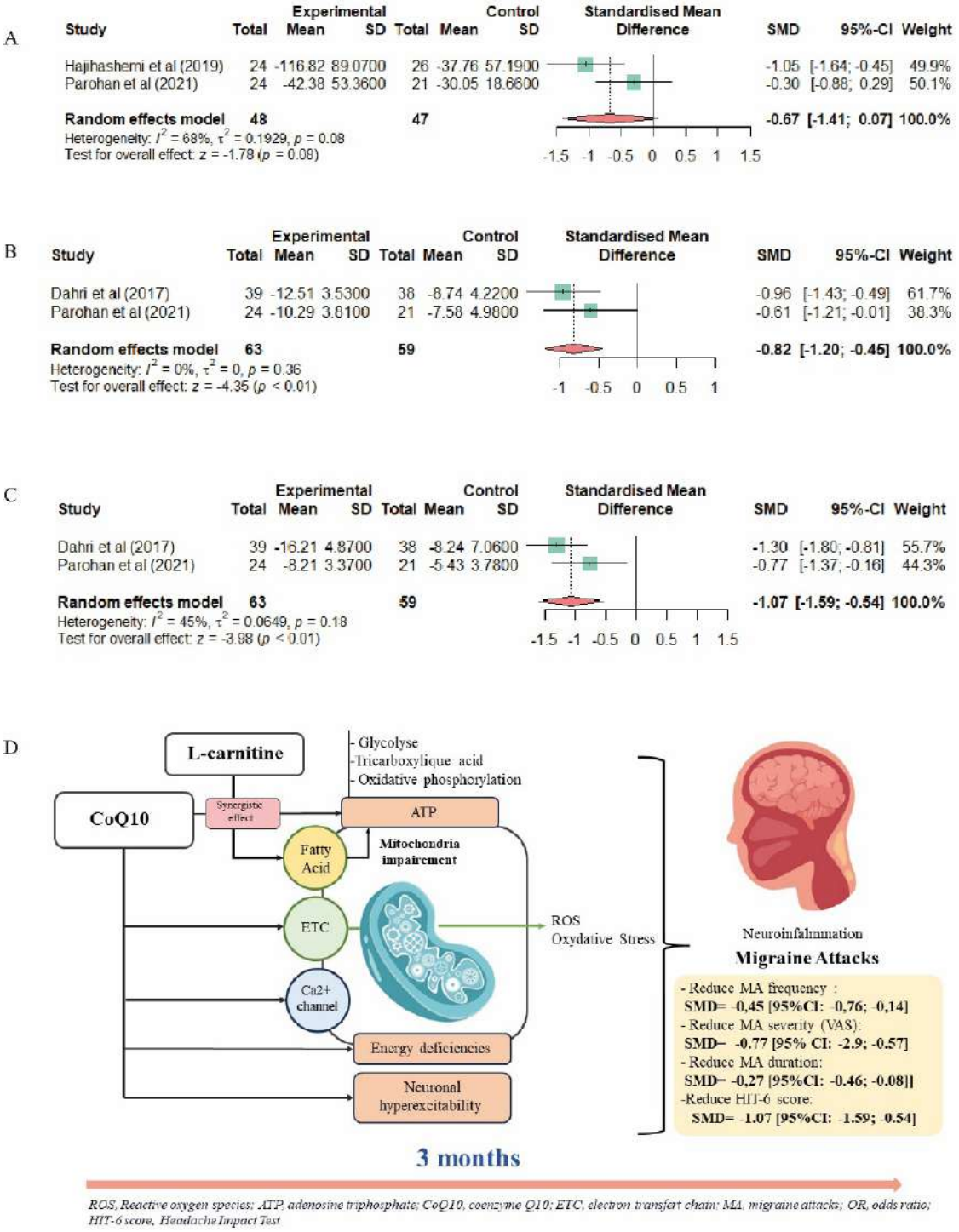

Figure 6. Evaluation of CoQ10 impact on headache diary results and quality of life. (A) Forest plot of the CoQ10 impact on headache diary results. (B) Forest plot of the CoQ10 impact on HIT-6 score. (C) Forest plot of the CoQ10 impact on MIDAS score. Diamonds represent the combined effect size, horizontal lines indicate the confidence intervals, green squares represent the effect size in each study, and the dashed, vertical line shows the null effect. (D) Role of mitochondria in MAs and the target site of coenzyme Q10 as a supplement. Three microorganisms contribute to the development of MAs within mitochondria: dysfunction of adenosine triphosphate (ATP) production, resulting in energy deficiency; impairment of the electron transport chain (ETC); and disruption of calcium channels. These microorganisms prompt neuroinflammation, and generate reactive oxygen species (ROS) and oxidative stress, ultimately triggering MAs. Coenzyme Q10 specifically targets these three microorganisms as part of its mechanism of action. Therefore, it possesses anti-inflammatory properties. Additionally, it reduces neuronal hyperexcitability and alleviates the duration, severity, and frequency of MAs, thereby improving the overall quality of life.

plexes I/II and III within the mitochondria [24]. This can help to reduce the dysfunction occurring in the ETC during migraine by facilitating ATP production and potentially reducing neuronal hyperexcitability [24]. Additionally, by reducing inflammation, CoQ10 may help prevent or modulate migraine attacks [24]. Dahri et al. showed that CoQ10 supplementation significantly reduced calcitonin gene-related peptide and TNF-α [17]. CoQ10 plays a crucial antioxidant role by stabilizing the plasma membrane and other intracellular membranes [24]. This act decreases the generation of free radicals and the synthesis of lipid peroxides, which can potentially induce damage to neuron membranes [25]. Although the exact mode of action of CoQ10 on migraine remains unclear, the potential benefits discussed above warrant further research. The interesting interplay between CoQ10 and migraine, particularly in the context of mitochondrial dysfunction, offers a promising avenue for novel therapeutic strategies.

Interestingly, we observed a significantly positive impact of CoQ10/CoQ10+ on MA characteristics when administered via capsules in five studies and through the oral route [12-15,22]. However, the oral form exhibited poor bioavailability [26]. This is attributed to the fat-soluble nature of CoQ10, and its absorption is hindered by its limited solubility in water [26]. A recent study demonstrated that the oil associated as an excipient could significantly change this bioavailability [26]. Furthermore, the research showed that the inclusion of preservatives, such as vitamin C or E, could decrease the bioavailability [26]. We suggest expanding research to incorporate the advanced nano-CoQ10, a form generated through nanotechnology. This involves producing microscopic CoQ10 particles with a significantly enhanced surface area.

L-carnitine is a vital nutrient; only a small amount is synthesized in the body, with most obtained from the diet, primarily animal products [27]. It acts as a carrier molecule for fatty acids, aiding in their transport across the mitochondrial membranes [27]. The involvement of L-carnitine ensures an efficient mechanism for delivering fatty acids to the mitochondrial matrix [27]. Assisting the entry of fatty acids facilitates their conversion through β-oxidation, resulting in the breakdown of these molecules into acetyl-CoA units generating ATP [27]. Furthermore, a significant reduction in serum lactate levels was observed in treated patients [28]. Thus, L-carnitine plays a crucial role in cellular energy production within the mitochondria [27]. However, Hagen et al. found no effect of L-carnitine alone [29]. These findings, combined with our results, suggest a potential synergistic role of L-carnitine when used in conjunction with CoQ10. It is noteworthy that there are no existing studies investigating the interaction of L-carnitine with CoQ10.

Figure 6D depicts the primary locations within mitochondria where CoQ10 and L-carnitine act to mitigate migraine episodes.

Our meta-analysis has notable strengths. The inclusion criteria focused on adults and double-blind randomized controlled trials, enhancing the statistical significance of the results without introducing heterogeneity. Nevertheless, our research may have some limits. All studies comprised a small number of patients. Thus, larger clinical trials are needed to confirm the efficacy of CoQ10 on patients with migraine. For this NMA, assessing inconsistency between direct and indirect comparisons was considered challenging due to the lack of a closed-loop connection (a direct comparison between all interventions involved). Overall, the results should be interpreted with caution owing to the small sample numbers.

Conclusion

Through this meta-analysis, we suggest a favorable impact of CoQ10/CoQ10+ on migraine characteristics. Although our discoveries align with previous meta-analyses regarding the benefits of reducing migraine frequency per month and duration, our study is the first to propose a significant impact of CoQ10/CoQ10+ on the severity of migraines and quality of life. Additionally, our NMA revealed that the association of CoQ10 with L-carnitine was more effective on migraine characteristics.

Conflict of Interests

None.

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None.

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