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Title page

Title: COENZYME Q10 SUPPLEMENTATION FOR PROPHYLAXIS IN ADULT PATIENTS WITH MIGRAINE –A META-ANALYSIS

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Abstract

Objective To determine the effects of coenzyme Q10 (CoQ10) supplementation for migraine prophylaxis in adult patients.

Design Systematic review and meta- analysis.

Data sources Cochrane Central Register of Controlled Trials CENTRAL and MEDLINE (1966 to present) were reviewed and last updated until 23rd April 2019.

Study selection All blinded and open-label randomized control trials (RCTs) comparing CoQ10 with placebo or used as an adjunct treatment included in this meta-analysis. Cross-over designs and controlled clinical trials (CCT) were excluded. Eligibility of the study trials, data extraction and study quality were assessed by three authors independently.

Data synthesis Heterogeneity at face value by comparing populations, settings, interventions and outcomes were measured and statistical heterogeneity were assessed by means of the I^2 statistic. The treatment effect for dichotomous outcomes were using risk ratios (RRs) and risk difference (RD), and for continuous outcomes, mean differences (MDs) or standardized mean difference (SMD); both with 95% confidence intervals (CIs) were used. Subgroup analyses were carried out for CoQ10 dosage. Sensitivity analysis was used to investigate the impact risk of bias for sequence generation and allocation concealment of included studies.

Results Six studies with a total of 723 participants were included in meta-analysis. There is no statistically significant reduction in severity of migraine headache with CoQ10 supplementation. CoQ10 supplementation reduced the duration of headache attacks compared to the control group (mean difference -0.19, 95% CI -0.27 to -0.11; random effects; I^2 statistic = 0%; $P < 0.00001$). CoQ10 usage reduced the frequency of migraine headache compared to the control group (MD -1.52, 95% CI -2.40 to -0.65; random effects; I^2 statistic = 0%; $P = <0.001$).

Conclusion CoQ10 appears to have beneficial effects in reducing duration and frequency of migraine attack and may recommends for migraine prophylaxis.

PROSPERO registration number CRD42019126127; protocol

Strengths and limitations of this study

Strengths

- The meta-analysis only included randomized controlled trials
- The overall level of evidence was assessed using the GRADE approach
- This meta-analysis also provides the effects of coenzyme Q10 on secondary outcomes (number of days with nausea due to migraine headache, numbers of acute migraine medication usage, quality of life and adverse effects)

Limitation

- Data on side effects of coenzyme Q10 are limited

Introduction

Migraine is an episodic disorder, the centrepiece of which is a severe headache generally associated with nausea and/or light and sound sensitivity. Migraine is a common disorder that affects up to 12% of the general population(1). Migraine is a debilitating brain disorder with serious social and financial consequences for the individual and the society(2). Migraine medications usually aim to reduce the frequency and intensity of headache attacks and some of it acts as preventive medication. Headache attack frequency and frequency of acute migraine medication use often influence modification in migraine treatment(3).

Low levels of the micronutrients such as riboflavin, magnesium and coenzyme in plasma and in the brain are reported in migraine patients(4). A deficit of these nutrients is thought to cause the migraine attacks. The cortical spreading depression is hypothesized to cause the elevation level of MMP-9 is associated with blood-brain barrier dysfunction and inflammation of nerves exacerbates migraine attacks(5, 6). The CoQ10, also known as ubiquinone, is one of the most important antioxidants that acts against hydrogen peroxide and other inflammatory markers of migraine along with reduction of expression cytokines and MMPs(7). CoQ10 is a vitamin-like compound, which can be synthesized by the body from phenylalanine and tyrosine. It has many roles in the body especially in mitochondria and is thought to play a role in migraines but the link is unknown(4). It acts as an important factor in the electron transport chain of mitochondria, which helps in energy metabolism and oxygen utilization in the brain and muscles(8). CoQ10 can be administered orally or parenterally. Peak blood levels occur 5–10 hours after oral administration. Elimination half-life is 33.19 hours(9). This meta-analysis aimed to determine the effectiveness of CoQ10 supplements as a prophylaxis for migraine in adult patients. The protocol for this meta-analysis is registered in International Prospective Register of Systematic review (PROSPERO) with trial number CRD42019126127, available from https://www.crd.york.ac.uk/prospero.

Methods

Only randomized control trials (RCTs) comparing CoQ10 with placebo or as an adjunct treatment were accepted. All blinded and open-label studies were included in this meta-analysis. Cross-over designs and controlled clinical trials (CCT) were excluded. Participants that were included in this study were adults aged 18 till 50 years old of either sex or of any ethnicity. Supplementation with oral CoQ10 as monotherapy or in combinations with other dietary products regardless in duration of therapy. Migraine were diagnosed by neurologist or physician according to either International Classification of Headache Disorder II (ICHD-II) or International Headache Society criteria (IHS). The primary outcomes and secondary outcomes were followed up for a minimum of 6 weeks after been given interventions.

Identification of study

We searched the Cochrane Central Register of Controlled Trials CENTRAL (latest Issue), MEDLINE (1966 to present). We used the search strategy (refer to Supplementary file 1) to search in MEDLINE and CENTRAL. We checked the reference list of identified RCTs and review articles in order to find unpublished trials or trials not identified by electronic searches. We contacted the experts in the field and pharmaceutical companies which market CoQ10 to identify unpublished trials. We searched for ongoing trials through the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) https://www.who.int/ictrp/en/ and www.clinicaltrials.gov. We excluded trials published other than English language. We scanned the titles and abstracts from the searches and obtain full-text articles when they appear to meet the eligibility criteria, or when there was insufficient information to assess the eligibility. We assessed the eligibility of the trials independently and documented all the reasons for exclusion. We resolved any disagreements between the review authors by discussion. We contacted the authors if clarification is needed.

Data Collection and analysis

Three authors extracted data independently. We extracted data on dosage and frequency of CoQ10 supplementation, criteria for diagnosis of migraine, age, sex, ethnicity, and outcomes of each trials which include severity of headache attack, duration of headache in migraine attack, frequency of migraine attack in a month, numbers of days with nausea, numbers of analgesic used during headache attack, numbers of acute migraine medication used, quality of life and adverse effects of CoQ10 using data extraction form.

Three authors assessed each trial's risk of bias independently. We assessed selection bias (randomisation, allocation concealment) performance bias (blinding of participant and health personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias (recall bias, transfer bias and etc). We resolved any disagreements by discussion. We assessed the quality of evidence for primary and secondary outcomes according to GRADE methodology for risk of bias, inconsistency, indirectness, imprecision, and publication bias; classified as very low, low, moderate, or high(10).

We analysed data using Review Manager 5.3 software(11) and if appropriate, used random-effects model to pool data. We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by comparing populations, settings, interventions and outcomes. Then, we assessed statistical heterogeneity by means of the I^2 statistic. We interpreted the heterogeneity as; 0% to 40% represent might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% would be considerable heterogeneity.

We measured the treatment effect using risk ratios (RRs) and risk difference (RD) for dichotomous outcomes and mean differences (MDs) or standardized mean difference (SMD);

both with 95% confidence intervals (CIs) for continuous outcomes. We conducted subgroup analyses based on the different dosage of CoQ10 and if it is combined with another supplementation. We explored the potential sources of heterogeneity when it is present. We checked all included trials for unit of analysis errors. Unit of analysis errors can occur when trials randomize participants to intervention or control groups in clusters, but analysed the results using the total number of individual participants. We adjusted results from trials showed unit of analysis errors based on the mean cluster size and intracluster correlation coefficient(12). We contacted the original trial's authors to request missing or inadequately reported data. We performed analyses on the available data if missing data are not available. We performed sensitivity analysis to investigate the impact of risk of bias for sequence generation and allocation concealment of included studies.

Results

We retrieved 65 records from the search of the electronic databases and one record from other sources (refer Supplementary file 2, figure 1). We screened a total of 60 records. We reviewed full text of 16 studies and excluded 10 studies because all of it were non-randomized controlled trials(4, 13-21). Therefore, we included only six studies in this review.

We included six studies with a total of 723 participants(22-27). Two out of six studies (and one study that contributed to the primary outcome) declared funding from drug manufacturers(24, 27). Two of the six studies were multicentre trials in high-income countries(24, 27). Three studies involved a total of 182 female gender only as participants(22, 23, 26) and another three studies included on both sexes and involving 210 participants(24, 25, 27). All participants in the studies were randomised into intervention and control groups. Three studies reported using CoQ10 with other elements such as multivitamin(24), L-carnitine(25) and preventive medication in intervention group(22). One study used the medication in liquid formulation of

water dispersed into nanoparticles(27), five studies used the medication in capsule formulation(22-26). Different dosages of CoQ10 were administered in the studies: minimum of 30 mg per day(25), 300 mg per day(27), 400 mg per day(23), 600 mg per day(24), and 800 mg per day(22, 26). There was only one study t added preventive medication for migraine in the control group(22). Duration of treatment differs and was reported as 8 weeks in one study(25), and 3 months in five studies(22-24, 26, 27). Table 1 summarised the characteristics of the included trials.

All trials followed up the participants for a minimum of six weeks(22-27). Six study were included in the meta-analysis for the primary outcomes(22-27). We have also analysed according to subgroup by dosage of more and less than 400 mg of CoQ10. Secondary outcomes were reported in three trials(22, 24, 27). One study reported using several questionnaire for assessing quality of life affected by migraine(22), which were headache impact test (HIT-6) and migraine specific quality of life (MSQ) questionnaires to assess wellbeing and daily functioning; meanwhile migraine disability assessment (MIDAS) questionnaire to assess disability caused by migraine. The HIT-6 used scoring of 36–49 with higher scores indicate more severe effect of migraine, the MSQ reported the scores between zero and 100 with higher scores indicate better quality of life and the MIDAS reported the scores between zero and 35 with higher scores indicate severe disability. We excluded 10 studies and all were non-randomized controlled trials(4, 13-21).

Table 1: Characteristics of included trials in meta-analysis

Studies	Size, n	Age	% Female	BMI	Diagnosis of migraine criteria	CoQ10 enzyme maximum dose/ day
Sandor, 2005	42	38.65	80.9	Not mention	International Headache Society (IHS)	100 mg
Nattagh - Eshtivani, 2018	46	32.7	100	25.16	International Headache Society (IHS)	800mg
Dahri, 2018	52	32.36	100	25.55	International Headache Society (IHS)	400mg
Hajihashemi, 2019	56	32.44	87.5	24.47	International Headache Society (IHS)	30mg
Gaul, 2015	112	38.4	86.6	38.4	International Headache Society (IHS)	600mg
Dahri, 2017	84	33.71	100	25.43	International Headache Society (IHS)	400mg

Risk of bias

Assessment risk of bias is presented in graph and summary (refer supplementary file 3, figure 2a and figure 2b). The proportion of studies assessed as low, high or unclear risk of bias for each risk of bias domain (refer supplementary file 3, figure 2a). Detection bias domain had 50% of low risk with attrition and reporting bias domains around 80% of low risk. The risk of bias summary for individual studies showed in supplementary file 3, figure 2b. Three studies had unclear risk for detection bias(22, 26, 27) and for attrition and reporting bias, only one trial had high risk of bias(24).

Six studies described the method of randomisation used and all studies randomised the participants according to block randomization(22-27). Allocation concealment was mentioned in all six studies(22-27). Six studies mentioned about blinding the personnel and participants(22-27). Three studies did not state on the assessment of outcomes(22, 26, 27). All six studies measured the primary outcomes and were assessed at three months post intervention(22-27). All six studies had less than 20% loss to follow-up. Three studies measured the secondary outcomes(22, 24, 27). Only one study carried out an intention-to-treat analysis in which the participants were analysed according to the groups that they were initially assigned(22). All studies reported the outcomes as specified in their methods section(22-27). We detected no other potential sources of bias.

Effects of interventions

a) Primary outcomes

Six studies reported severity of headache during migraine attack after taking CoQ10 for at least six weeks(22-27). The meta-analysis found no significant reduction in severity of headache with CoQ10 (MD -1.33, 95% CI: -2.97 to 0.31; I^2 statistic = 99%; P = 0.110; 6 trials; 371 participants) (refer Supplementary file 4, Figure 3a). With more than 400 mg (MD -1.33, 95%

CI -2.75 to 0.08, random effects; I^2 statistic = 0%; P = 0.07; 3 trials; 167 participants) or less than 400 mg (MD -1.27; 95% CI -3.42 to 0.89; random effects; I^2 statistic = 100%; P = 0.25; 3 trials; 204 participants) per day of CoQ10, there is no difference in the severity of headache compared to the control group.

All six studies reported on the duration of headache attacks per month(22-27). CoQ10 reduce the duration of headache attacks compared to the control group (MD -0.19, 95% CI -0.27 to -0.11; random effects; I^2 statistic = 0%; P < 0.00001; 6 trials, 372 participants) (refer Supplementary file 4, figure 3b).

Five studies reported on the frequency of migraine headache per month(22, 23, 25-27). CoQ10 reduce the frequency of migraine headache compared to the control group (MD -1.52, 95% CI -2.40 to -0.65; random effects; I^2 statistic = 0%; P = <0.001; 5 trials, 259 participants) (refer Supplementary file 4, Figure 3c).

b) Secondary outcomes

One study reported on number of days with nausea due to migraine headache during the study period(27). The study showed significant difference between the CoQ10 supplementation and control groups in the reduction of nausea due to migraine headache (MD -1.70; 95% CI -2.92 to -0.48; P = 0.006; 1 trial, 42 participants). No other study reported on this outcome. One study reported the numbers of acute migraine medication during the study period (MD 0.02; 95% CI -0.42 to 0.46; P = 0.91; 1 trial, 42 participants)(27).

Only one trial measured the quality of life among patients with migraine headache(22). Migraine-specific quality of life (MSQ) questionnaire reported on role restrictive (MD 17.85; 95% CI 9.59 to 26.11; P < 0.0001; 1 trial, 77 participants), role preventive (MD 17.16; 95% CI 8.75 to 25.57; P < 0.0001; 1 trial, 77 participants) and emotional functioning (MD 16.68, 95% CI 6.70 to 26.66; P = 0.001; 1 trial, 77 participants). The Headache Impact Test (HIT-6) score

reported on impact of the well-being and daily performance (MD -4.29; 95% CI -7.19 to -1.39; P = 0.004; 1 trial: 77 participants) and Migraine Disability Assessment (MIDAS) score on disability (MD -6.00; 95% CI -9.93 to -2.07; P = 0.003; 1 trial: 77 participants). One trial involving 10 participants reported the adverse effects outcome on diarrhoea (OR 4.44; 95% CI 0.90 to 21.79; P = 0.07) and chromaturia (OR 19.45; 95% CI 1.10 to 344.70; P = 0.04)(24) and they are not different compared to the control group.

DISCUSSION

Summary of main results

This review was designed to include all RCTs addressing the effectiveness of CoQ10 as one of the ways to prevent migraine. There was significant reduction in duration of migraine by 0.19 point and frequency of migraine by 1.52 point during the follow up. Meanwhile, there were no significant difference in severity of headache during attack compared to control group even by subgroup analysis according to the different dosages of CoQ10. Nausea event caused by migraine improved with CoQ10 but was limited in the number of trials. Report on adverse events was limited to minor side effects, which included episodes of diarrhoea and chromaturia and showed no difference with CoQ10.

Overall completeness and applicability of evidence

We performed a comprehensive and extensive literature review to assess the effectiveness of CoQ10 supplement as prevention for migraine. In all those study, females are more compared to males in all study populations as it was one of the risk factors for migraine(28, 29). On this review we limited the participants to adults only because of limited studies and a few of it showed other supplements such as riboflavin also can prevent migraine(30). All studies had small number of participants and this limit the applicability of CoQ10 thus the samples size needed to be increased for better result. From the reported incidence of adverse events, we were

able to detect side effects, which are diarrhoea and chromaturia. The information on adverse events came from one trial involving 10 participants and there is a lack of information on more rare and serious adverse events.

Quality of the evidence

Generally, there were a low risk of bias for most studies in most domains. There was no evidence of selective reporting bias although there was one study with high bias, but other studies had clear protocols. Besides that, in this meta-analysis showed few of unclear risk of bias on blinding of outcome assessment that can lead to treatment effect bias in the original study and the subsequent review. The risk of attrition bias was present in one trial. Attrition bias was high risk in one study due to high proportion of sample excluded in both intervention and control study with no intention to treat analysis been stated in the study (Supplementary file 3, Figure 2b). Loss to follow-up was less than 20% in all six trials and one trial carried out intention-to-treat analysis. Only one trial declared funding from pharmaceuticals company. For most of our meta-analysis we encountered low study samples. Therefore, the overall level of evidence contributing to this review as assessed using the GRADE approach is of low to moderate quality.

Potential biases in the review process

We attempted to reduce publication bias by checking the reference lists of all related studies for further references and searching multiple databases without language restriction. However, we cannot be certain that we have located all the trials in this area. There were six included studies and we were not able to construct a funnel plot for detecting publication bias. Not all included studies reported all outcomes. Although the included studies all showed the same direction of effect, we encountered low to high heterogeneity in our primary outcomes. The high heterogeneity was not able to be explained through the subgroup analysis.

Agreements and disagreements with other studies or reviews

There were other two systematic review and meta-analysis been published in year 2019 regarding on effects of CoQ10 supplementation on clinical features of migraine and vitamins and minerals for migraine prophylaxis(31, 32). Okoli et al. evaluated the efficacy of all types of vitamins including CoQ10 as migraine prophylaxis(31). Three out of 18 trials included in the review evaluated CoQ10(24, 27, 33). They found no reduction in frequency, duration and severity of migraine with CoQ10. Parohan et al.(32) included four trials(23, 27, 34, 35) in which two of the trials were included in our meta-analysis(23, 27). We removed the remaining two of trials because the study methods were not matched to our reviewed(34, 35). It reported that CoQ10 reduced the frequency migraine attack but no significant effect on severity and duration of migraine attacks. We found no other systematic reviews that reported on our other pre specified secondary outcomes.

Limitation of review

Quality of life with validated measurement tool should be assessed in more trials. Data on side effects are limited thus need to be explored further. New studies should be performed on bigger samples.

Conclusion

CoQ10 appears to have beneficial effect on reduction of headache duration during attack and frequency of migraine attack. Therefore, the usage of CoQ10 can be recommended as prophylaxis in migraine.

CONTRIBUTION OF AUTHORS

SB involved in designing the review, writing the protocol, reviewed the articles to decide for inclusion, carried out data extraction, assessing the quality of included articles, giving comments in interpreting results from data analysis and gave advice for writing the discussion.

SS involved in preparing the protocol, writing the protocol, searching literatures and reviewed articles to decide for inclusion, carried out data extraction, entering data and carried out data analysis, assessing quality of articles and writing discussions of review results.

NMN involved in coordinating the flow of the review process, reviewing literatures and articles to decide for inclusion, carried out data extraction and assisting results interpretation from data analysis, assessing quality of articles and gave advice for writing results of review and discussion.

NSI involved in coordinating the flow of the review process, gave comments and ideas in designing the review and gave advice for writing the discussion.

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None.

PATIENT AND PUBLIC INVOLVEMENT

No patient or public involvement in this meta-analysis.

COMPETING INTERESTS

None declared.

DATA SHARING

No additional data available.

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Supplementary file 1: DETAILED SEARCH STRATEGY

MEDLINE search strategy

Pubmed - (migraine[Title/Abstract]) AND coenzyme q10[Title/Abstract]

MeSH data based"coenzyme Q10"[All Fields] OR coenzyme q10[Text Word]

migraine[Title/Abstract] AND q10[Title/Abstract]

migraine[Title/Abstract] AND ubiquinone[Title/Abstract]

CENTRAL search strategy

migraine in Title Abstract Keyword AND coenzyme q10 in Title Abstract Keyword

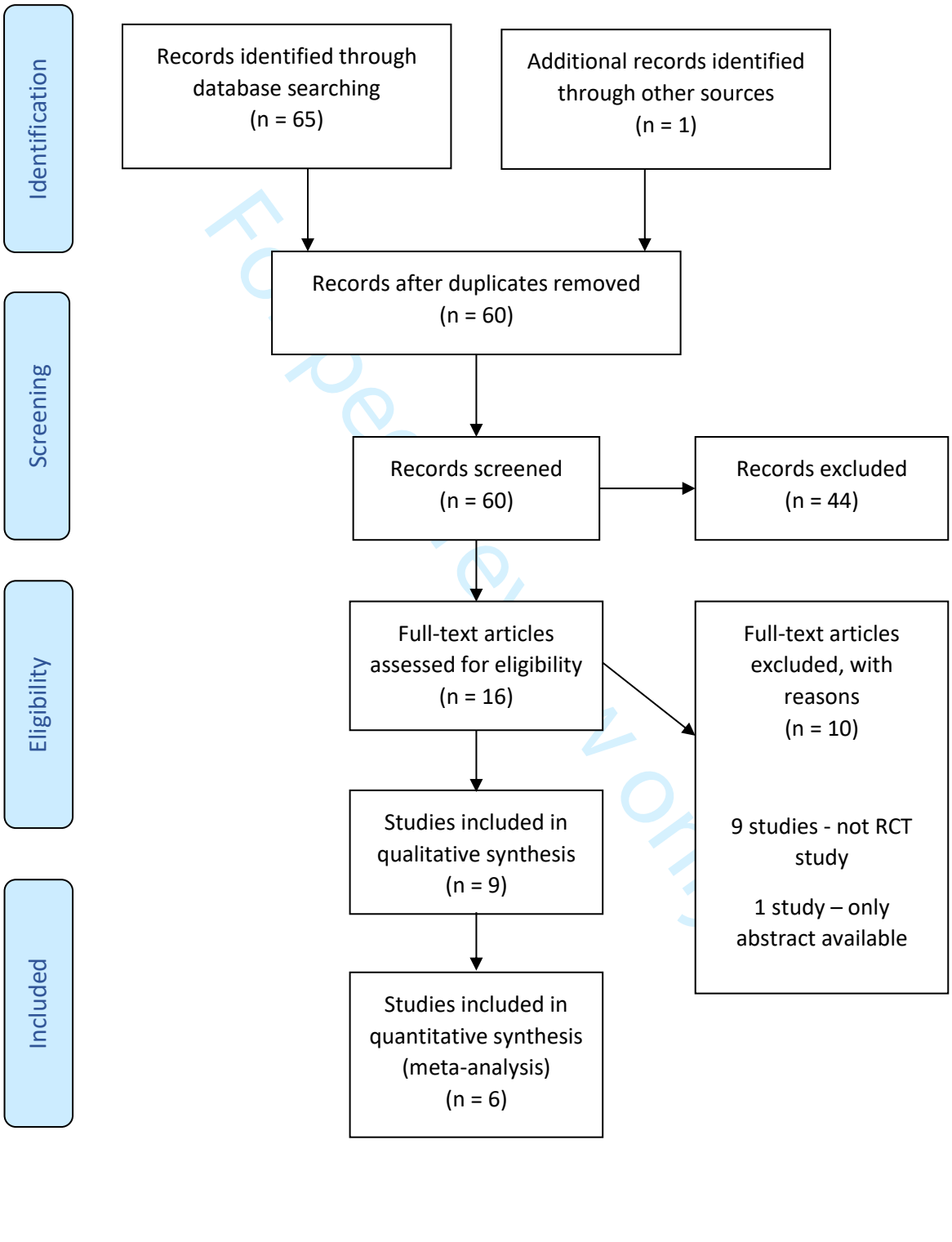
migraine in Title Abstract Keyword AND ubiquinone in Title Abstract Keyword

migraine in Title Abstract Keyword AND q10 in Title Abstract Keyword

MeSH data based"coenzyme Q10"[All Fields] OR coenzyme q10[Text Word]

Supplementary file 2: PRISMA FLOWCHART

Figure 1. PRISMA flowchart



Supplementary file 3: RISK OF BIAS ASSESSMENT (QUADAS 2)

Figure 2a: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

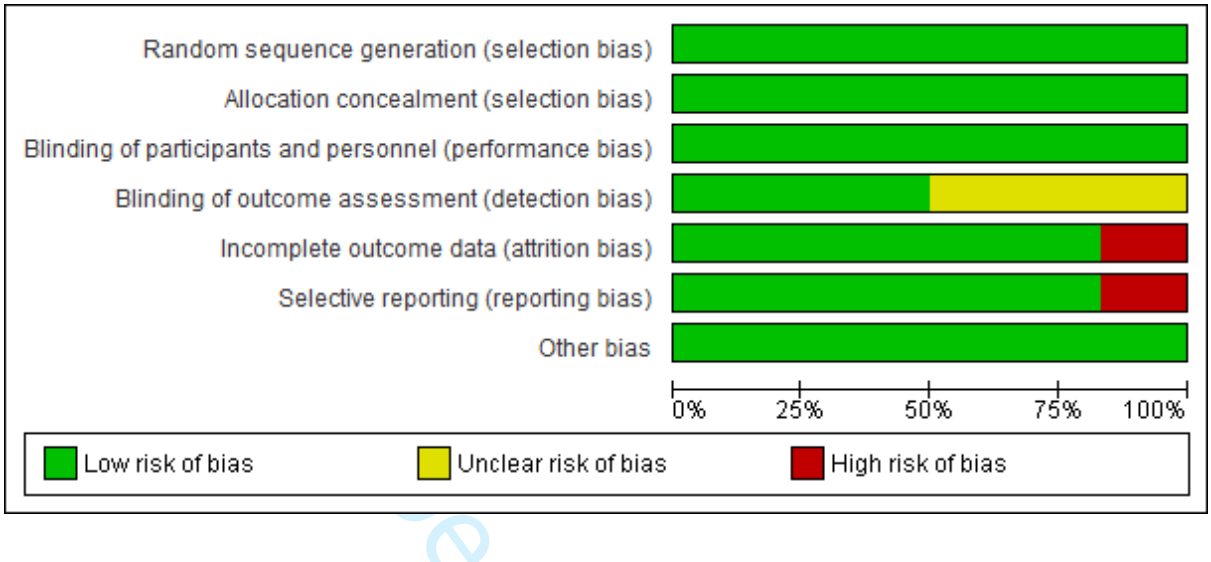


Figure 2b: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Supplementary file 4: FOREST PLOT OF PRIMARY OUTCOMES

Figure 3a: Forest plot of effects coenzyme Q10 versus control on severity of headache during attack

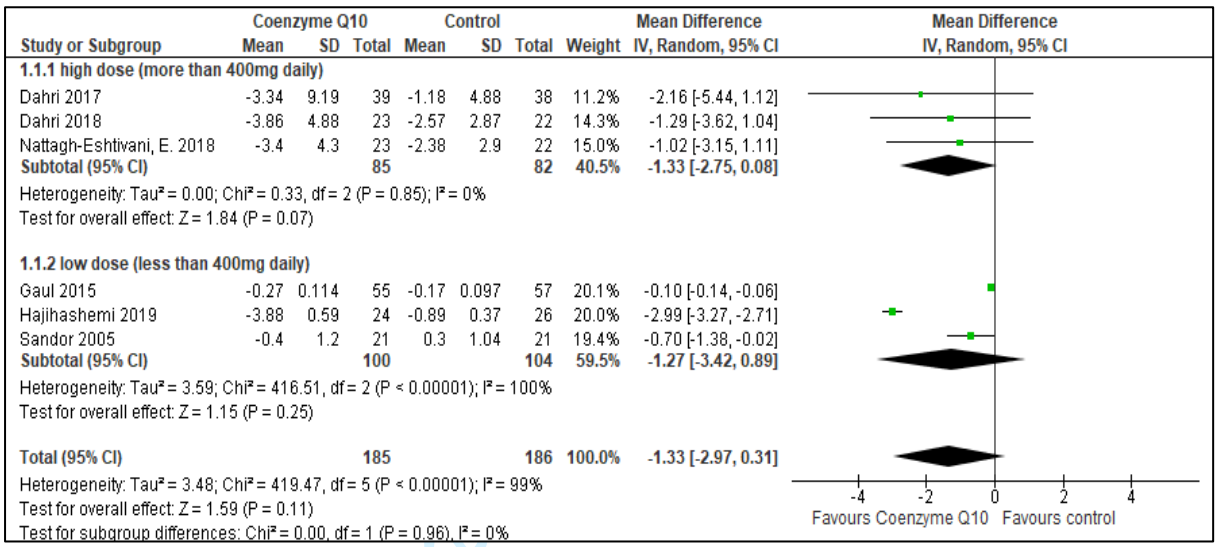
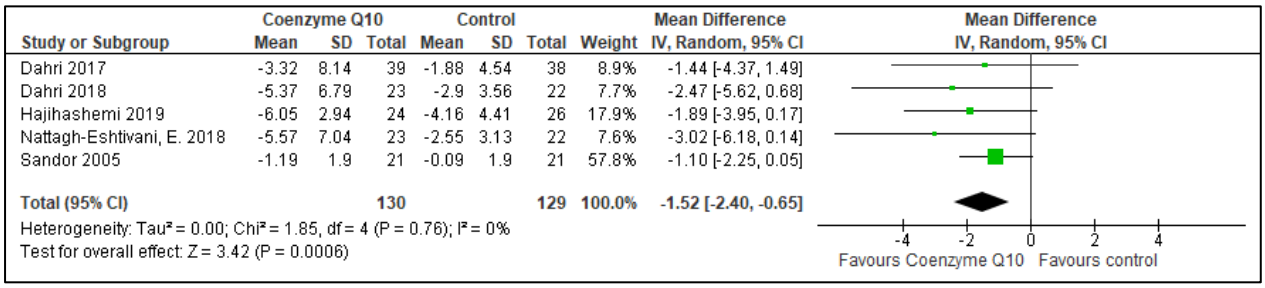


Figure 3b: Forest plot of effects coenzyme Q10 versus control on duration of headache attacks per month

Figure 3c: Forest plot of effects coenzyme Q10 versus control on frequency of migraine headache per month



Appendix I: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page # of manuscript file (unless otherwise indicated)
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Supplementary file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8, Supplementary file 2 (figure 1)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Supplementary file 2 (figure 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12, Supplementary file 3 (figure 2a,2b)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-13, Supplementary file 4 (figure 3a, 3b,3c)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12, Supplementary file 3 (figure 2a,2b)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

BMJ Open

COENZYME Q10 SUPPLEMENTATION FOR PROPHYLAXIS IN ADULT PATIENTS WITH MIGRAINE –A META-ANALYSIS

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Title: COENZYME Q10 SUPPLEMENTATION FOR PROPHYLAXIS IN ADULT PATIENTS WITH MIGRAINE –A META-ANALYSIS

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Keyword: Coenzyme Q10, Migraine, Supplementation

Word count: 3361 words with exclusion of abstract, table and references.

Abstract

Objective To determine the effects of coenzyme Q10 (CoQ10) for reduction the severity, frequency of migraine attacks and duration of headache in adult patients with migraine.

Design Systematic review and meta- analysis.

Data sources Cochrane Central Register of Controlled Trials, CENTRAL, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Psychological Information Database (PsycINFO) from inception till December 2019.

Study selection All randomized control trials (RCTs) comparing CoQ10 with placebo or used as an adjunct treatment included in this meta-analysis. Crossover designs and controlled clinical trials (CCT) were excluded.

Data synthesis Heterogeneity at face value by comparing populations, settings, interventions and outcomes were measured and statistical heterogeneity was assessed by means of the I^2 statistic. The treatment effect for dichotomous outcomes were using risk ratios (RRs) and risk difference (RD), and for continuous outcomes, mean differences (MDs) or standardized mean difference (SMD); both with 95% confidence intervals (CIs) were used. Subgroup analyses were carried out for dosage of CoQ10 and if CoQ10 combined with another supplementation. Sensitivity analysis was used to investigate the impact risk of bias for sequence generation and allocation concealment of included studies.

Results Six studies with a total of 371 participants were included in meta-analysis. There is no statistically significant reduction in severity of migraine headache with CoQ10 supplementation. CoQ10 supplementation reduced the duration of headache attacks compared to the control group (mean difference -0.19, 95% CI -0.27 to -0.11; random effects; I^2 statistic = 0%; $P < 0.00001$). CoQ10 usage reduced the frequency of migraine headache compared to

the control group (MD -1.52, 95% CI -2.40 to -0.65; random effects; I^2 statistic = 0%; P = <0.001).

Conclusion CoQ10 appears to have beneficial effects in reducing duration and frequency of migraine attack.

PROSPERO registration number CRD42019126127

Strengths and limitations of this study

Strengths

- The meta-analysis included randomized controlled trials only.
- The overall level of evidences assessed using the GRADE approach.
- Subgroup analysis and potential sources of heterogeneity explored.

Limitation

- Small numbers of the included studies.

Introduction

Migraine is an episodic disorder, the centrepiece of which is a severe headache generally associated with nausea and/or light and sound sensitivity. Migraine is a common disorder that affects up to 12% of the general population(1). Migraine is a debilitating brain disorder with serious social and financial consequences for the individual and the society(2). Migraine medications usually aim to reduce the frequency and intensity of headache attacks and few of the medications acts as preventive medication.

Low levels of the micronutrients such as riboflavin, magnesium and coenzyme in plasma and in the brain are reported in migraine patients(3). A deficit of these nutrients is thought to cause the migraine attacks. The cortical spreading depression is hypothesized to cause the elevation level of MMP-9 is associated with blood-brain barrier dysfunction and inflammation of nerves exacerbates migraine attacks(4, 5). The CoQ10, also known as ubiquinone, is one of the most important antioxidants that acts against hydrogen peroxide and other inflammatory markers of migraine along with reduction of expression cytokines and MMPs(6). CoQ10 is a vitamin-like compound, which can be synthesized by the body from phenylalanine and tyrosine. It has many roles in the body, especially in mitochondria and is thought to play a role in migraines, but the link is unknown(3). It acts as an important factor in the electron transport chain of mitochondria, which helps in energy metabolism and oxygen utilization in the brain and muscles(7). CoQ10 can be administered orally or parenterally. Peak blood levels occur 5–10 hours after oral administration. Elimination half-life is 33.19 hours(8). This meta-analysis aimed to determine the effectiveness of CoQ10 supplements as a prophylaxis for migraine in adult patients. The protocol for this meta-analysis is registered in International Prospective Register of Systematic review (PROSPERO) with trial number CRD42019126127, available from https://www.crd.york.ac.uk/prospero.

Methods

Only randomized control trials (RCTs) comparing CoQ10 with placebo or as an adjunct treatment were accepted in the meta-analysis. All blinded and open-label studies were included in this meta-analysis. Crossover designs and controlled clinical trials (CCT) were excluded. We included the adult participants aged 18 till 50 years old of either sex or of any ethnicity. Supplementation with oral CoQ10 as monotherapy or in combinations with other dietary products, regardless in duration of therapy were included in the meta-analysis. Participants with migraine diagnosed by neurologist or physician according to either International Classification of Headache Disorder II (ICHD-II) or International Headache Society criteria (IHS) were included criteria for the meta-analysis. The primary outcomes and secondary outcomes in the trials that have been followed up for a minimum of 6 weeks after giving the interventions included in the meta-analysis.

Identification of study

We searched the Cochrane Central Register of Controlled Trials, CENTRAL, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Psychological Information Database (PsycINFO) from inception till December 2019. We used the search terms “coenzyme Q10”, “ubiquinone” and “migraine” with Boolean operators of AND and OR (Refer Supplementary file 1). We checked the reference list of identifying RCTs and review articles to find unpublished trials or trials not identified by electronic searches. We contacted the experts in the field and pharmaceutical companies which market CoQ10 to identify unpublished trials. We searched for ongoing trials through the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), https://www.who.int/ictrp/en/ and www.clinicaltrials.gov. We excluded trials published other than the English language. We scanned the titles and abstracts from the searches and obtain

full-text articles when they appear to meet the eligibility criteria, or when there was insufficient information to assess the eligibility. We assessed the eligibility of the trials independently and documented all the reasons for exclusion. We resolved any disagreements between the review authors by discussion. We contacted the authors if clarification is needed.

Data Collection and analysis

Three authors extracted data independently. We extracted data on the dosage and frequency of CoQ10 supplementation, criteria for diagnosis of migraine, age, sex, ethnicity, and the outcomes of each trials which include severity of the headache attacks, duration of headache in migraine attacks, frequency of migraine attacks in a month, numbers of days with nausea, numbers of analgesic used during headache attacks, numbers of acute migraine medication used, quality of life and adverse effects of CoQ10 using data extraction form. Disagreements between the review authors were resolved by discussion with the fourth author.

The Cochrane Collaboration's risk-of-bias tools was used to assess the risk of bias in of the included studies(9). Three authors assessed each trial's risk of bias independently. We assessed selection bias (randomisation, allocation concealment), performance bias (blinding of participant and health personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias (recall bias, transfer bias and etc). We resolved any disagreements by the discussion with the fourth author. We assessed the quality of evidence for primary and secondary outcomes, according to the GRADE methodology for risk of bias, inconsistency, indirectness, imprecision, and publication bias; classified as very low, low, moderate, or high(10).

We analysed data using Review Manager 5.3 software(11). We used random-effects model to pool data. We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by comparing populations, settings, interventions and outcomes.

Then, we assessed statistical heterogeneity by means of the I^2 statistic. We interpreted the heterogeneity as; 0% to 40% represent might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% would be considerable heterogeneity(9).

We measured the treatment effect using risk ratios (RRs) and risk difference (RD) for dichotomous outcomes and mean differences (MDs) or standardized mean difference (SMD); both with 95% confidence intervals (CIs) for continuous outcomes. We conducted subgroup analyses based on the different dosage of CoQ10 and if CoQ10 is combined with another supplementation. We explored the potential sources of heterogeneity when it is present. We checked all included trials for unit of analysis errors. Unit of analysis errors can occur when trials randomize participants to intervention or control groups in clusters, but analysed the results using the total number of individual participants. We adjusted results from trials showed unit of analysis errors based on the mean cluster size and intracluster correlation coefficient(9). We contacted the original trial's authors to request missing or inadequately reported data. We performed analyses on the available data if missing data are not available. We performed sensitivity analysis to investigate the impact of risk of bias for sequence generation and allocation concealment of included studies.

Results

We retrieved 65 records from the search of the electronic databases and one record from other sources (Supplementary file 2, Figure 1). We screened a total of 60 records. We reviewed full text of 16 studies and excluded another 10 studies because all of the studies were non-randomized controlled trials(3, 12-20). Therefore, we included only six studies in this review.

We included six studies with a total of 371 participants(21-26). In all the trials, diagnosis of migraine was done based on International Headache Society criteria. Two out of six studies

(and one study that contributed to the primary outcome) declared funding from drug manufacturers(23, 26). Two out of six studies were multicentre trials in high-income countries(23, 26). Three studies involved a total of 167 female gender only as participants(21, 22, 25) and another three studies involved on both genders and a total of 204 participants(23, 24, 26). All the participants in the included studies were randomised into intervention and control groups. Three studies reported using CoQ10 with other elements such as multivitamin(23), L-carnitine(24) and preventive medication in the intervention group(21). One study used the medication in liquid formulation of water dispersed into nanoparticles (26), five studies used the medication in a capsule formulation(21-25). Different dosages of CoQ10 were administered in the studies: minimum of 30 mg per day(24), 300 mg per day(26), 400 mg per day(22), 600 mg per day(23), and 800 mg per day(21, 25). All six trials excluded any participants who on migraine preventive drugs in the last six months, who have history of using CoQ10 or other antioxidants supplementation for at least 3 months prior to the enrolment(21-26). One trial also excluded participants who failed to respond to the usage of more than two different prophylactic agents in the past or any patients who were resistant to all acute migraine drugs(23). All six included studies used placebo(21-26) and there was only one trial added the preventive migraine medication to the placebo(21); however, the preventive medication was used for both the intervention and control groups in this trial(21). Duration of CoQ10 treatment differs among the trials and was reported at 8 weeks in one study(24), and at 3 months in five other studies(21-23, 25, 26). Table 1 summarised the characteristics of the included trials.

Table 1: Characteristics of included trials in the meta-analysis

Studies	Size, n	Mean Age, years	Female, %	BMI, kg/m^2	Diagnosis of migraine	Interventions	CoQ10 maximum dose per day
Sandor, 2005	42	38.65	80.9	Not mention	International Headache Society (IHS) criteria	**Intervention:** CoQ10 liquid formulation of water dispersed nanoparticles **Control**: Placebo	100 mg
Nattagh - Eshtivani, 2018	45	32.7	100.0	25.16	International Headache Society (IHS) criteria	**Intervention:** CoQ10 capsule **Control**: Placebo	800mg
Dahri, 2018	45	32.36	100.0	25.55	International Headache Society (IHS) criteria	**Intervention:** CoQ10 capsule **Control**: Placebo	400mg
Hajihashemi, 2019	50	32.44	87.5	24.47	International Headache Society (IHS) criteria	**Intervention:** CoQ10 capsule and L-carnitine **Control:** placebo	30mg
Gaul, 2015	112	38.4	86.6	38.4	International Headache Society (IHS) criteria	**Intervention:** CoQ10 with multivitamins combination **Control:** Placebo	600mg
Dahri, 2017	77	33.71	100.0	25.43	International Headache Society (IHS) criteria	**Intervention:** CoQ10 capsule plus preventive drugs **Control:** Placebo plus preventive drugs	400mg

All six included trials followed-up the participants for a minimum of six weeks(21-26). Six studies were included in analyses of the primary outcomes(21-26). We also analysed according to subgroup by dosage of more and less than 400 mg of CoQ10. Secondary outcomes reported in the three trials(21, 23, 26). One study reported using several questionnaires for assessing quality of life affected by migraine(21), which were headache impact test (HIT-6) and migraine specific quality of life (MSQ) questionnaires to assess wellbeing and daily functioning; meanwhile migraine disability assessment (MIDAS) questionnaire to assess disability caused by migraine. The HIT-6 used scoring of 36–49 with higher scores indicate more severe effect of migraine, the MSQ reported the scores between zero and 100 with higher scores indicate better quality of life and the MIDAS reported the scores between zero and 35 with higher scores indicate severe disability(21). We excluded 10 studies and all of the studies are non-randomized controlled trials(3, 12-20).

Risk of bias

Assessment risk of bias is shown in Figure 2a and Figure 2b (Refer Supplementary file 3, Figure 2a and Figure 2b). The proportion of studies assessed as low, high or unclear risk of bias for each risk of bias domain is presented in Figure 2a (Refer Supplementary file 3, Figure 2a). Detection bias domain had 50% of low risk with attrition and reporting bias domains around 80% of low risk. The risk of bias summary for individual studies is showed in Figure 2b (Refer Supplementary file 3, Figure 2b). Three studies had unclear risk for detection bias (21, 25, 26) and for attrition and reporting bias, only one trial had high risk of bias(23).

All six studies described the method of randomisation used and randomised the participants according to block randomization(21-26). Allocation concealment was mentioned in all six included studies(21-26). All six studies mentioned about blinding the personnel and the participants(21-26). All six studies had less than 20% lost to follow-up and the reasons such as

major protocol violation(23), refused to continue the study(25, 26), failed to return to clinic(21, 22), pregnancy(21, 22, 24) and failed to keep diary(21, 22) and there were balanced between both groups. Only one study carried out an intention-to-treat analysis in which the participants were analysed according to the groups that they were initially assigned(21). All six studies reported the outcomes as specified in their methods section(21-26). We detected no other potential sources of bias.

Effects of interventions

All six studies measured the primary outcomes and assessed at three months post intervention(21-26). Three studies measured the secondary outcomes(21, 23, 26). Three studies did not state on the assessment of outcomes(21, 25, 26).

Primary outcomes

All six included studies reported severity of headache during migraine attack after taking CoQ10 for at least six weeks(21-26). The meta-analysis found no significant reduction in severity of headache with CoQ10 (MD -1.33, 95% CI: -2.97 to 0.31; I^2 statistic = 99%; P = 0.110; 6 trials; 371 participants) (Refer Supplementary file 3, Figure 3). With more than 400 mg (MD -1.33, 95% CI -2.75 to 0.08, random effects; I^2 statistic = 0%; P = 0.07; 3 trials; 167 participants) or less than 400 mg per day of CoQ10 (MD -1.27; 95% CI -3.42 to 0.89; random effects; I^2 statistic = 100%; P = 0.25; 3 trials; 204 participants), there is no difference in the severity of headache compared to the control group.

All six studies reported on the duration of headache attacks per month(21-26). There was significant reduction of duration of headache attacks with CoQ10 as compared to the control group (MD -0.19, 95% CI -0.27 to -0.11; random effects; I^2 statistic = 0%; P < 0.00001; 6 trials, 371 participants) (Refer Supplementary file 3, Figure 4).

Five studies reported on the frequency of migraine headache per month(21, 22, 24-26). There was significant reduction in the frequency of migraine headache with the CoQ10 as compared to the control group (MD -1.52, 95% CI -2.40 to -0.65; random effects; I^2 statistic = 0%; P = <0.001; 5 trials, 259 participants) (Refer Supplementary file 3, Figure 5).

a) Secondary outcomes

One study reported on the number of days with nausea due to migraine headache during the study period(26). The CoQ10 supplementation reduced the number of days with nausea due to migraine headache (MD -1.70; 95% CI -2.92 to -0.48; P = 0.006; 1 trial, 42 participants). No other study reported on this outcome. The same study reported the number of acute migraine medications usage during the study period(26). The CoQ10 supplementation reduced the number of acute migraine medications usage (MD 0.02; 95% CI -0.42 to 0.46; P = 0.91; 1 trial, 42 participants)(26).

Only one trial measured the quality of life among patients with migraine headache(21). Three types of questionnaire including Migraine-specific quality of life (MSQ), The Headache Impact Test (HIT-6) score and Migraine Disability Assessment (MIDAS) score were used to measure the impact of the treatment on migraine headache on quality of life(21). Migraine-specific quality of life (MSQ) questionnaire reported on role restrictive, role preventive and emotional functioning. There were no significant improvements in MSQ questionnaire on role restrictive (MD 17.85; 95% CI 9.59 to 26.11; P < 0.0001; 1 trial, 77 participants), role preventive (MD 17.16; 95% CI 8.75 to 25.57; P < 0.0001; 1 trial, 77 participants) and emotional functioning (MD 16.68, 95% CI 6.70 to 26.66; P = 0.001; 1 trial, 77 participants) with the CoQ10 supplementation. The CoQ10 supplementation showed improvement in The Headache Impact Test (HIT-6) score (MD -4.29; 95% CI -7.19 to -1.39; P = 0.004; 1 trial: 77 participants) and improvement in Migraine Disability Assessment (MIDAS) score (MD -6.00; 95% CI -9.93 to

-2.07; P = 0.003; 1 trial: 77 participants). One trial reported on the adverse effects outcome on diarrhoea (OR 4.44; 95% CI 0.90 to 21.79; P = 0.07) and chromaturia (OR 19.45; 95% CI 1.10 to 344.70; P = 0.04)(23) and they not different in the CoQ10 group.

DISCUSSION

Summary of main results

This review was designed to include all RCTs addressing the effectiveness of CoQ10 as one of the alternative medications for migraine prophylaxis. There was significant reduction in the duration of migraine by 0.19 point and the frequency of migraine by 1.52 point during the follow-up. Meanwhile, there was no significant reduction in severity of headache during attack even by subgroup analysis according to the different dosages of the CoQ10. Nausea event caused by migraine improved with CoQ10 but there was limited in the number of the trials. Report on adverse events was limited to the minor side effects, which include episodes of diarrhoea and chromaturia and showed no difference with CoQ10.

Overall completeness and applicability of evidence

We performed a comprehensive and extensive literature review to assess the effectiveness of CoQ10 supplement as prevention for migraine. The numbers of female participants higher than males in all of the included studies as the highest population diagnosed with migraine is female(27, 28). On this review, we limited the participants to adult population because there was limited number of studies done in paediatric population and a few of the studies done involved other supplements such as riboflavin in paediatric population(29). All the included studies had small number of participants and this limit the applicability of CoQ10 thus the larger samples size is needed for a better result. The information on adverse events came from only one trial which are diarrhoea and chromaturia. There is limited information from the trials on other serious adverse events.

Quality of the evidence

Generally, there were low risk of bias in most of the included studies in the domains. There was no evidence of selective reporting bias in all included trials. Although there was one study with high bias, the other studies had complete protocols. This meta-analysis found that there were a few of the studies has unclear risk of bias on blinding of the outcome assessment which can lead to the treatment effect bias in the original study and the subsequent review. The risk of attrition bias was present in one trial. Attrition bias in one study is due to high proportion of sample excluded in both intervention and control study with no intention to treat analysis been stated in the study (see Supplementary file 3, Figure 2b). We encountered low study samples in all trials. Therefore, the overall level of evidence contributing to outcomes of this review is low to moderate as assessed using the GRADE approach (Refer Table 2).

Table 2: The GRADE quality assessment for CoQ10

Summary of findings:

Coenzyme Q10 compared to control for migraine prophylaxis

Patient or population: Adults patient with migraine

Setting: Health care centres

Intervention: Coenzyme Q10

Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	**Risk with Coenzyme Q10**			
Severity of headache during attack follow up: 6 weeks	The mean severity of headache during attack was **0**	MD **1.33 lower** (2.97 lower to 0.31 higher)	-	371 (6 RCTs)	⊕⊕◯◯ LOW [a]
Duration of headache attacks follow up: 6 weeks	The mean duration of headache attacks was **0**	MD **0.19 lower** (0.27 lower to 0.11 lower)	-	371 (6 RCTs)	⊕⊕⊕◯ MODERATE[b]
Frequency of migraine headache per month follow up: 6 weeks	The mean frequency of migraine headache per month was **0**	MD **1.52 lower** (2.4 lower to 0.65 lower)	-	259 (5 RCTs)	⊕⊕⊕◯ MODERATE[b]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] There is presence of the statistical heterogeneity, inconsistency and imprecision existed.
[b] Downgraded due to large confidence intervals from a small sample size and small number of included studies.

Potential biases in the review process

We attempted to reduce publication bias by checking the reference lists of all related studies for further references and searching multiple databases. However, we cannot be certain that we have located all the trials in this area. There were six included studies, and we were not able to construct a funnel plot for detecting publication bias. Not all included studies reported all outcomes. Although the included studies all showed the same direction of effect, we encountered low to high heterogeneity in our primary outcomes. The high heterogeneity was not able to be explained through the subgroup analysis.

Agreements and disagreements with other studies or reviews

There were other two systematic review and meta-analysis been published in year 2019 regarding the effects of CoQ10 supplementation on clinical features of migraine and vitamins and minerals for migraine prophylaxis(30, 31). Okoli *et al* evaluated the efficacy of all types of vitamins including CoQ10 as migraine prophylaxis(30). Three out of 18 trials included in the review evaluated CoQ10(23, 26, 32). They found no reduction in frequency, duration and severity of migraine with CoQ10. Parohan *et al*(31) included four trials(22, 26, 33, 34) in which two of the trials were included in our meta-analysis(22, 26). We removed the remaining two of trials because the study methods were not match to our reviewed(33, 34). They reported that CoQ10 reduced the frequency migraine attack but no significant effect on severity and duration of migraine attacks. We found no other systematic reviews that reported on our other pre specified secondary outcomes.

For future research, we recommend that quality of life with validated measurement tool should be used. Data on side effects are limited thus need to be explored further. New studies should be performed on bigger samples.

Conclusion

CoQ10 appears to have beneficial effect on reduction of headache duration during attack and frequency of migraine attack.

CONTRIBUTION OF AUTHORS

SB was involved in designing the review, writing the protocol, reviewed the articles to decide for inclusion, carried out data extraction, assessed the quality of articles, giving input in interpreting results from data analysis and gave input for writing the discussion.

SS was involved in preparing the protocol, writing the protocol, searching literatures and reviewed articles to decide for inclusion, carried out data extraction, entering data and carried out data analysis, assessing the quality of articles and writing the discussion of review results.

NMN was involved in co-ordinating the flow of the review process, reviewing literatures and articles to decide for inclusion, and assisting results interpretation from data analysis, assessing the quality of articles and gave input for writing results of review and discussion.

NSI was involved in co-ordinating the flow of the review process, gave input in designing the review, carried out data extraction and gave input for writing the discussion.

FUNDING

None.

PATIENT AND PUBLIC INVOLVEMENT

No patient or public involvement in this meta-analysis.

COMPETING INTERESTS

None declared.

DATA SHARING

No additional data available.

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Supplementary file 1: DETAILED SEARCH STRATEGY

MEDLINE search strategy

Pubmed - (migraine[Title/Abstract]) AND coenzyme q10[Title/Abstract]

MeSH data based"coenzyme Q10"[All Fields] OR coenzyme q10[Text Word]

migraine[Title/Abstract] AND q10[Title/Abstract]

migraine[Title/Abstract] AND ubiquinone[Title/Abstract]

CENTRAL search strategy

migraine in Title Abstract Keyword AND coenzyme q10 in Title Abstract Keyword

migraine in Title Abstract Keyword AND ubiquinone in Title Abstract Keyword

migraine in Title Abstract Keyword AND q10 in Title Abstract Keyword

MeSH data based"coenzyme Q10"[All Fields] OR coenzyme q10[Text Word]

Supplementary file 2: PRISMA FLOWCHART

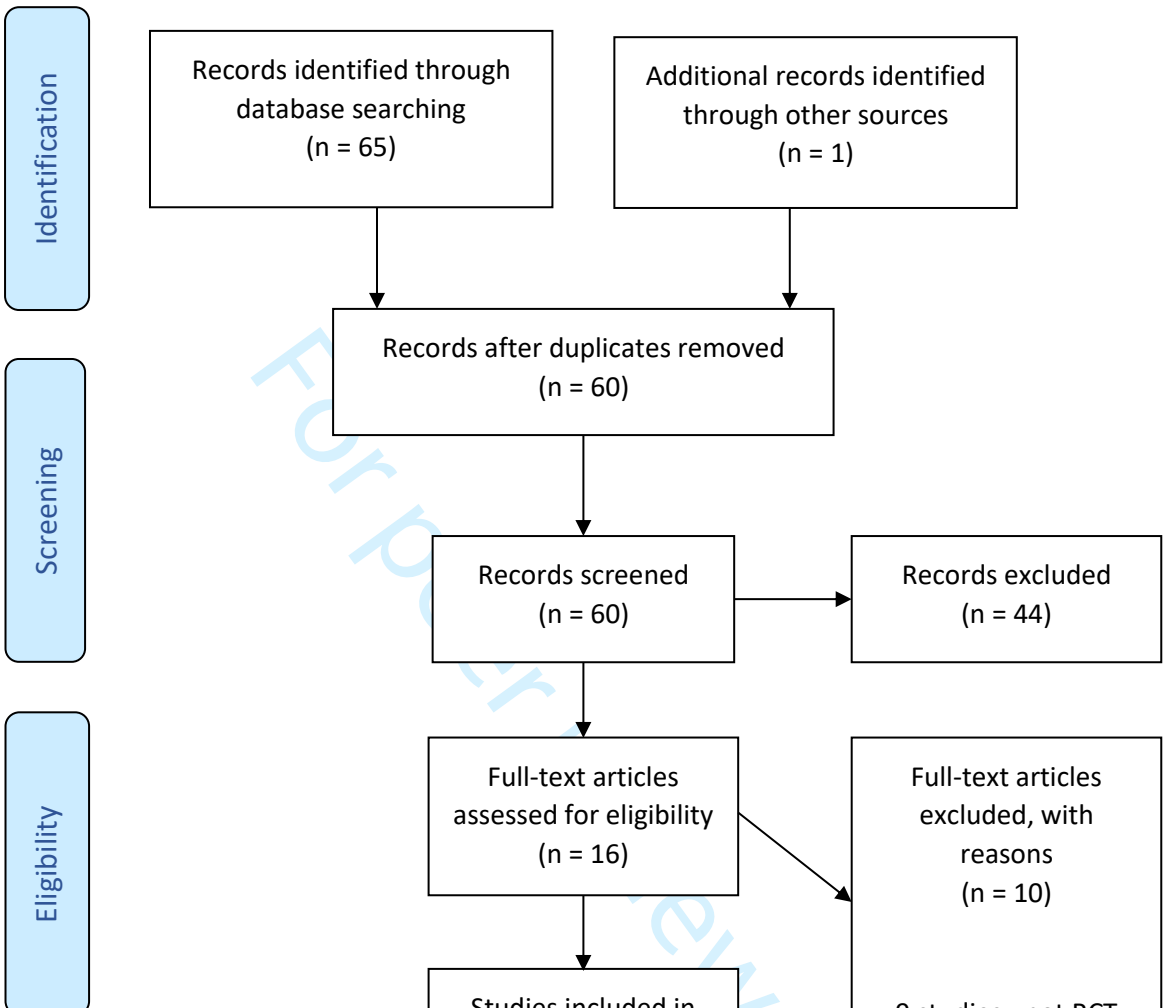

Figure 1: PRISMA Study flow diagram

Supplementary file 3: RISK OF BIAS ASSESSMENT

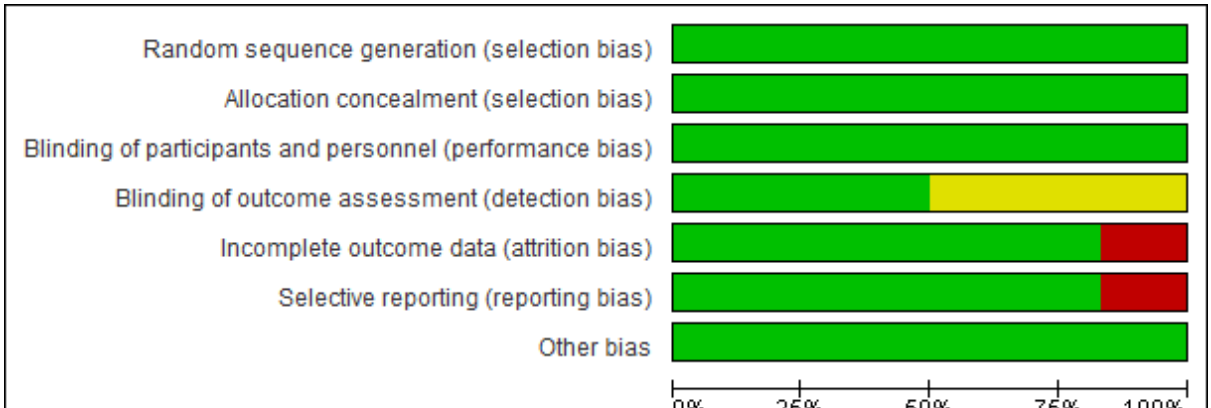

Figure 2a: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

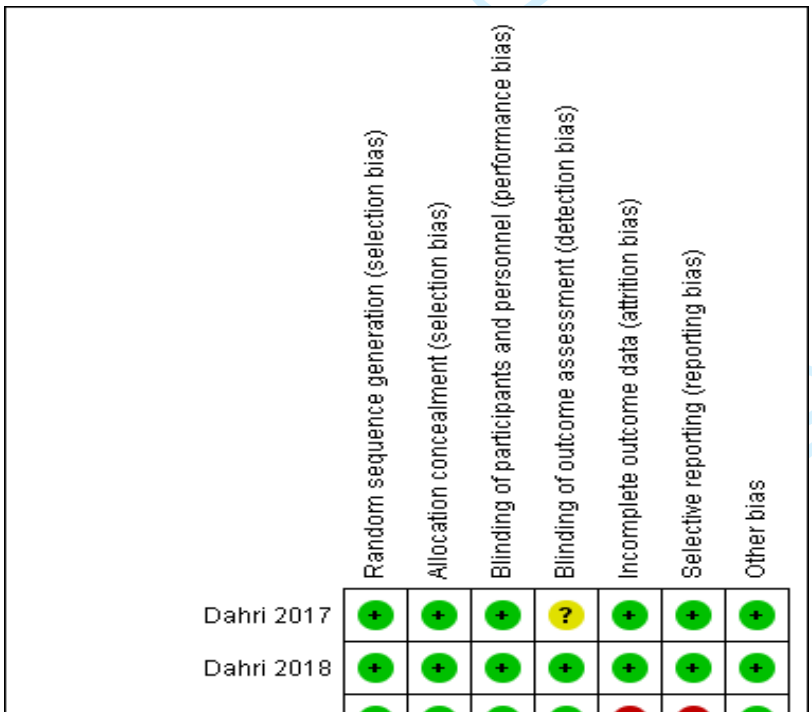

Figure 2b: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Supplementary file 4: FOREST PLOT OF PRIMARY OUTCOMES

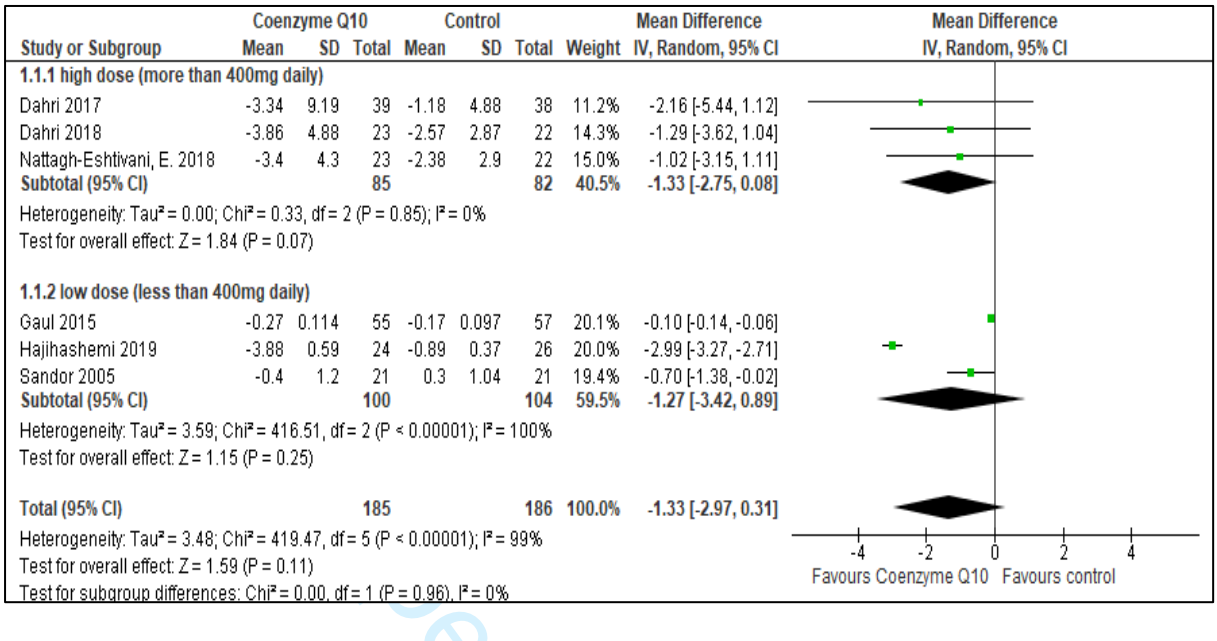

Figure 3: Forest plot of effects coenzyme Q10 versus control on severity of headache during attack

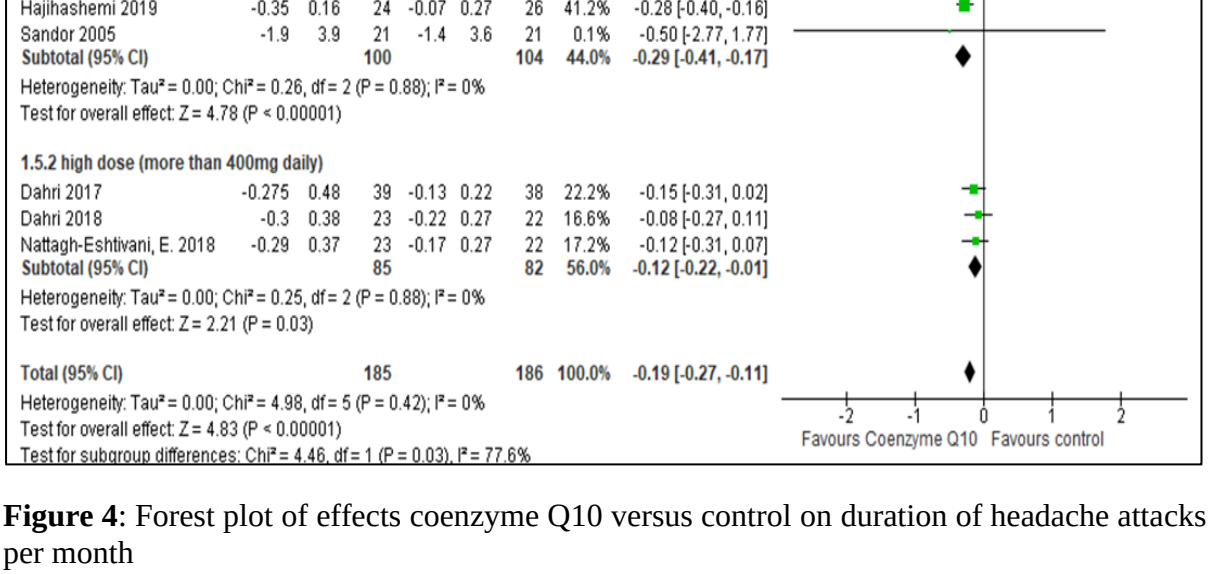

Figure 4: Forest plot of effects coenzyme Q10 versus control on duration of headache attacks per month

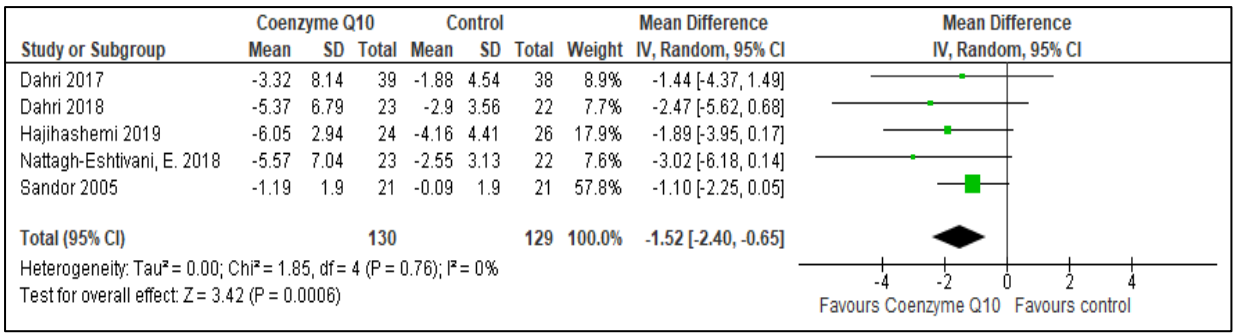

Figure 5: Forest plot of effects coenzyme Q10 versus control on frequency of migraine headache per month

Appendix I: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page # of manuscript file (unless otherwise indicated)
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Supplementary file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8, Supplementary file 2: Figure1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9

Section/topic	#	Checklist item	Reported on page # of manuscript file (unless otherwise indicated)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Supplementary file 2 (figure 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12, Supplementary file 3 (figure 2a,2b)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-13, Supplementary file 4 (figure 4, 5,6)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-13, Supplementary file 3 (figure 2a,2b)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-17, Table 2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

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COENZYME Q10 SUPPLEMENTATION FOR PROPHYLAXIS IN ADULT PATIENTS WITH MIGRAINE –A META-ANALYSIS

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Complementary medicine
Keywords:	Migraine < NEUROLOGY, COMPLEMENTARY MEDICINE, Neurology < INTERNAL MEDICINE

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Title: COENZYME Q10 SUPPLEMENTATION FOR PROPHYLAXIS IN ADULT PATIENTS WITH MIGRAINE –A META-ANALYSIS

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Keyword: Coenzyme Q10, Migraine, Supplementation

Word count: 3492 words with exclusion of abstract, table and references.

Abstract

Objective To determine the effects of coenzyme Q10 (CoQ10) for reduction the severity, frequency of migraine attacks and duration of headache in adult patients with migraine.

Design Systematic review and meta- analysis.

Data sources Cochrane Central Register of Controlled Trials, CENTRAL, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Psychological Information Database (PsycINFO) from inception till December 2019.

Study selection All randomized control trials (RCTs) comparing CoQ10 with placebo or used as an adjunct treatment included in this meta-analysis. Crossover designs and controlled clinical trials (CCT) were excluded.

Data synthesis Heterogeneity at face value by comparing populations, settings, interventions and outcomes were measured and statistical heterogeneity was assessed by means of the I^2 statistic. The treatment effect for dichotomous outcomes were using risk ratios (RRs) and risk difference (RD), and for continuous outcomes, mean differences (MDs) or standardized mean difference (SMD); both with 95% confidence intervals (CIs) were used. Subgroup analyses were carried out for dosage of CoQ10 and if CoQ10 combined with another supplementation. Sensitivity analysis was used to investigate the impact risk of bias for sequence generation and allocation concealment of included studies.

Results Six studies with a total of 371 participants were included in meta-analysis. There is no statistically significant reduction in severity of migraine headache with CoQ10 supplementation. CoQ10 supplementation reduced the duration of headache attacks compared to the control group (mean difference -0.19, 95% CI -0.27 to -0.11; random effects; I^2 statistic = 0%; $P < 0.00001$). CoQ10 usage reduced the frequency of migraine headache compared to

the control group (MD -1.52, 95% CI -2.40 to -0.65; random effects; I^2 statistic = 0%; P = <0.001).

Conclusion CoQ10 appears to have beneficial effects in reducing duration and frequency of migraine attack.

PROSPERO registration number CRD42019126127

Strengths and limitations of this study

Strengths

- The meta-analysis included randomized controlled trials only.
- The overall level of evidences assessed using the GRADE approach.
- Subgroup analysis and potential sources of heterogeneity explored.

Limitation

- Small numbers of the included studies.

Introduction

Migraine is an episodic disorder, the centrepiece of which is a severe headache generally associated with nausea and/or light and sound sensitivity. Migraine is a common disorder that affects up to 12% of the general population(1). Migraine is a debilitating brain disorder with serious social and financial consequences for the individual and the society(2). Migraine medications usually aim to reduce the frequency and intensity of headache attacks and few of the medications acts as preventive medication.

Low levels of the micronutrients such as riboflavin, magnesium and coenzyme in plasma and in the brain are reported in migraine patients(3). A deficit of these nutrients is thought to cause the migraine attacks. The cortical spreading depression is hypothesized to cause the elevation level of MMP-9 is associated with blood-brain barrier dysfunction and inflammation of nerves exacerbates migraine attacks(4, 5). The CoQ10, also known as ubiquinone, is one of the most important antioxidants that acts against hydrogen peroxide and other inflammatory markers of migraine along with reduction of expression cytokines and MMPs(6). CoQ10 is a vitamin-like compound, which can be synthesized by the body from phenylalanine and tyrosine. It has many roles in the body, especially in mitochondria and is thought to play a role in migraines, but the link is unknown(3). It acts as an important factor in the electron transport chain of mitochondria, which helps in energy metabolism and oxygen utilization in the brain and muscles(7). CoQ10 can be administered orally or parenterally. Peak blood levels occur 5–10 hours after oral administration. Elimination half-life is 33.19 hours(8). This meta-analysis aimed to determine the effectiveness of CoQ10 supplements as a prophylaxis for migraine in adult patients. The protocol for this meta-analysis is registered in International Prospective Register of Systematic review (PROSPERO) with trial number CRD42019126127, available from https://www.crd.york.ac.uk/prospero.

Methods

Only randomized control trials (RCTs) comparing CoQ10 with placebo or as an adjunct treatment were accepted in the meta-analysis. All blinded and open-label studies were included in this meta-analysis. Crossover designs and controlled clinical trials (CCT) were excluded. We included the adult participants aged 18 till 50 years old of either sex or of any ethnicity. Supplementation with oral CoQ10 as monotherapy or in combinations with other dietary products, regardless in duration of therapy were included in the meta-analysis. Participants with migraine diagnosed by neurologist or physician according to either International Classification of Headache Disorder II (ICHD-II) or International Headache Society criteria (IHS) were included criteria for the meta-analysis. The primary outcomes and secondary outcomes in the trials that have been followed up for a minimum of 6 weeks after giving the interventions included in the meta-analysis.

Identification of study

We searched the Cochrane Central Register of Controlled Trials, CENTRAL, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Psychological Information Database (PsycINFO) from inception till December 2019. We used the search terms “coenzyme Q10”, “ubiquinone” and “migraine” with Boolean operators of AND and OR (Refer Supplementary file 1). We checked the reference list of identifying RCTs and review articles to find unpublished trials or trials not identified by electronic searches. We contacted the experts in the field and pharmaceutical companies which market CoQ10 to identify unpublished trials. We searched for ongoing trials through the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), https://www.who.int/ictrp/en/ and www.clinicaltrials.gov. We excluded trials published other than the English language. We scanned the titles and abstracts from the searches and obtain

full-text articles when they appear to meet the eligibility criteria, or when there was insufficient information to assess the eligibility. We assessed the eligibility of the trials independently and documented all the reasons for exclusion. We resolved any disagreements between the review authors by discussion. We contacted the authors if clarification is needed.

Data Collection and analysis

Three authors extracted data independently. We extracted data on the dosage and frequency of CoQ10 supplementation, criteria for diagnosis of migraine, age, sex, ethnicity, and the outcomes of each trials which include severity of the headache attacks using the visual analogue scale (VAS), duration of headache in migraine attacks in hour per month, frequency of migraine attacks in a month, numbers of days with nausea, numbers of analgesic used during headache attacks, numbers of acute migraine medication used, quality of life and adverse effects of CoQ10 using data extraction form. Disagreements between the review authors were resolved by discussion with the fourth author.

The Cochrane Collaboration's risk-of-bias tools was used to assess the risk of bias in of the included studies(9). Three authors assessed each trial's risk of bias independently. We assessed selection bias (randomisation, allocation concealment), performance bias (blinding of participant and health personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias (recall bias, transfer bias and etc). We resolved any disagreements by the discussion with the fourth author. We assessed the quality of evidence for primary and secondary outcomes, according to the GRADE methodology for risk of bias, inconsistency, indirectness, imprecision, and publication bias; classified as very low, low, moderate, or high(10).

We analysed data using Review Manager 5.3 software(11). We used random-effects model to pool data. We assessed the presence of heterogeneity in two steps. First, we assessed obvious

heterogeneity at face value by comparing populations, settings, interventions and outcomes. Then, we assessed statistical heterogeneity by means of the I^2 statistic. We interpreted the heterogeneity as; 0% to 40% represent might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% would be considerable heterogeneity(9).

We measured the treatment effect using risk ratios (RRs) and risk difference (RD) for dichotomous outcomes and mean differences (MDs) or standardized mean difference (SMD); both with 95% confidence intervals (CIs) for continuous outcomes. We conducted subgroup analyses based on the different dosage of CoQ10 and if CoQ10 is combined with another supplementation. We explored the potential sources of heterogeneity when it is present. We checked all included trials for unit of analysis errors. Unit of analysis errors can occur when trials randomize participants to intervention or control groups in clusters, but analysed the results using the total number of individual participants. We adjusted results from trials showed unit of analysis errors based on the mean cluster size and intracluster correlation coefficient(9). We contacted the original trial's authors to request missing or inadequately reported data. We performed analyses on the available data if missing data are not available. We performed sensitivity analysis to investigate the impact of risk of bias for sequence generation and allocation concealment of included studies.

Results

We retrieved 65 records from the search of the electronic databases and one record from other sources (Supplementary file 2, Figure 1). We screened a total of 60 records. We reviewed full text of 16 studies and excluded another 10 studies because all of the studies were non-randomized controlled trials(3, 12-20). Therefore, we included only six studies in this review.

We included six studies with a total of 371 participants(21-26). In all the trials, diagnosis of migraine was done based on International Headache Society criteria. Two out of six studies (and one study that contributed to the primary outcome) declared funding from drug manufacturers(23, 26). Two out of six studies were multicentre trials in high-income countries(23, 26). All included trials used International Headache Society criteria (IHS) for diagnosis of migraine. Three studies involved a total of 167 female gender only as participants(21, 22, 25) and another three studies involved on both genders and a total of 204 participants(23, 24, 26). All the participants in the included studies were randomised into intervention and control groups. Three studies reported using CoQ10 with other elements such as multivitamin(23), L-carnitine(24) and preventive medication in the intervention group(21). One study used the medication in liquid formulation of water dispersed into nanoparticles (26), five studies used the medication in a capsule formulation(21-25). Different dosages of CoQ10 were administered in the studies: minimum of 30 mg per day(24), 300 mg per day(26), 400 mg per day(22), 600 mg per day(23), and 800 mg per day(21, 25). All six trials excluded any participants who on migraine preventive drugs in the last six months, who have history of using CoQ10 or other antioxidants supplementation for at least three months prior to the enrolment(21-26). One trial also excluded participants who failed to respond to the usage of more than two different prophylactic agents in the past or any patients who were resistant to all acute migraine drugs(23). All six included studies used placebo(21-26) and there was only one trial added the preventive migraine medication to the placebo(21); however, the preventive medication was used for both the intervention and control groups in this trial(21). Duration of CoQ10 treatment differs among the trials and was reported at 8 weeks in one study(24), and at 3 months in five other studies(21-23, 25, 26). Table 1 summarised the characteristics of the included trials.

Table 1: Characteristics of included trials in the meta-analysis

Studies	Size, n	Mean Age, years	Female, %	BMI, kg/m^2	Interventions	CoQ10 maximum dose per day
Sandor, 2005	42	38.65	80.9	Not mention	**Intervention:** CoQ10 liquid formulation of water dispersed nanoparticles **Control**: Placebo	100 mg
Nattagh - Eshtivani, 2018	45	32.7	100.0	25.16	**Intervention:** CoQ10 capsule **Control**: Placebo	800mg
Dahri, 2018	45	32.36	100.0	25.55	**Intervention:** CoQ10 capsule **Control**: Placebo	400mg
Hajihashemi, 2019	50	32.44	87.5	24.47	**Intervention:** CoQ10 capsule and L-carnitine **Control:** Placebo	30mg
Gaul, 2015	112	38.4	86.6	38.4	**Intervention:** CoQ10 with multivitamins combination **Control:** Placebo	600mg
Dahri, 2017	77	33.71	100.0	25.43	**Intervention:** CoQ10 capsule plus preventive drugs **Control:** Placebo plus preventive drugs	400mg

All six included trials followed-up the participants for a minimum of six weeks(21-26). Six studies were included in analyses of the primary outcomes(21-26). We also analysed according to subgroup by dosage of more and less than 400 mg of CoQ10. Secondary outcomes reported in the three trials(21, 23, 26). One study reported using several questionnaires for assessing quality of life affected by migraine(21), which were headache impact test (HIT-6) and migraine specific quality of life (MSQ) questionnaires to assess wellbeing and daily functioning; meanwhile migraine disability assessment (MIDAS) questionnaire to assess disability caused by migraine. The HIT-6 used scoring of 36–49 with higher scores indicate more severe effect of migraine, the MSQ reported the scores between zero and 100 with higher scores indicate better quality of life and the MIDAS reported the scores between zero and 35 with higher scores indicate severe disability(21). We excluded 10 studies and all of the studies are non-randomized controlled trials(3, 12-20).

Risk of bias

Assessment risk of bias is shown in Figure 2a and Figure 2b (Refer Supplementary file 3, Figure 2a and Figure 2b). The proportion of studies assessed as low, high or unclear risk of bias for each risk of bias domain is presented in Figure 2a (Refer Supplementary file 3, Figure 2a). Detection bias domain had 50% of low risk with attrition and reporting bias domains around 80% of low risk. The risk of bias summary for individual studies is showed in Figure 2b (Refer Supplementary file 3, Figure 2b). Three studies had unclear risk for detection bias (21, 25, 26) and for attrition and reporting bias, only one trial had high risk of bias(23).

All six studies described the method of randomisation used and randomised the participants according to block randomization(21-26). Allocation concealment was mentioned in all six included studies(21-26). All six studies mentioned about blinding the personnel and the participants(21-26). All six studies had less than 20% lost to follow-up and the reasons such as

major protocol violation(23), refused to continue the study(25, 26), failed to return to clinic(21, 22), pregnancy(21, 22, 24) and failed to keep diary(21, 22) and there were balanced between both groups. Only one study carried out an intention-to-treat analysis in which the participants were analysed according to the groups that they were initially assigned(21). All six studies reported the outcomes as specified in their methods section(21-26). We detected no other potential sources of bias.

Effects of interventions

All six studies measured the primary outcomes and assessed at three months post intervention(21-26). Three studies measured the secondary outcomes(21, 23, 26). Three studies did not state on the assessment of outcomes(21, 25, 26).

Primary outcomes

All six included studies reported severity of headache during migraine attack using the visual analogue scale (VAS) after taking CoQ10 for at least six weeks(21-26). The meta-analysis found no significant reduction in severity of headache with CoQ10 (MD -1.33, 95% CI: -2.97 to 0.31; I^2 statistic = 99%; P = 0.110; 6 trials; 371 participants) (Refer Supplementary file 3, Figure 3). With more than 400 mg (MD -1.33, 95% CI -2.75 to 0.08, random effects; I^2 statistic = 0%; P = 0.07; 3 trials; 167 participants) or less than 400 mg per day of CoQ10 (MD -1.27; 95% CI -3.42 to 0.89; random effects; I^2 statistic = 100%; P = 0.25; 3 trials; 204 participants), there is no difference in the severity of headache compared to the control group.

All six studies reported on the duration of headache attacks in hour per month(21-26). There was significant reduction of duration of headache attacks with CoQ10 as compared to the control group (MD -0.19 hours, 95% CI -0.27 to -0.11; random effects; I^2 statistic = 0%; P < 0.00001; 6 trials, 371 participants) (Refer Supplementary file 3, Figure 4).

Five studies reported on the frequency of migraine headache attack per month(21, 22, 24-26). There was significant reduction in the frequency of migraine headache with the CoQ10 as compared to the control group (MD -1.52 times per month, 95% CI -2.40 to -0.65; random effects; I^2 statistic = 0%; P = <0.001; 5 trials, 259 participants) (Refer Supplementary file 3, Figure 5).

a) Secondary outcomes

One study reported on the number of days with nausea due to migraine headache during the study period(26). The CoQ10 supplementation reduced the number of days with nausea due to migraine headache (MD -1.70; 95% CI -2.92 to -0.48; P = 0.006; 1 trial, 42 participants). No other study reported on this outcome. The same study reported the number of acute migraine medications usage during the study period(26). The CoQ10 supplementation reduced the number of acute migraine medications usage (MD 0.02; 95% CI -0.42 to 0.46; P = 0.91; 1 trial, 42 participants)(26).

Only one trial measured the quality of life among patients with migraine headache(21). Three types of questionnaire including Migraine-specific quality of life (MSQ), The Headache Impact Test (HIT-6) score and Migraine Disability Assessment (MIDAS) score were used to measure the impact of the treatment on migraine headache on quality of life(21). Migraine-specific quality of life (MSQ) questionnaire reported on role restrictive, role preventive and emotional functioning. There were no significant improvements in MSQ questionnaire on role restrictive (MD 17.85; 95% CI 9.59 to 26.11; P < 0.0001; 1 trial, 77 participants), role preventive (MD 17.16; 95% CI 8.75 to 25.57; P < 0.0001; 1 trial, 77 participants) and emotional functioning (MD 16.68, 95% CI 6.70 to 26.66; P = 0.001; 1 trial, 77 participants) with the CoQ10 supplementation. The CoQ10 supplementation showed improvement in The Headache Impact Test (HIT-6) score (MD -4.29; 95% CI -7.19 to -1.39; P = 0.004; 1 trial: 77 participants) and

improvement in Migraine Disability Assessment (MIDAS) score (MD -6.00; 95% CI -9.93 to -2.07; P = 0.003; 1 trial: 77 participants). One trial reported on the adverse effects outcome on diarrhoea (OR 4.44; 95% CI 0.90 to 21.79; P = 0.07) and chromaturia (OR 19.45; 95% CI 1.10 to 344.70; P = 0.04)(23) and they not different in the CoQ10 group.

DISCUSSION

Summary of main results

This review was designed to include all RCTs addressing the effectiveness of CoQ10 as one of the alternative medications for migraine prophylaxis. There was significant reduction in the duration by 0.19 hours of headache during attack per month and reduction in the frequency of migraine by 1.52 times per month. Meanwhile, there was no significant reduction in severity of headache during attack even by subgroup analysis according to the different dosages of the CoQ10. Nausea event caused by migraine improved with CoQ10 but there was limited in the number of the trials. Report on adverse events was limited to the minor side effects, which include episodes of diarrhoea and chromaturia and showed no difference with CoQ10.

Overall completeness and applicability of evidence

We performed a comprehensive and extensive literature review to assess the effectiveness of CoQ10 supplement as prevention for migraine. The numbers of female participants higher than males in all of the included studies as the highest population diagnosed with migraine is female(27, 28). On this review, we limited the participants to adult population because there was limited number of studies done in paediatric population and a few of the studies done involved other supplements such as riboflavin in paediatric population(29). All the included studies had small number of participants and this limit the applicability of CoQ10 thus the larger samples size is needed for a better result. The information on adverse events came from

only one trial which are diarrhoea and chromaturia. There is limited information from the trials on other serious adverse events.

Quality of the evidence

Generally, there were low risk of bias in most of the included studies in the domains. There was no evidence of selective reporting bias in all included trials. Although there was one study with high bias, the other studies had complete protocols. This meta-analysis found that there were a few of the studies has unclear risk of bias on blinding of the outcome assessment which can lead to the treatment effect bias in the original study and the subsequent review. The risk of attrition bias was present in one trial. Attrition bias in one study is due to high proportion of sample excluded in both intervention and control study with no intention to treat analysis been stated in the study (see Supplementary file 3, Figure 2b). We encountered low study samples in all trials. Therefore, the overall level of evidence contributing to outcomes of this review is low to moderate as assessed using the GRADE approach (Refer Table 2).

Table 2: The GRADE quality assessment for CoQ10

Summary of findings:

Coenzyme Q10 compared to control for migraine prophylaxis

Patient or population: Adults patient with migraine

Setting: Health care centres

Intervention: Coenzyme Q10

Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	**Risk with Coenzyme Q10**			
Severity of headache during attack follow up: 6 weeks	The mean severity of headache during attack was **0**	MD **1.33 lower** (2.97 lower to 0.31 higher)	-	371 (6 RCTs)	⊕⊕◯◯ LOW [a]
Duration of headache attacks follow up: 6 weeks	The mean duration of headache attacks was **0**	MD **0.19 lower** (0.27 lower to 0.11 lower)	-	371 (6 RCTs)	⊕⊕⊕◯ MODERATE[b]
Frequency of migraine headache per month follow up: 6 weeks	The mean frequency of migraine headache per month was **0**	MD **1.52 lower** (2.4 lower to 0.65 lower)	-	259 (5 RCTs)	⊕⊕⊕◯ MODERATE[b]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] There is presence of the statistical heterogeneity, inconsistency and imprecision existed.
[b] Downgraded due to large confidence intervals from small sample size and small number of included studies.

Potential biases in the review process

We attempted to reduce publication bias by checking the reference lists of all related studies for further references and searching multiple databases. We have checked the protocols, the consistency between objectives, methodology and results of each trials to reduce the publication bias. There were six included studies, and we were not able to construct a funnel plot for detecting publication bias. Not all included studies reported all outcomes. We did not perform the meta regression analysis to analyse publication bias in this meta-analysis. Although the included studies all showed the same direction of effect, we encountered low to high heterogeneity in our primary outcomes. The high heterogeneity was not able to be explained through the subgroup analysis.

Agreements and disagreements with other studies or reviews

There were another two systematic reviews and meta-analyses published in year 2019 done by Okoli *et al* and Parohan *et al*(30, 31). Okoli *et al* evaluated the efficacy of all types of vitamins including CoQ10 as migraine prophylaxis(30). Three out of 18 trials included in the review evaluated CoQ10(23, 26, 32). They found no reduction in frequency, duration and severity of migraine with CoQ10. Parohan *et al*(31) performed the meta-analysis regarding the effects of CoQ10 supplementation on clinical features of migraine and the study included four trials(22, 26, 33, 34) in which, two of the trials were included in our meta-analysis(22, 26). We removed the remaining two trials because the study methods not match to our reviewed(33, 34). They reported that CoQ10 reduced the frequency migraine attack but no significant effect on severity and duration of migraine attacks. We found no other systematic reviews that reported on our other pre specified secondary outcomes.

For future research, we recommended that the quality of life with validated measurement tool should be used. Data on side effects of coenzyme Q10 are limited thus, need to be explored further. New studies should be performed on bigger samples.

Conclusion

CoQ10 might have beneficial effect on reduction of the headache duration during attack and the frequency of migraine attack. The total number of trials on coenzyme Q10 supplementation for migraine prophylaxis is still limited. Due to the small number of trials contributing to the analyses and small effect sizes, the results presented should be considered with caution, thus further bigger sample size and high-quality trials are needed to determine the beneficial effects of the coenzyme Q10 in migraine.

CONTRIBUTION OF AUTHORS

SB was involved in designing the review, writing the protocol, reviewed the articles to decide for inclusion, carried out data extraction, assessed the quality of articles, giving input in interpreting results from data analysis and gave input for writing the discussion.

SS was involved in preparing the protocol, writing the protocol, searching literatures and reviewed articles to decide for inclusion, carried out data extraction, entering data and carried out data analysis, assessing the quality of articles and writing the discussion of review results.

NMN was involved in co-ordinating the flow of the review process, reviewing literatures and articles to decide for inclusion, and assisting results interpretation from data analysis, assessing the quality of articles and gave input for writing results of review and discussion.

NSI was involved in co-ordinating the flow of the review process, gave input in designing the review, carried out data extraction and gave input for writing the discussion.

FUNDING

None.

PATIENT AND PUBLIC INVOLVEMENT

No patient or public involvement in this meta-analysis.

COMPETING INTERESTS

None declared.

DATA SHARING

No additional data available.

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Supplementary file 1: DETAILED SEARCH STRATEGY

MEDLINE search strategy

Pubmed - (migraine[Title/Abstract]) AND coenzyme q10[Title/Abstract]

MeSH data based"coenzyme Q10"[All Fields] OR coenzyme q10[Text Word]

migraine[Title/Abstract] AND q10[Title/Abstract]

migraine[Title/Abstract] AND ubiquinone[Title/Abstract]

CENTRAL search strategy

migraine in Title Abstract Keyword AND coenzyme q10 in Title Abstract Keyword

migraine in Title Abstract Keyword AND ubiquinone in Title Abstract Keyword

migraine in Title Abstract Keyword AND q10 in Title Abstract Keyword

MeSH data based"coenzyme Q10"[All Fields] OR coenzyme q10[Text Word]

Supplementary file 2: PRISMA FLOWCHART

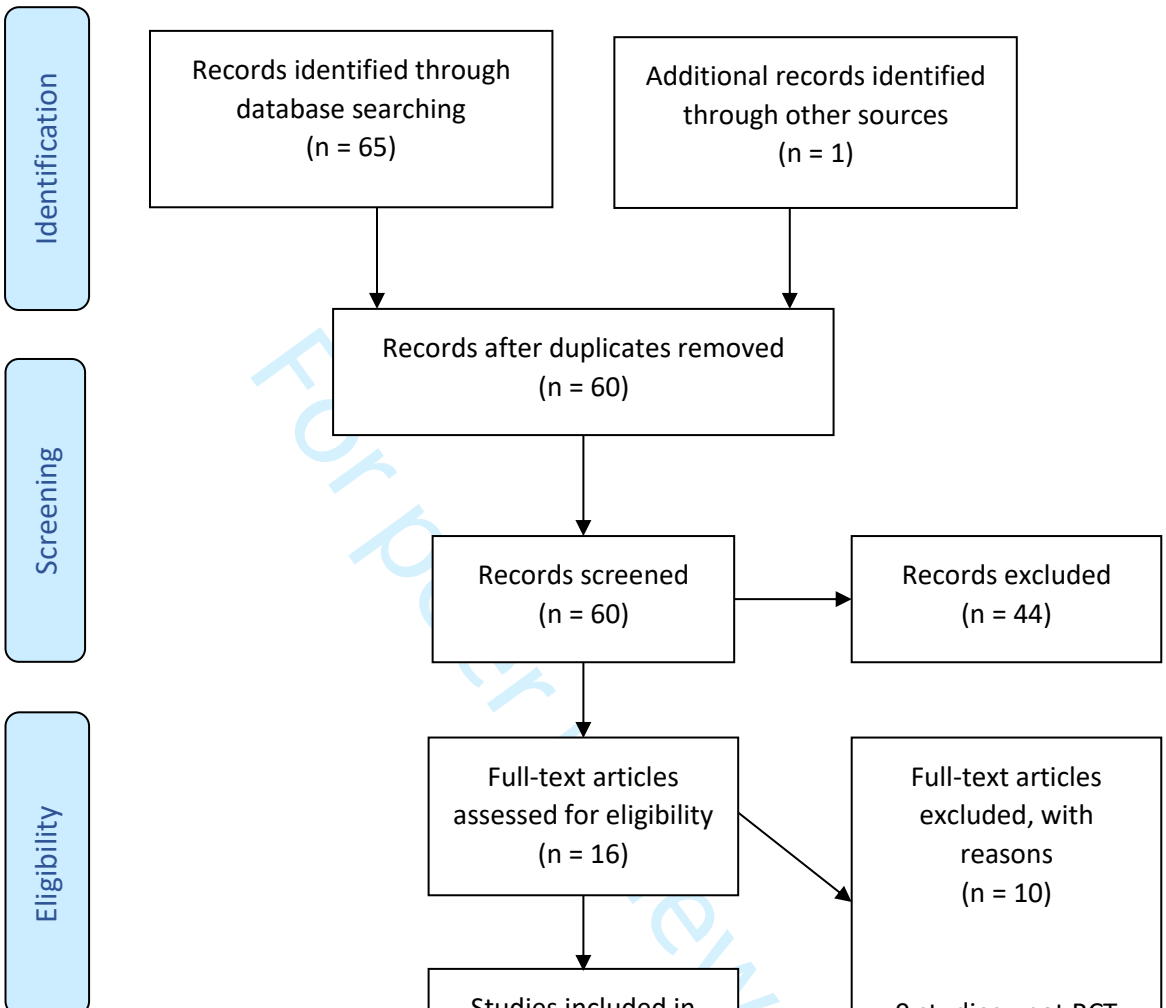

Figure 1: PRISMA Study flow diagram

Supplementary file 3: RISK OF BIAS ASSESSMENT

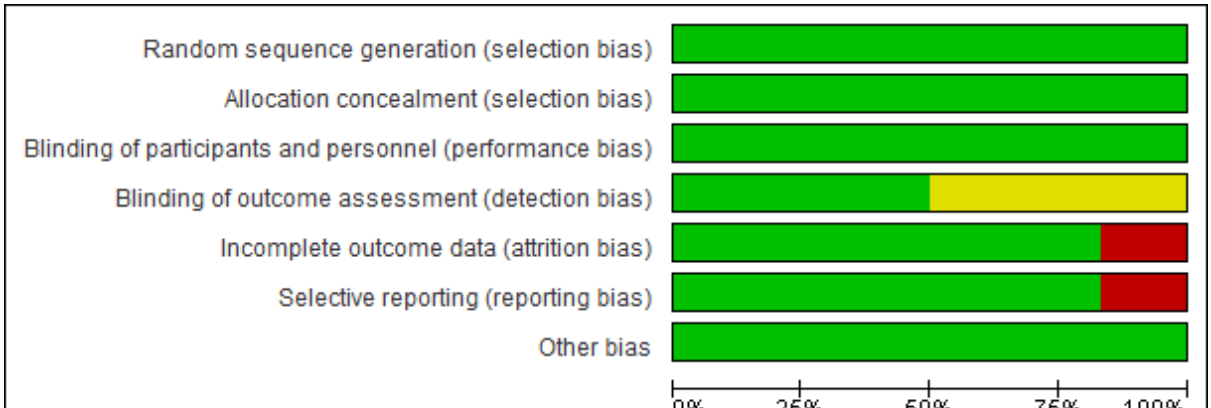

Figure 2a: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

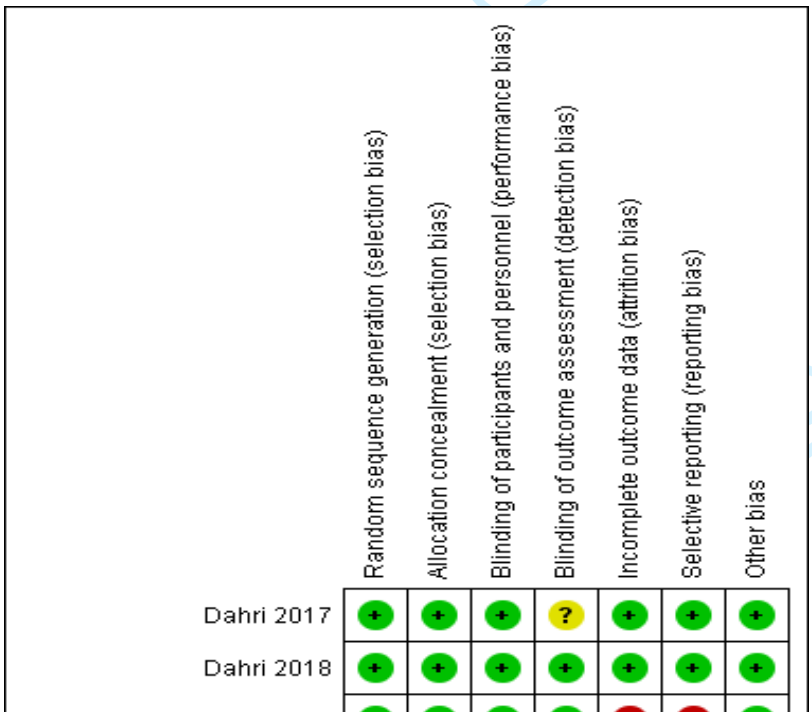

Figure 2b: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Supplementary file 4: FOREST PLOT OF PRIMARY OUTCOMES

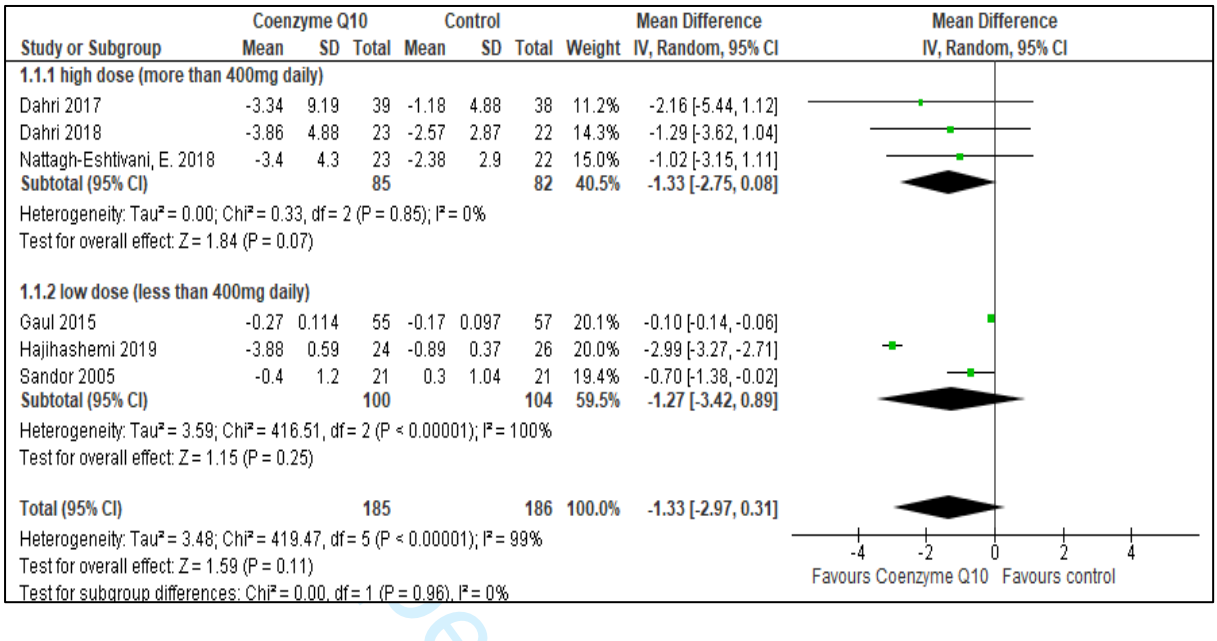

Figure 3: Forest plot of effects coenzyme Q10 versus control on severity of headache during attack

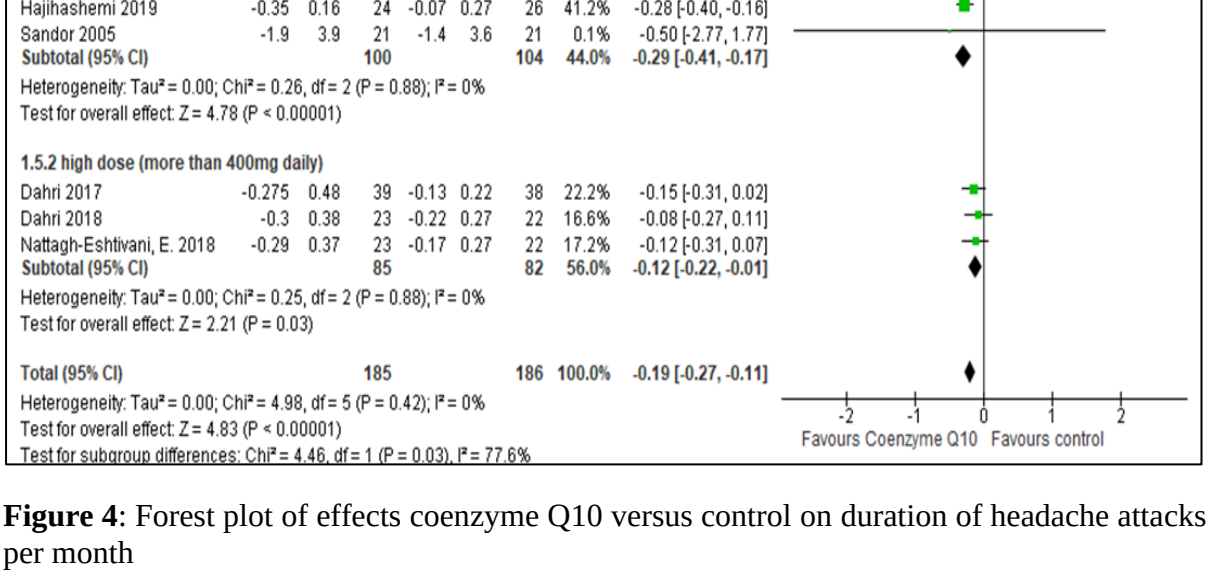

Figure 4: Forest plot of effects coenzyme Q10 versus control on duration of headache attacks per month

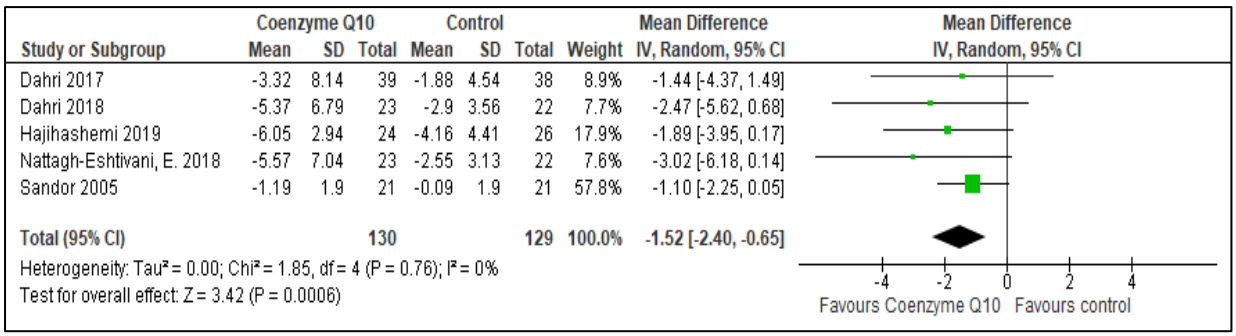

Figure 5: Forest plot of effects coenzyme Q10 versus control on frequency of migraine headache per month

Appendix I: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page # of manuscript file (unless otherwise indicated)
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Supplementary file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8, Supplementary file 2: Figure1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9

Section/topic	#	Checklist item	Reported on page # of manuscript file (unless otherwise indicated)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Supplementary file 2 (figure 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12, Supplementary file 3 (figure 2a,2b)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-13, Supplementary file 4 (figure 4, 5,6)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-13, Supplementary file 3 (figure 2a,2b)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-17, Table 2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20