

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039358
Article Type:	Original research
Date Submitted by the Author:	14-Apr-2020
Complete List of Authors:	Sazali, Suhairul; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Badrin, Salziyan; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Norhayati, Mohd Noor; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Idris, Nur Suhaila; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine
Keywords:	Migraine < NEUROLOGY, COMPLEMENTARY MEDICINE, Neurology < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Suhairul Sazali¹, Salziyan Badrin¹, Norhayati Mohd Noor¹, Nur Suhaila Idris¹

Authors:

1. Suhairul Sazali
MD
Department of Family Medicine
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian
Kelantan, Malaysia
Email: suhairul_sazali@yahoo.com
2. Salziyan Badrin (**Corresponding author**)
MD, MMed (Family Medicine)
Department of Family Medicine
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian
Kelantan, Malaysia
Email: salziyan@usm.my
Telephone number: +609-7676608
Fax number: +609-7653370
3. Norhayati Mohd Noor
MBBS, M.Comm.Med, Ph.D
Department of Family Medicine
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian
Kelantan, Malaysia
Email: hayatikk@usm.my
4. Nur Suhaila Idris
MD, MMed (Family Medicine)
Department of Family Medicine
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian
Kelantan, Malaysia
Email: nursuhaila@usm.my

1
2
3 **Keyword:** Coenzyme Q10, Migraine, Supplementation
4

5 **Word count:** 3058 with exclusion of abstract, table, figures and references
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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%; $P = <0.001$).

1
2
3 **Conclusion** CoQ10 appears to have beneficial effects in reducing duration and frequency of
4
5 migraine attack and may recommends for migraine prophylaxis.
6
7

8 **PROSPERO registration number** CRD42019126127; protocol
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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/prospere>.

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);

1
2
3 both with 95% confidence intervals (CIs) for continuous outcomes. We conducted subgroup
4 analyses based on the different dosage of CoQ10 and if it is combined with another
5 supplementation. We explored the potential sources of heterogeneity when it is present. We
6 checked all included trials for unit of analysis errors. Unit of analysis errors can occur when
7 trials randomize participants to intervention or control groups in clusters, but analysed the
8 results using the total number of individual participants. We adjusted results from trials showed
9 unit of analysis errors based on the mean cluster size and intracluster correlation
10 coefficient(12). We contacted the original trial's authors to request missing or inadequately
11 reported data. We performed analyses on the available data if missing data are not available.
12 We performed sensitivity analysis to investigate the impact of risk of bias for sequence
13 generation and allocation concealment of included studies.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28

29 **Results**

30
31
32 We retrieved 65 records from the search of the electronic databases and one record from other
33 sources (refer Supplementary file 2, figure 1). We screened a total of 60 records. We reviewed
34 full text of 16 studies and excluded 10 studies because all of it were non-randomized controlled
35 trials(4, 13-21). Therefore, we included only six studies in this review.
36
37
38
39
40
41

42 We included six studies with a total of 723 participants(22-27). Two out of six studies (and one
43 study that contributed to the primary outcome) declared funding from drug manufacturers(24,
44 27). Two of the six studies were multicentre trials in high-income countries(24, 27). Three
45 studies involved a total of 182 female gender only as participants(22, 23, 26) and another three
46 studies included on both sexes and involving 210 participants(24, 25, 27). All participants in
47 the studies were randomised into intervention and control groups. Three studies reported using
48 CoQ10 with other elements such as multivitamin(24), L-carnitine(25) and preventive
49 medication in intervention group(22). One study used the medication in liquid formulation of
50
51
52
53
54
55
56
57
58
59
60

1
2
3 water dispersed into nanoparticles(27), five studies used the medication in capsule
4 formulation(22-26). Different dosages of CoQ10 were administered in the studies: minimum
5 of 30 mg per day(25), 300 mg per day(27), 400 mg per day(23), 600 mg per day(24), and 800
6 mg per day(22, 26). There was only one study t added preventive medication for migraine in
7 the control group(22). Duration of treatment differs and was reported as 8 weeks in one
8 study(25), and 3 months in five studies(22-24, 26, 27). Table 1 summarised the characteristics
9 of the included trials.
10
11
12
13
14
15
16
17
18
19

20 All trials followed up the participants for a minimum of six weeks(22-27). Six study were
21 included in the meta-analysis for the primary outcomes(22-27). We have also analysed
22 according to subgroup by dosage of more and less than 400 mg of CoQ10. Secondary outcomes
23 were reported in three trials(22, 24, 27). One study reported using several questionnaire for
24 assessing quality of life affected by migraine(22), which were headache impact test (HIT-6)
25 and migraine specific quality of life (MSQ) questionnaires to assess wellbeing and daily
26 functioning; meanwhile migraine disability assessment (MIDAS) questionnaire to assess
27 disability caused by migraine. The HIT-6 used scoring of 36–49 with higher scores indicate
28 more severe effect of migraine, the MSQ reported the scores between zero and 100 with higher
29 scores indicate better quality of life and the MIDAS reported the scores between zero and 35
30 with higher scores indicate severe disability. We excluded 10 studies and all were non-
31 randomized controlled trials(4, 13-21).
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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; I² statistic = 99%; P = 0.110; 6 trials; 371 participants) (refer Supplementary file 4, Figure 3a). With more than 400 mg (MD -1.33, 95%

1
2
3 CI -2.75 to 0.08, random effects; I^2 statistic = 0%; $P = 0.07$; 3 trials; 167 participants) or less
4
5 than 400 mg (MD -1.27; 95% CI -3.42 to 0.89; random effects; I^2 statistic = 100%; $P = 0.25$; 3
6
7 trials; 204 participants) per day of CoQ10, there is no difference in the severity of headache
8
9 compared to the control group.
10
11

12
13 All six studies reported on the duration of headache attacks per month(22-27). CoQ10 reduce
14
15 the duration of headache attacks compared to the control group (MD -0.19, 95% CI -0.27 to -
16
17 0.11; random effects; I^2 statistic = 0%; $P < 0.00001$; 6 trials, 372 participants) (refer
18
19 Supplementary file 4, figure 3b).
20
21

22
23 Five studies reported on the frequency of migraine headache per month(22, 23, 25-27). CoQ10
24
25 reduce the frequency of migraine headache compared to the control group (MD -1.52, 95% CI
26
27 -2.40 to -0.65; random effects; I^2 statistic = 0%; $P = <0.001$; 5 trials, 259 participants) (refer
28
29 Supplementary file 4, Figure 3c).
30
31

32 33 *b) Secondary outcomes* 34

35
36 One study reported on number of days with nausea due to migraine headache during the study
37
38 period(27). The study showed significant difference between the CoQ10 supplementation and
39
40 control groups in the reduction of nausea due to migraine headache (MD -1.70; 95% CI -2.92
41
42 to -0.48; $P = 0.006$; 1 trial, 42 participants). No other study reported on this outcome. One study
43
44 reported the numbers of acute migraine medication during the study period (MD 0.02; 95% CI
45
46 -0.42 to 0.46; $P = 0.91$; 1 trial, 42 participants)(27).
47
48

49
50 Only one trial measured the quality of life among patients with migraine headache(22).
51
52 Migraine-specific quality of life (MSQ) questionnaire reported on role restrictive (MD 17.85;
53
54 95% CI 9.59 to 26.11; $P < 0.0001$; 1 trial, 77 participants), role preventive (MD 17.16; 95% CI
55
56 8.75 to 25.57; $P < 0.0001$; 1 trial, 77 participants) and emotional functioning (MD 16.68, 95%
57
58 CI 6.70 to 26.66; $P = 0.001$; 1 trial, 77 participants). The Headache Impact Test (HIT-6) score
59
60

1
2
3 reported on impact of the well-being and daily performance (MD -4.29; 95% CI -7.19 to -1.39;
4
5 P = 0.004; 1 trial: 77 participants) and Migraine Disability Assessment (MIDAS) score on
6
7 disability (MD -6.00; 95% CI -9.93 to -2.07; P = 0.003; 1 trial: 77 participants). One trial
8
9 involving 10 participants reported the adverse effects outcome on diarrhoea (OR 4.44; 95% CI
10
11 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
12
13 they are not different compared to the control group.
14
15

16 17 **DISCUSSION**

18 19 **Summary of main results**

20
21
22 This review was designed to include all RCTs addressing the effectiveness of CoQ10 as one of
23
24 the ways to prevent migraine. There was significant reduction in duration of migraine by 0.19
25
26 point and frequency of migraine by 1.52 point during the follow up. Meanwhile, there were no
27
28 significant difference in severity of headache during attack compared to control group even by
29
30 subgroup analysis according to the different dosages of CoQ10. Nausea event caused by
31
32 migraine improved with CoQ10 but was limited in the number of trials. Report on adverse
33
34 events was limited to minor side effects, which included episodes of diarrhoea and chromaturia
35
36 and showed no difference with CoQ10.
37
38
39
40
41
42

43 44 **Overall completeness and applicability of evidence**

45
46 We performed a comprehensive and extensive literature review to assess the effectiveness of
47
48 CoQ10 supplement as prevention for migraine. In all those study, females are more compared
49
50 to males in all study populations as it was one of the risk factors for migraine(28, 29). On this
51
52 review we limited the participants to adults only because of limited studies and a few of it
53
54 showed other supplements such as riboflavin also can prevent migraine(30). All studies had
55
56 small number of participants and this limit the applicability of CoQ10 thus the samples size
57
58 needed to be increased for better result. From the reported incidence of adverse events, we were
59
60

1
2
3 able to detect side effects, which are diarrhoea and chromaturia. The information on adverse
4 events came from one trial involving 10 participants and there is a lack of information on more
5
6 rare and serious adverse events.
7
8
9

10 **Quality of the evidence**

11
12
13
14 Generally, there were a low risk of bias for most studies in most domains. There was no
15 evidence of selective reporting bias although there was one study with high bias, but other
16 studies had clear protocols. Besides that, in this meta-analysis showed few of unclear risk of
17 bias on blinding of outcome assessment that can lead to treatment effect bias in the original
18 study and the subsequent review. The risk of attrition bias was present in one trial. Attrition
19 bias was high risk in one study due to high proportion of sample excluded in both intervention
20 and control study with no intention to treat analysis been stated in the study (Supplementary
21 file 3, Figure 2b). Loss to follow-up was less than 20% in all six trials and one trial carried out
22 intention-to-treat analysis. Only one trial declared funding from pharmaceuticals company. For
23 most of our meta-analysis we encountered low study samples. Therefore, the overall level of
24 evidence contributing to this review as assessed using the GRADE approach is of low to
25 moderate quality.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41

42 **Potential biases in the review process**

43
44
45 We attempted to reduce publication bias by checking the reference lists of all related studies
46 for further references and searching multiple databases without language restriction. However,
47 we cannot be certain that we have located all the trials in this area. There were six included
48 studies and we were not able to construct a funnel plot for detecting publication bias. Not all
49 included studies reported all outcomes. Although the included studies all showed the same
50 direction of effect, we encountered low to high heterogeneity in our primary outcomes. The
51 high heterogeneity was not able to be explained through the subgroup analysis.
52
53
54
55
56
57
58
59
60

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.

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.

REFERENCES

1. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001;41(7):646-57.
2. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? *J Headache Pain*. 2018;19(1):17-.
3. Lipton RB. Tracing transformation. *Neurology*. 2009;72(5 Supplement 1):S3.
4. Hershey AD, Powers SW, Vockell AL, Lecates SL, Ellinor PL, Segers A, et al. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. *Headache*. 2007;47(1):73-80.
5. Ashina M, Tvedskov JF, Lipka K, Bilello J, Penkowa M, Olesen J. Matrix metalloproteinases during and outside of migraine attacks without aura. *Cephalalgia*. 2010;30(3):303-10.
6. Gursoy-Ozdemir Y, Qiu J, Matsuoka N, Bolay H, Bermpohl D, Jin H, et al. Cortical spreading depression activates and upregulates MMP-9. *The Journal of clinical investigation*. 2004;113(10):1447-55.
7. Sanoobar M, Eghtesadi S, Azimi A, Khalili M, Khodadadi B, Jazayeri S, et al. Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double blind, placebo, controlled randomized clinical trial. *Nutr Neurosci*. 2015;18(4):169-76.
8. Hagen K, Brenner E, Linde M, Gravdahl GB, Tronvik EA, Engstrom M, et al. Acetyl-L-carnitine versus placebo for migraine prophylaxis: A randomized, triple-blind, crossover study. *Cephalalgia*. 2015;35(11):987-95.
9. Bhagavan HN, Chopra RK. Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free radical research*. 2006;40(5):445-53.
10. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ (Clinical research ed)*. 2008;336(7651):995-8.
11. The Nordic Cochrane Centre TCC. Review Manager (RevMan). Version 5.3.: Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
12. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019): *Cochrane*; 2019. Available from: Available from www.training.cochrane.org/handbook.
13. Airola G, Allais G, Castagnoli Gabellari I, Rolando S, Mana O, Benedetto C. Non-pharmacological management of migraine during pregnancy. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2010;31 Suppl 1:S63-5.
14. Bianchi A, Salomone S, Caraci F, Pizza V, Bernardini R, D'Amato CC. Role of magnesium, coenzyme Q10, riboflavin, and vitamin B12 in migraine prophylaxis. *Vitamins and hormones*. 2004;69:297-312.
15. Carotenuto M, Esposito M. Nutraceuticals safety and efficacy in migraine without aura in a population of children affected by neurofibromatosis type I. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2013;34(11):1905-9.
16. Dalla Volta G, Carli D, Zavarise P, Ngonga G, Vollaro S. P026. Pilot study on the use of coenzyme Q10 in a group of patients with episodic migraine without aura. *Journal of headache and pain (varpagings)*. 2015;16(no pagination).
17. Daniel O, Mauskop A. Nutraceuticals in Acute and Prophylactic Treatment of Migraine. *Current treatment options in neurology*. 2016;18(4):14.
18. Di Lorenzo C. The use of a phytotherapeutic compound containing Tanacetum Parthenium and Andrographis, in combination with CoQ10 and Riboflavin, for migraine prophylaxis: a randomized double blind versus placebo clinical trial. Journal of headache and pain Conference: 12th european headache federation congress and the 32nd national congress of the italian society for the study of headaches Italy. 2018;19.

19. Esposito M, Carotenuto M. Ginkgolide B complex efficacy for brief prophylaxis of migraine in school-aged children: an open-label study. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2011;32(1):79-81.
20. Gaul C, Danesch U, Diener H. A proprietary supplement containing riboflavin, magnesium and Q10 improves migraine symptoms in a randomized placebo-controlled double-blind trial. *Cephalalgia*. 2015;35(6 SUPPL. 1):45.
21. Rozen TD, Oshinsky ML, Gebeline CA, Bradley KC, Young WB, Shechter AL, et al. Open label trial of coenzyme Q10 as a migraine preventive. *Cephalalgia*. 2002;22(2):137-41.
22. Dahri M, Hashemilar M, Asghari-Jafarabadi M, Tarighat-Esfanjani A. Efficacy of coenzyme Q10 for the prevention of migraine in women: a randomized, double-blind, placebo-controlled study. *European Journal Of Integrative Medicine*. 2017;16:8-14.
23. Dahri M, Tarighat-Esfanjani A, Asghari-Jafarabadi M, Hashemilar M. Oral coenzyme Q10 supplementation in patients with migraine: effects on clinical features and inflammatory markers. *Nutritional Neuroscience*. 2018:1-9.
24. Gaul C, Diener HC, Danesch U. Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: a randomized, placebo-controlled, double-blind, multicenter trial. *Journal Of Headache And Pain*. 2015;16:516.
25. Hajhashemi P, Askari G, Khorvash F, Reza Maracy M, Nourian M. The effects of concurrent Coenzyme Q10, L-carnitine supplementation in migraine prophylaxis: A randomized, placebo-controlled, double-blind trial. *Cephalalgia*. 2019:333102418821661.
26. Nattagh-Eshtivani E, Dahri M, Hashemilar M, Tarighat-Esfanjani A. The effect of Coenzyme Q10 supplementation on serum levels of lactate, pyruvate, matrix metalloproteinase 9 and nitric oxide in women with migraine. A double blind, placebo, controlled randomized clinical trial. *European Journal Of Integrative Medicine*. 2018;21:70-6.
27. Sandor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology*. 2005;64(4):713-5.
28. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5):343-9.
29. Manzoni GC, Torelli P. Epidemiology of migraine. *J Headache Pain*. 2003;4(Suppl 1):s18-s22.
30. Talebian A, Soltani B, Banafshe HR, Moosavi GA, Talebian M, Soltani S. Prophylactic effect of riboflavin on pediatric migraine: a randomized, double-blind, placebo-controlled trial. *Electron Physician*. 2018;10(2):6279-85.
31. Okoli GN, Rabbani R, Kashani HH, Wierzbowski AK, Neilson C, Mansouri B, et al. Vitamins and Minerals for Migraine Prophylaxis: A Systematic Review and Meta-analysis. *Can J Neurol Sci*. 2019;46(2):224-33.
32. Parohan M, Sarraf P, Javanbakht MH, Ranji-Burachaloo S, Djalali M. Effect of coenzyme Q10 supplementation on clinical features of migraine: a systematic review and dose-response meta-analysis of randomized controlled trials. *Nutr Neurosci*. 2019:1-8.
33. Khorvash F, Bagheri L, Ghasemi M, Ghaed-Amini A, Maracy MR. Coenzyme q10 in migraine prophylaxis: a randomized, double-blind, placebo-controlled clinical trial. *Journal of isfahan medical school*. 2016;33(358):1904-11.
34. Slater SK, Nelson TD, Kabbouche MA, LeCates SL, Horn P, Segers A, et al. A randomized, double-blinded, placebo-controlled, crossover, add-on study of CoEnzyme Q10 in the prevention of pediatric and adolescent migraine. *Cephalalgia*. 2011;31(8):897-905.
35. Shoeibi A, Olfati N, Soltani Sabi M, Salehi M, Mali S, Akbari Oryani M. Effectiveness of coenzyme Q10 in prophylactic treatment of migraine headache: an open-label, add-on, controlled trial. *Acta Neurologica Belgica*. 2017;117(1):103-9.

1
2
3 **Supplementary file 1: DETAILED SEARCH STRATEGY**
4
5
6
7

8 **MEDLINE search strategy**
9

10 Pubmed - (migraine[Title/Abstract]) AND coenzyme q10[Title/Abstract]
11
12

13 MeSH data based"coenzyme Q10"[All Fields] OR coenzyme q10[Text Word]
14
15

16 migraine[Title/Abstract] AND q10[Title/Abstract]
17
18

19 migraine[Title/Abstract] AND ubiquinone[Title/Abstract]
20
21
22
23
24

25 **CENTRAL search strategy**
26
27

28 migraine in Title Abstract Keyword AND coenzyme q10 in Title Abstract Keyword
29
30

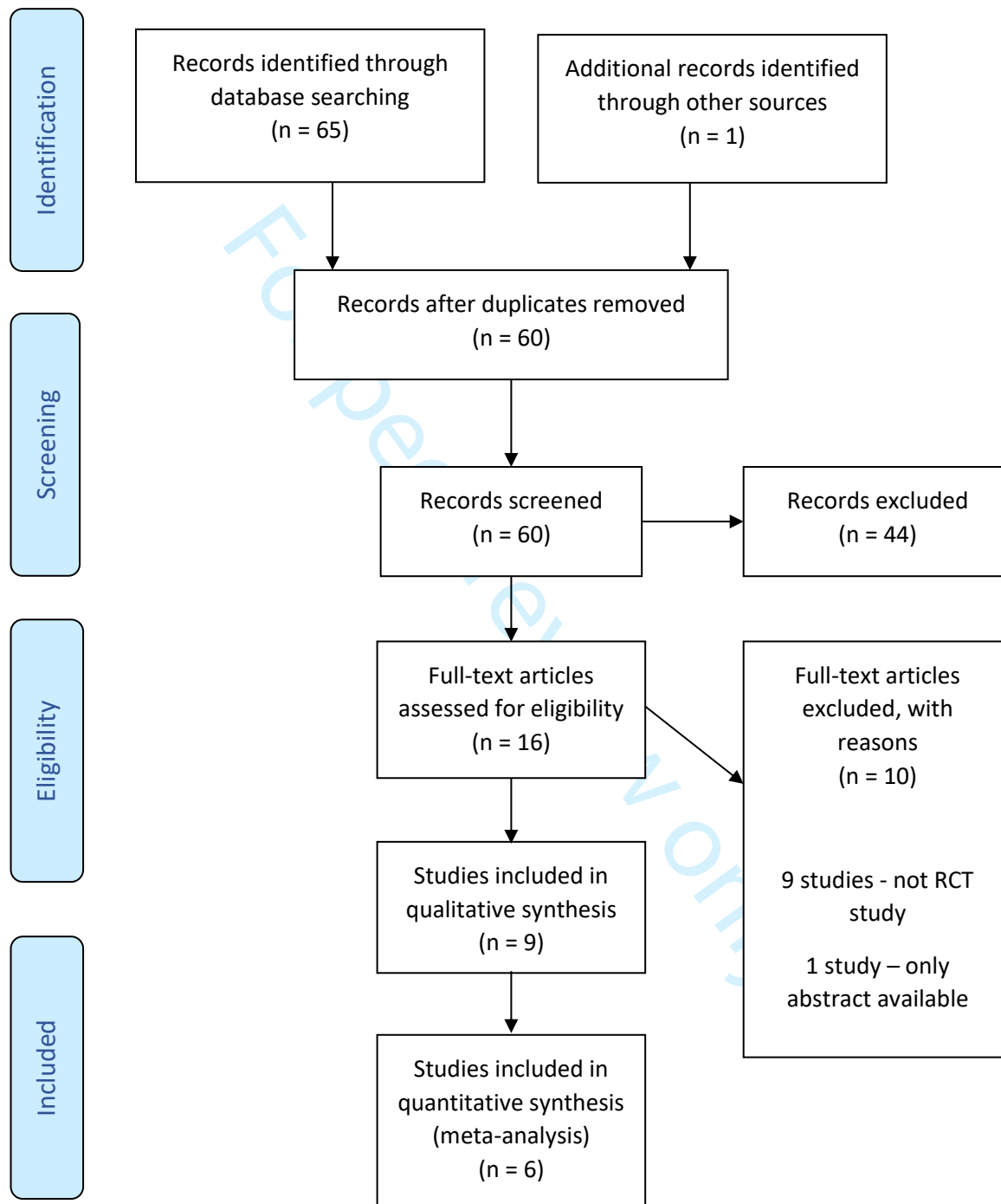
31 migraine in Title Abstract Keyword AND ubiquinone in Title Abstract Keyword
32
33

34 migraine in Title Abstract Keyword AND q10 in Title Abstract Keyword
35
36

37 MeSH data based"coenzyme Q10"[All Fields] OR coenzyme q10[Text Word]
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

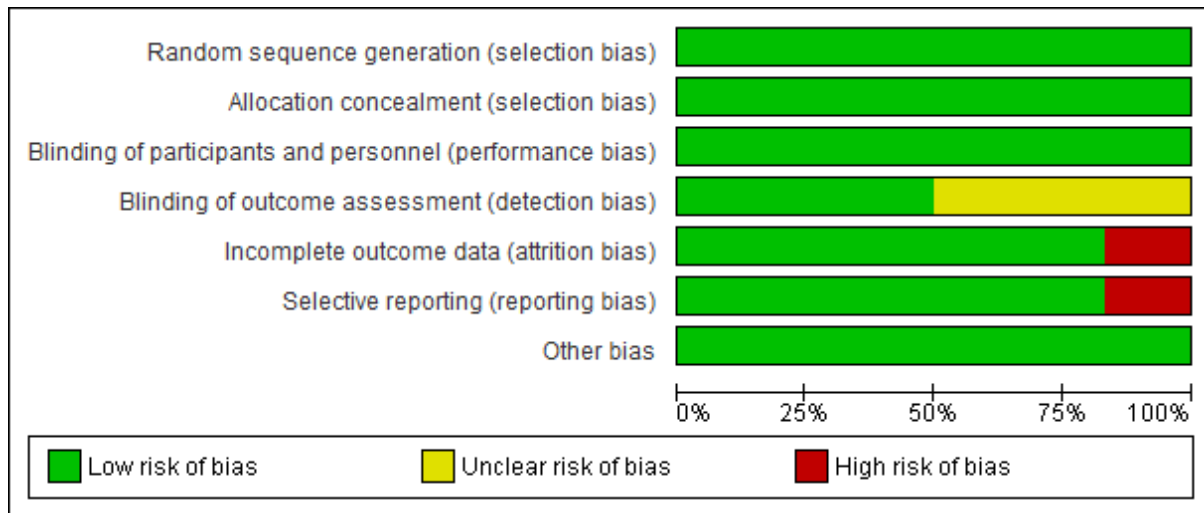


Figure 2b: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dahri 2017	+	+	+	?	+	+	+
Dahri 2018	+	+	+	+	+	+	+
Gaul 2015	+	+	+	+	-	-	+
Hajihashemi 2019	+	+	+	+	+	+	+
Nattagh-Eshtivani, E. 2018	+	+	+	?	+	+	+
Sandor 2005	+	+	+	?	+	+	+

Supplementary file 4: FOREST PLOT OF PRIMARY OUTCOMES

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

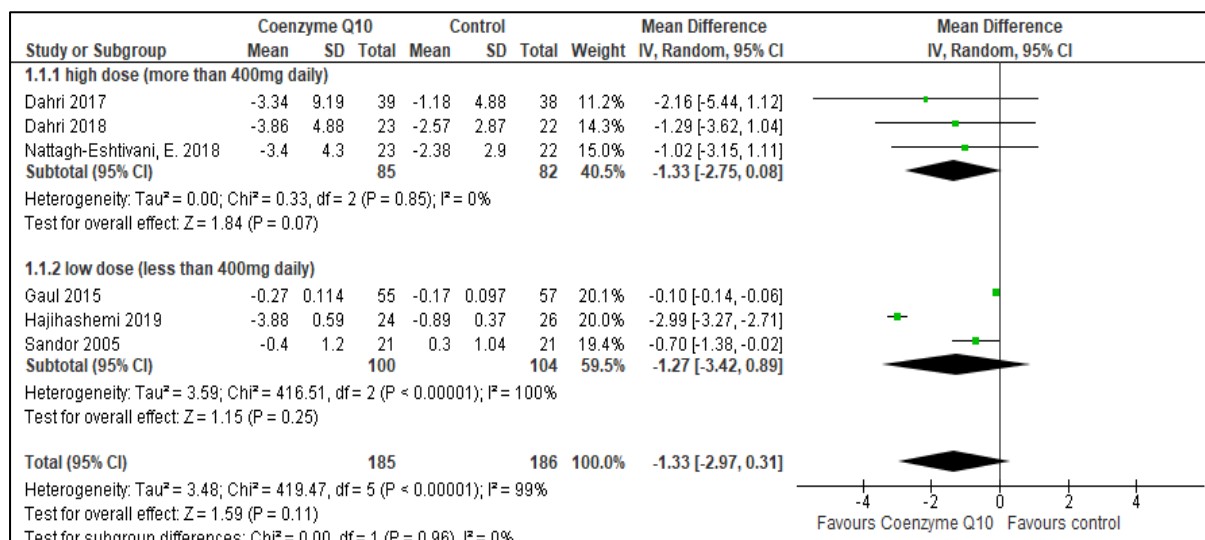


Figure 3b: Forest plot of effects coenzyme Q10 versus control on duration of headache attacks per month

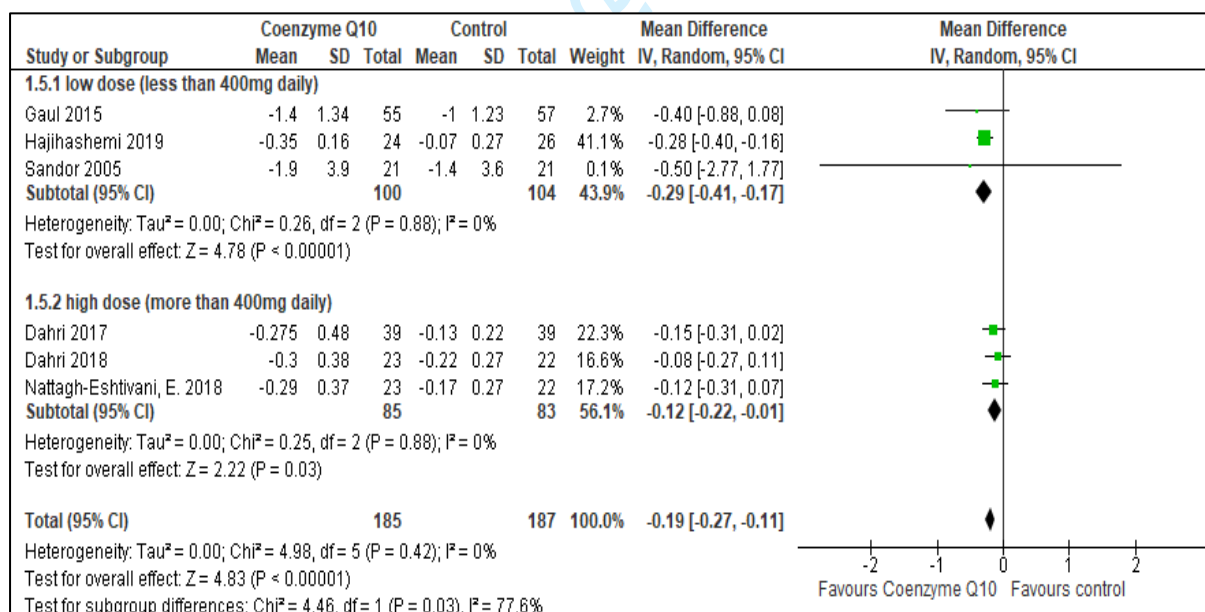
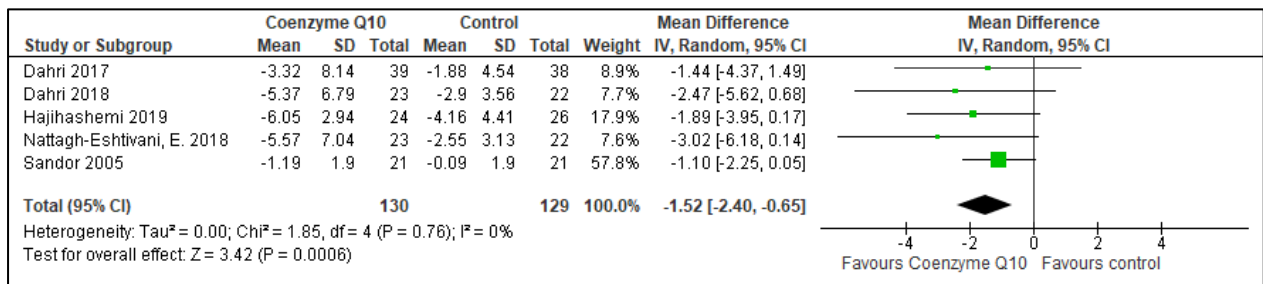


Figure 3c: Forest plot of effects coenzyme Q10 versus control on frequency of migraine headache per month



1
2 **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

3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

1	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
2	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
3				
4	Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
5				
6	RESULTS			
7				
8	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)
9				
10	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
11				
12	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)
13				
14	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)
15				
16				
17				
18	Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-13
19				
20	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)
21				
22	Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-14
23				
24	DISCUSSION			
25				
26	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
27				
28	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
29				
30	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
31				
32	FUNDING			
33				
34	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
35				
36				
37				
38				
39				
40				
41				
42				
43				
44				
45				
46				
47				

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039358.R1
Article Type:	Original research
Date Submitted by the Author:	29-Oct-2020
Complete List of Authors:	Sazali, Suhairul; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Badrin, Salziyan; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Norhayati, Mohd Noor; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Idris, Nur Suhaila; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Complementary medicine
Keywords:	Migraine < NEUROLOGY, COMPLEMENTARY MEDICINE, Neurology < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **Title: COENZYME Q10 SUPPLEMENTATION FOR PROPHYLAXIS IN ADULT**
4
5 **PATIENTS WITH MIGRAINE –A META-ANALYSIS**
6
7

8
9 Suhairul Sazali¹, Salziyan Badrin¹, Norhayati Mohd Noor¹, Nur Suhaila Idris¹
10

11 ¹ Department of Family Medicine, School of Medical Sciences, Universiti Sains Malaysia,
12 16150 Kubang Kerian, Kelantan, Malaysia
13

14
15 **Authors:**

16 1. Suhairul Sazali

17 MD

18 Department of Family Medicine

19 School of Medical Sciences

20 Universiti Sains Malaysia

21 16150 Kubang Kerian

22 Kelantan, Malaysia

23 Email: suhairul_sazali@yahoo.com
24
25

26 2. Salziyan Badrin (**Corresponding author**)

27 MD, MMed (Family Medicine)

28 Department of Family Medicine

29 School of Medical Sciences

30 Universiti Sains Malaysia

31 16150 Kubang Kerian

32 Kelantan, Malaysia

33 Email: salziyan@usm.my

34 Telephone number: +609-7676608

35 Fax number: +609-7653370
36
37

38
39 3. Norhayati Mohd Noor

40 MBBS, M.Comm.Med, Ph.D

41 Department of Family Medicine

42 School of Medical Sciences

43 Universiti Sains Malaysia

44 16150 Kubang Kerian

45 Kelantan, Malaysia

46 Email: hayatikk@usm.my
47
48

49 4. Nur Suhaila Idris

50 MD, MMed (Family Medicine)

51 Department of Family Medicine

52 School of Medical Sciences

53 Universiti Sains Malaysia

54 16150 Kubang Kerian

55 Kelantan, Malaysia

56 Email: nursuhaila@usm.my
57
58
59
60

1
2
3 **Keyword:** Coenzyme Q10, Migraine, Supplementation
4

5 **Word count:** 3361 words with exclusion of abstract, table and references.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

1
2
3 the control group (MD -1.52, 95% CI -2.40 to -0.65; random effects; I² statistic = 0%; P =
4
5 <0.001).
6
7

8 **Conclusion** CoQ10 appears to have beneficial effects in reducing duration and frequency of
9
10 migraine attack.
11
12

13 **PROSPERO registration number** CRD42019126127
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

1
2
3 full-text articles when they appear to meet the eligibility criteria, or when there was insufficient
4 information to assess the eligibility. We assessed the eligibility of the trials independently and
5
6 documented all the reasons for exclusion. We resolved any disagreements between the review
7
8 authors by discussion. We contacted the authors if clarification is needed.
9
10

11 12 13 ***Data Collection and analysis*** 14

15
16 Three authors extracted data independently. We extracted data on the dosage and frequency of
17
18 CoQ10 supplementation, criteria for diagnosis of migraine, age, sex, ethnicity, and the
19
20 outcomes of each trials which include severity of the headache attacks, duration of headache
21
22 in migraine attacks, frequency of migraine attacks in a month, numbers of days with nausea,
23
24 numbers of analgesic used during headache attacks, numbers of acute migraine medication
25
26 used, quality of life and adverse effects of CoQ10 using data extraction form. Disagreements
27
28 between the review authors were resolved by discussion with the fourth author.
29
30

31
32 The Cochrane Collaboration's risk-of-bias tools was used to assess the risk of bias in of the
33
34 included studies(9). Three authors assessed each trial's risk of bias independently. We assessed
35
36 selection bias (randomisation, allocation concealment), performance bias (blinding of
37
38 participant and health personnel), detection bias (blinding of outcome assessment), attrition
39
40 bias (incomplete outcome data), reporting bias (selective reporting) and other bias (recall bias,
41
42 transfer bias and etc). We resolved any disagreements by the discussion with the fourth author.
43
44 We assessed the quality of evidence for primary and secondary outcomes, according to the
45
46 GRADE methodology for risk of bias, inconsistency, indirectness, imprecision, and publication
47
48 bias; classified as very low, low, moderate, or high(10).
49
50
51

52
53 We analysed data using Review Manager 5.3 software(11). We used random-effects model to
54
55 pool data. We assessed the presence of heterogeneity in two steps. First, we assessed obvious
56
57 heterogeneity at face value by comparing populations, settings, interventions and outcomes.
58
59
60

1
2
3 Then, we assessed statistical heterogeneity by means of the I^2 statistic. We interpreted the
4 heterogeneity as; 0% to 40% represent might not be important, 30% to 60% may represent
5 moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100%
6 would be considerable heterogeneity(9).
7
8
9
10
11

12
13 We measured the treatment effect using risk ratios (RRs) and risk difference (RD) for
14 dichotomous outcomes and mean differences (MDs) or standardized mean difference (SMD);
15 both with 95% confidence intervals (CIs) for continuous outcomes. We conducted subgroup
16 analyses based on the different dosage of CoQ10 and if CoQ10 is combined with another
17 supplementation. We explored the potential sources of heterogeneity when it is present. We
18 checked all included trials for unit of analysis errors. Unit of analysis errors can occur when
19 trials randomize participants to intervention or control groups in clusters, but analysed the
20 results using the total number of individual participants. We adjusted results from trials showed
21 unit of analysis errors based on the mean cluster size and intraclass correlation coefficient(9).
22
23 We contacted the original trial's authors to request missing or inadequately reported data. We
24 performed analyses on the available data if missing data are not available. We performed
25 sensitivity analysis to investigate the impact of risk of bias for sequence generation and
26 allocation concealment of included studies.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43

44 **Results**

45
46 We retrieved 65 records from the search of the electronic databases and one record from other
47 sources (Supplementary file 2, Figure 1). We screened a total of 60 records. We reviewed full
48 text of 16 studies and excluded another 10 studies because all of the studies were non-
49 randomized controlled trials(3, 12-20). Therefore, we included only six studies in this review.
50
51
52
53
54
55

56 We included six studies with a total of 371 participants(21-26). In all the trials, diagnosis of
57 migraine was done based on International Headache Society criteria. Two out of six studies
58
59
60

1
2
3 (and one study that contributed to the primary outcome) declared funding from drug
4 manufacturers(23, 26). Two out of six studies were multicentre trials in high-income
5 countries(23, 26). Three studies involved a total of 167 female gender only as participants(21,
6 22, 25) and another three studies involved on both genders and a total of 204 participants(23,
7 24, 26). All the participants in the included studies were randomised into intervention and
8 control groups. Three studies reported using CoQ10 with other elements such as
9 multivitamin(23), L-carnitine(24) and preventive medication in the intervention group(21).
10 One study used the medication in liquid formulation of water dispersed into nanoparticles (26),
11 five studies used the medication in a capsule formulation(21-25). Different dosages of CoQ10
12 were administered in the studies: minimum of 30 mg per day(24), 300 mg per day(26), 400 mg
13 per day(22), 600 mg per day(23), and 800 mg per day(21, 25). All six trials excluded any
14 participants who on migraine preventive drugs in the last six months, who have history of using
15 CoQ10 or other antioxidants supplementation for at least 3 months prior to the enrolment(21-
16 26). One trial also excluded participants who failed to respond to the usage of more than two
17 different prophylactic agents in the past or any patients who were resistant to all acute migraine
18 drugs(23). All six included studies used placebo(21-26) and there was only one trial added the
19 preventive migraine medication to the placebo(21); however, the preventive medication was
20 used for both the intervention and control groups in this trial(21). Duration of CoQ10 treatment
21 differs among the trials and was reported at 8 weeks in one study(24), and at 3 months in five
22 other studies(21-23, 25, 26). Table 1 summarised the characteristics of the included trials.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 All six included trials followed-up the participants for a minimum of six weeks(21-26). Six
4 studies were included in analyses of the primary outcomes(21-26). We also analysed according
5 to subgroup by dosage of more and less than 400 mg of CoQ10. Secondary outcomes reported
6 in the three trials(21, 23, 26). One study reported using several questionnaires for assessing
7 quality of life affected by migraine(21), which were headache impact test (HIT-6) and migraine
8 specific quality of life (MSQ) questionnaires to assess wellbeing and daily functioning;
9 meanwhile migraine disability assessment (MIDAS) questionnaire to assess disability caused
10 by migraine. The HIT-6 used scoring of 36–49 with higher scores indicate more severe effect
11 of migraine, the MSQ reported the scores between zero and 100 with higher scores indicate
12 better quality of life and the MIDAS reported the scores between zero and 35 with higher scores
13 indicate severe disability(21). We excluded 10 studies and all of the studies are non-
14 randomized controlled trials(3, 12-20).

31 ***Risk of bias***

32
33 Assessment risk of bias is shown in Figure 2a and Figure 2b (Refer Supplementary file 3,
34 Figure 2a and Figure 2b). The proportion of studies assessed as low, high or unclear risk of
35 bias for each risk of bias domain is presented in Figure 2a (Refer Supplementary file 3, Figure
36 2a). Detection bias domain had 50% of low risk with attrition and reporting bias domains
37 around 80% of low risk. The risk of bias summary for individual studies is showed in Figure
38 2b (Refer Supplementary file 3, Figure 2b). Three studies had unclear risk for detection bias
39 (21, 25, 26) and for attrition and reporting bias, only one trial had high risk of bias(23).

40
41 All six studies described the method of randomisation used and randomised the participants
42 according to block randomization(21-26). Allocation concealment was mentioned in all six
43 included studies(21-26). All six studies mentioned about blinding the personnel and the
44 participants(21-26). All six studies had less than 20% lost to follow-up and the reasons such as
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 major protocol violation(23), refused to continue the study(25, 26), failed to return to clinic(21,
4
5 22), pregnancy(21, 22, 24) and failed to keep diary(21, 22) and there were balanced between
6
7 both groups. Only one study carried out an intention-to-treat analysis in which the participants
8
9 were analysed according to the groups that they were initially assigned(21). All six studies
10
11 reported the outcomes as specified in their methods section(21-26). We detected no other
12
13 potential sources of bias.
14
15

16 17 18 ***Effects of interventions***

19
20 All six studies measured the primary outcomes and assessed at three months post
21
22 intervention(21-26). Three studies measured the secondary outcomes(21, 23, 26). Three studies
23
24 did not state on the assessment of outcomes(21, 25, 26).
25
26

27 28 ***Primary outcomes***

29
30 All six included studies reported severity of headache during migraine attack after taking
31
32 CoQ10 for at least six weeks(21-26). The meta-analysis found no significant reduction in
33
34 severity of headache with CoQ10 (MD -1.33, 95% CI: -2.97 to 0.31; I² statistic = 99%; P =
35
36 0.110; 6 trials; 371 participants) (Refer Supplementary file 3, Figure 3). With more than 400
37
38 mg (MD -1.33, 95% CI -2.75 to 0.08, random effects; I² statistic = 0%; P = 0.07; 3 trials; 167
39
40 participants) or less than 400 mg per day of CoQ10 (MD -1.27; 95% CI -3.42 to 0.89; random
41
42 effects; I² statistic = 100%; P = 0.25; 3 trials; 204 participants), there is no difference in the
43
44 severity of headache compared to the control group.
45
46
47

48
49 All six studies reported on the duration of headache attacks per month(21-26). There was
50
51 significant reduction of duration of headache attacks with CoQ10 as compared to the control
52
53 group (MD -0.19, 95% CI -0.27 to -0.11; random effects; I² statistic = 0%; P < 0.00001; 6 trials,
54
55 371 participants) (Refer Supplementary file 3, Figure 4).
56
57
58
59
60

1
2
3 Five studies reported on the frequency of migraine headache per month(21, 22, 24-26). There
4 was significant reduction in the frequency of migraine headache with the CoQ10 as compared
5 to the control group (MD -1.52, 95% CI -2.40 to -0.65; random effects; I^2 statistic = 0%; $P =$
6
7
8
9
10 <0.001; 5 trials, 259 participants) (Refer Supplementary file 3, Figure 5).
11

12
13 *a) Secondary outcomes*
14

15
16 One study reported on the number of days with nausea due to migraine headache during the
17 study period(26). The CoQ10 supplementation reduced the number of days with nausea due to
18 migraine headache (MD -1.70; 95% CI -2.92 to -0.48; $P = 0.006$; 1 trial, 42 participants). No
19 other study reported on this outcome. The same study reported the number of acute migraine
20 medications usage during the study period(26). The CoQ10 supplementation reduced the
21 number of acute migraine medications usage (MD 0.02; 95% CI -0.42 to 0.46; $P = 0.91$; 1
22 trial, 42 participants)(26).
23
24
25
26
27
28
29
30
31

32
33 Only one trial measured the quality of life among patients with migraine headache(21). Three
34 types of questionnaire including Migraine-specific quality of life (MSQ), The Headache Impact
35 Test (HIT-6) score and Migraine Disability Assessment (MIDAS) score were used to measure
36 the impact of the treatment on migraine headache on quality of life(21). Migraine-specific
37 quality of life (MSQ) questionnaire reported on role restrictive, role preventive and emotional
38 functioning. There were no significant improvements in MSQ questionnaire on role restrictive
39 (MD 17.85; 95% CI 9.59 to 26.11; $P < 0.0001$; 1 trial, 77 participants), role preventive (MD
40 17.16; 95% CI 8.75 to 25.57; $P < 0.0001$; 1 trial, 77 participants) and emotional functioning
41 (MD 16.68, 95% CI 6.70 to 26.66; $P = 0.001$; 1 trial, 77 participants) with the CoQ10
42 supplementation. The CoQ10 supplementation showed improvement in The Headache Impact
43 Test (HIT-6) score (MD -4.29; 95% CI -7.19 to -1.39; $P = 0.004$; 1 trial: 77 participants) and
44 improvement in Migraine Disability Assessment (MIDAS) score (MD -6.00; 95% CI -9.93 to
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 -2.07; P = 0.003; 1 trial: 77 participants). One trial reported on the adverse effects outcome on
4 diarrhoea (OR 4.44; 95% CI 0.90 to 21.79; P = 0.07) and chromaturia (OR 19.45; 95% CI 1.10
5 to 344.70; P = 0.04)(23) and they not different in the CoQ10 group.
6
7
8
9

10 **DISCUSSION**

11 **Summary of main results**

12
13
14
15
16
17 This review was designed to include all RCTs addressing the effectiveness of CoQ10 as one of
18 the alternative medications for migraine prophylaxis. There was significant reduction in the
19 duration of migraine by 0.19 point and the frequency of migraine by 1.52 point during the
20 follow-up. Meanwhile, there was no significant reduction in severity of headache during attack
21 even by subgroup analysis according to the different dosages of the CoQ10. Nausea event
22 caused by migraine improved with CoQ10 but there was limited in the number of the trials.
23 Report on adverse events was limited to the minor side effects, which include episodes of
24 diarrhoea and chromaturia and showed no difference with CoQ10.
25
26
27
28
29
30
31
32
33
34
35

36 **Overall completeness and applicability of evidence**

37
38
39 We performed a comprehensive and extensive literature review to assess the effectiveness of
40 CoQ10 supplement as prevention for migraine. The numbers of female participants higher than
41 males in all of the included studies as the highest population diagnosed with migraine is
42 female(27, 28). On this review, we limited the participants to adult population because there
43 was limited number of studies done in paediatric population and a few of the studies done
44 involved other supplements such as riboflavin in paediatric population(29). All the included
45 studies had small number of participants and this limit the applicability of CoQ10 thus the
46 larger samples size is needed for a better result. The information on adverse events came from
47 only one trial which are diarrhoea and chromaturia. There is limited information from the trials
48 on other serious adverse events.
49
50
51
52
53
54
55
56
57
58
59
60

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)	No 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.

For peer review only

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.

REFERENCES

1. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001;41(7):646-57.
2. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? *The journal of headache and pain*. 2018;19(1):17-.
3. Hershey AD, Powers SW, Vockell AL, Lecates SL, Ellinor PL, Segers A, et al. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. *Headache*. 2007;47(1):73-80.
4. Ashina M, Tvedskov JF, Lipka K, Bilello J, Penkowa M, Olesen J. Matrix metalloproteinases during and outside of migraine attacks without aura. *Cephalalgia : an international journal of headache*. 2010;30(3):303-10.
5. Gursoy-Ozdemir Y, Qiu J, Matsuoka N, Bolay H, Bempohl D, Jin H, et al. Cortical spreading depression activates and upregulates MMP-9. *The Journal of clinical investigation*. 2004;113(10):1447-55.
6. Sanoobar M, Eghtesadi S, Azimi A, Khalili M, Khodadadi B, Jazayeri S, et al. Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double blind, placebo, controlled randomized clinical trial. *Nutritional neuroscience*. 2015;18(4):169-76.
7. Hagen K, Brenner E, Linde M, Gravdahl GB, Tronvik EA, Engstrom M, et al. Acetyl-L-carnitine versus placebo for migraine prophylaxis: A randomized, triple-blind, crossover study. *Cephalalgia : an international journal of headache*. 2015;35(11):987-95.
8. Bhagavan HN, Chopra RK. Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free radical research*. 2006;40(5):445-53.
9. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane; 2019. Available from: Available from www.training.cochrane.org/handbook.
10. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ (Clinical research ed)*. 2008;336(7651):995-8.
11. The Nordic Cochrane Centre TCC. *Review Manager (RevMan)*. Version 5.3.: Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
12. Airola G, Allais G, Castagnoli Gabellari I, Rolando S, Mana O, Benedetto C. Non-pharmacological management of migraine during pregnancy. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2010;31 Suppl 1:S63-5.
13. Bianchi A, Salomone S, Caraci F, Pizza V, Bernardini R, D'Amato CC. Role of magnesium, coenzyme Q10, riboflavin, and vitamin B12 in migraine prophylaxis. *Vitamins and hormones*. 2004;69:297-312.
14. Carotenuto M, Esposito M. Nutraceuticals safety and efficacy in migraine without aura in a population of children affected by neurofibromatosis type I. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2013;34(11):1905-9.
15. Dalla Volta G, Carli D, Zavarise P, Ngonga G, Vollaro S. P026. Pilot study on the use of coenzyme Q10 in a group of patients with episodic migraine without aura. *Journal of headache and pain (varpagings)*. 2015;16(no pagination).
16. Daniel O, Mauskop A. Nutraceuticals in Acute and Prophylactic Treatment of Migraine. *Current treatment options in neurology*. 2016;18(4):14.
17. Di Lorenzo C. The use of a phytotherapeutic compound containing Tanacetum Parthenium and Andrographis, in combination with CoQ10 and Riboflavin, for migraine prophylaxis: a randomized double blind versus placebo clinical trial. *Journal of headache and pain Conference: 12th european*

- 1
2
3 headache federation congress and the 32nd national congress of the italian society for the study of
4 headaches Italy. 2018;19.
- 5 18. Esposito M, Carotenuto M. Ginkgolide B complex efficacy for brief prophylaxis of migraine in
6 school-aged children: an open-label study. *Neurological sciences : official journal of the Italian*
7 *Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2011;32(1):79-81.
- 8 19. Gaul C, Danesch U, Diener H. A proprietary supplement containing riboflavin, magnesium
9 and Q10 improves migraine symptoms in a randomized placebo-controlled double-blind trial.
10 *Cephalalgia : an international journal of headache*. 2015;35(6 SUPPL. 1):45.
- 11 20. Rozen TD, Oshinsky ML, Gebeline CA, Bradley KC, Young WB, Shechter AL, et al. Open label
12 trial of coenzyme Q10 as a migraine preventive. *Cephalalgia*. 2002;22(2):137-41.
- 13 21. Dahri M, Hashemilar M, Asghari-Jafarabadi M, Tarighat-Esfanjani A. Efficacy of coenzyme
14 Q10 for the prevention of migraine in women: a randomized, double-blind, placebo-controlled
15 study. *European Journal Of Integrative Medicine*. 2017;16:8-14.
- 16 22. Dahri M, Tarighat-Esfanjani A, Asghari-Jafarabadi M, Hashemilar M. Oral coenzyme Q10
17 supplementation in patients with migraine: effects on clinical features and inflammatory markers.
18 *Nutritional Neuroscience*. 2018:1-9.
- 19 23. Gaul C, Diener HC, Danesch U. Improvement of migraine symptoms with a proprietary
20 supplement containing riboflavin, magnesium and Q10: a randomized, placebo-controlled, double-
21 blind, multicenter trial. *Journal Of Headache And Pain*. 2015;16:516.
- 22 24. Hajhashemi P, Askari G, Khorvash F, Reza Maracy M, Nourian M. The effects of concurrent
23 Coenzyme Q10, L-carnitine supplementation in migraine prophylaxis: A randomized, placebo-
24 controlled, double-blind trial. *Cephalalgia*. 2019:333102418821661.
- 25 25. Nattagh-Eshivani E, Dahri M, Hashemilar M, Tarighat-Esfanjani A. The effect of Coenzyme
26 Q10 supplementation on serum levels of lactate, pyruvate, matrix metalloproteinase 9 and nitric
27 oxide in women with migraine. A double blind, placebo, controlled randomized clinical trial.
28 *European Journal Of Integrative Medicine*. 2018;21:70-6.
- 29 26. Sandor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, et al. Efficacy of
30 coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology*. 2005;64(4):713-5.
- 31 27. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence,
32 disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5):343-9.
- 33 28. Manzoni GC, Torelli P. Epidemiology of migraine. *The Journal of Headache and Pain*.
34 2003;4(Suppl 1):s18-s22.
- 35 29. Talebian A, Soltani B, Banafshe HR, Moosavi GA, Talebian M, Soltani S. Prophylactic effect of
36 riboflavin on pediatric migraine: a randomized, double-blind, placebo-controlled trial. *Electron*
37 *Physician*. 2018;10(2):6279-85.
- 38 30. Okoli GN, Rabbani R, Kashani HH, Wierzbowski AK, Neilson C, Mansouri B, et al. Vitamins and
39 Minerals for Migraine Prophylaxis: A Systematic Review and Meta-analysis. *Can J Neurol Sci*.
40 2019;46(2):224-33.
- 41 31. Parohan M, Sarraf P, Javanbakht MH, Ranji-Burachaloo S, Djalali M. Effect of coenzyme Q10
42 supplementation on clinical features of migraine: a systematic review and dose-response meta-
43 analysis of randomized controlled trials. *Nutr Neurosci*. 2019:1-8.
- 44 32. Khorvash F, Bagheri L, Ghasemi M, Ghaed-Amini A, Maracy MR. Coenzyme q10 in migraine
45 prophylaxis: a randomized, double-blind, placebo-controlled clinical trial. *Journal of isfahan medical*
46 *school*. 2016;33(358):1904-11.
- 47 33. Slater SK, Nelson TD, Kabbouche MA, LeCates SL, Horn P, Segers A, et al. A randomized,
48 double-blinded, placebo-controlled, crossover, add-on study of CoEnzyme Q10 in the prevention of
49 pediatric and adolescent migraine. *Cephalalgia*. 2011;31(8):897-905.
- 50 34. Shoeibi A, Olfati N, Soltani Sabi M, Salehi M, Mali S, Akbari Oryani M. Effectiveness of
51 coenzyme Q10 in prophylactic treatment of migraine headache: an open-label, add-on, controlled
52 trial. *Acta Neurologica Belgica*. 2017;117(1):103-9.
- 53
54
55
56
57
58
59
60

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

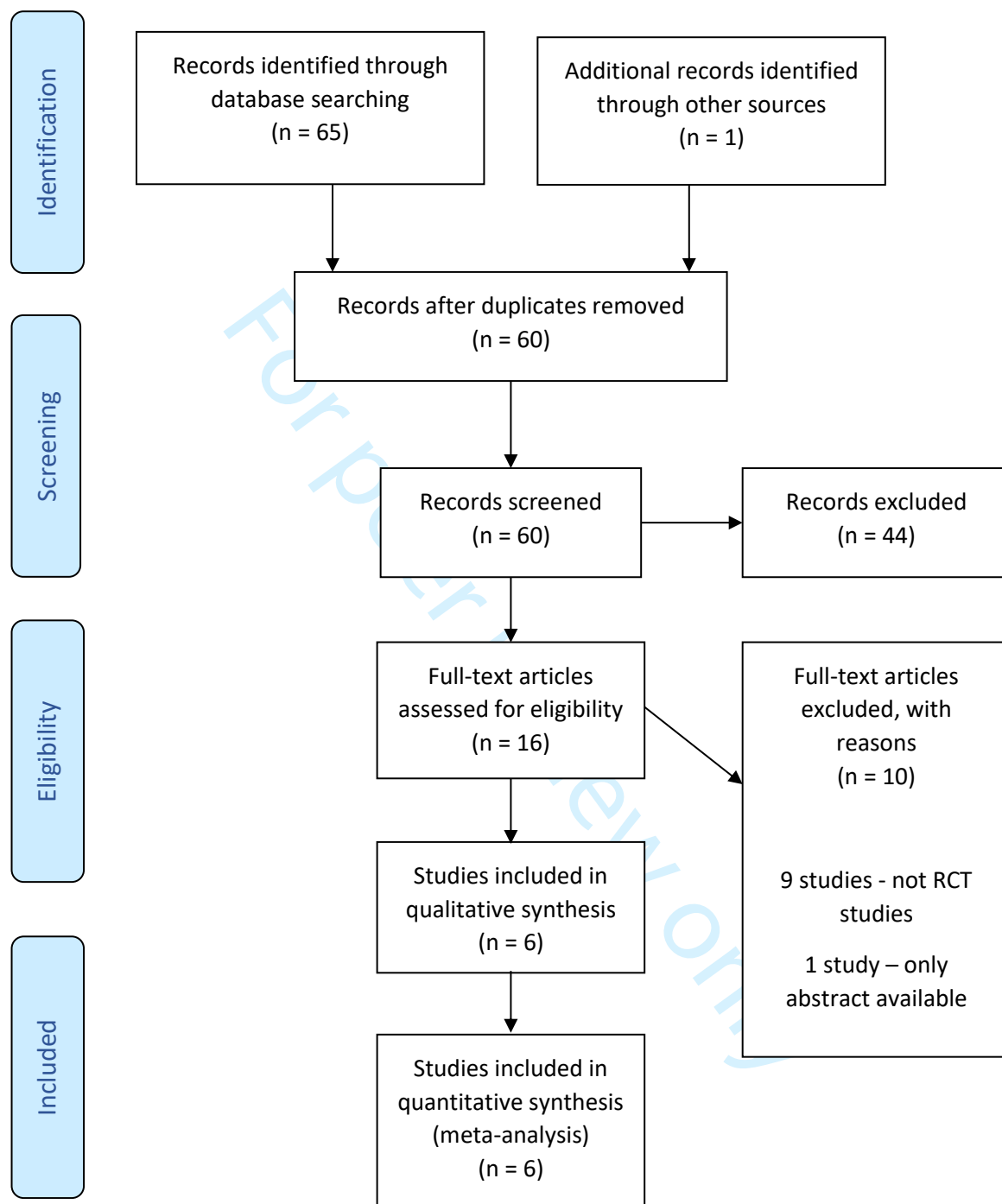


Figure 1: PRISMA Study flow diagram

Supplementary file 3: RISK OF BIAS ASSESSMENT

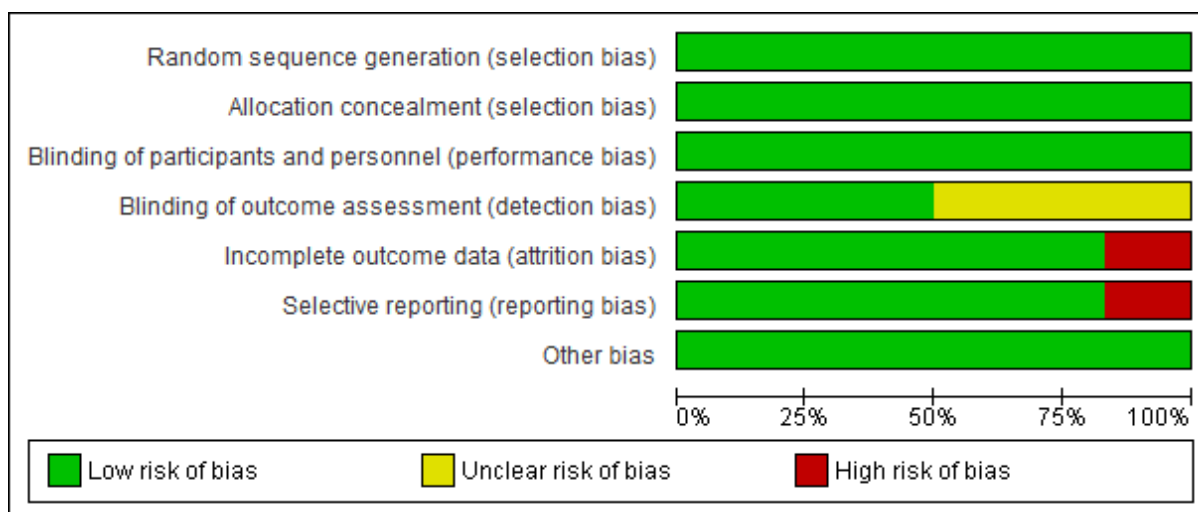


Figure 2a: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

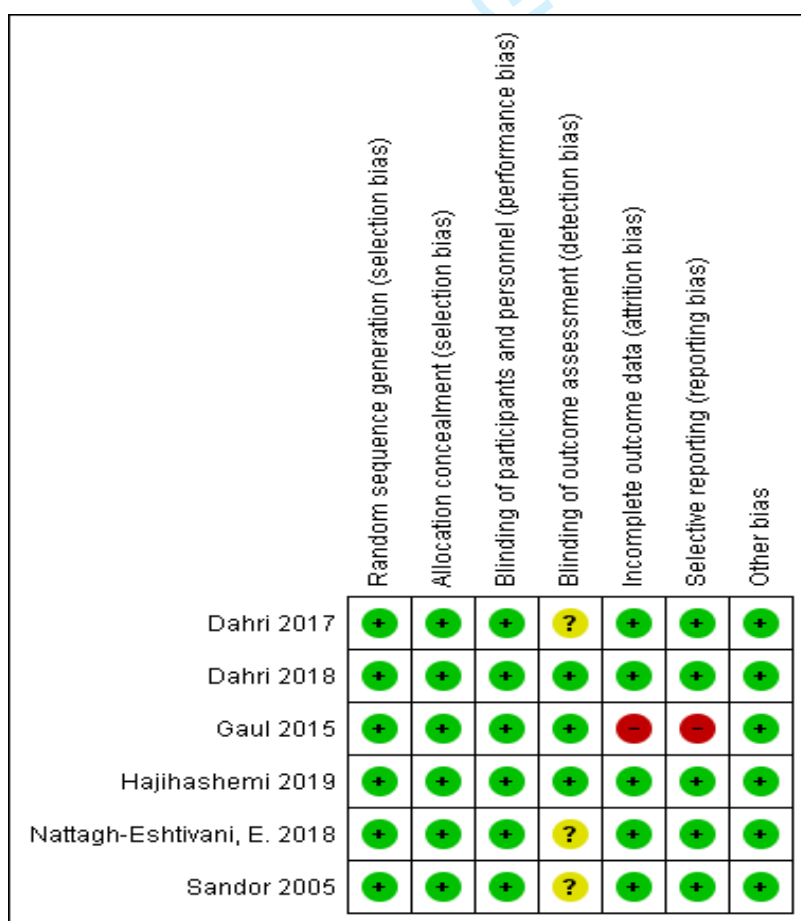


Figure 2b: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Supplementary file 4: FOREST PLOT OF PRIMARY OUTCOMES

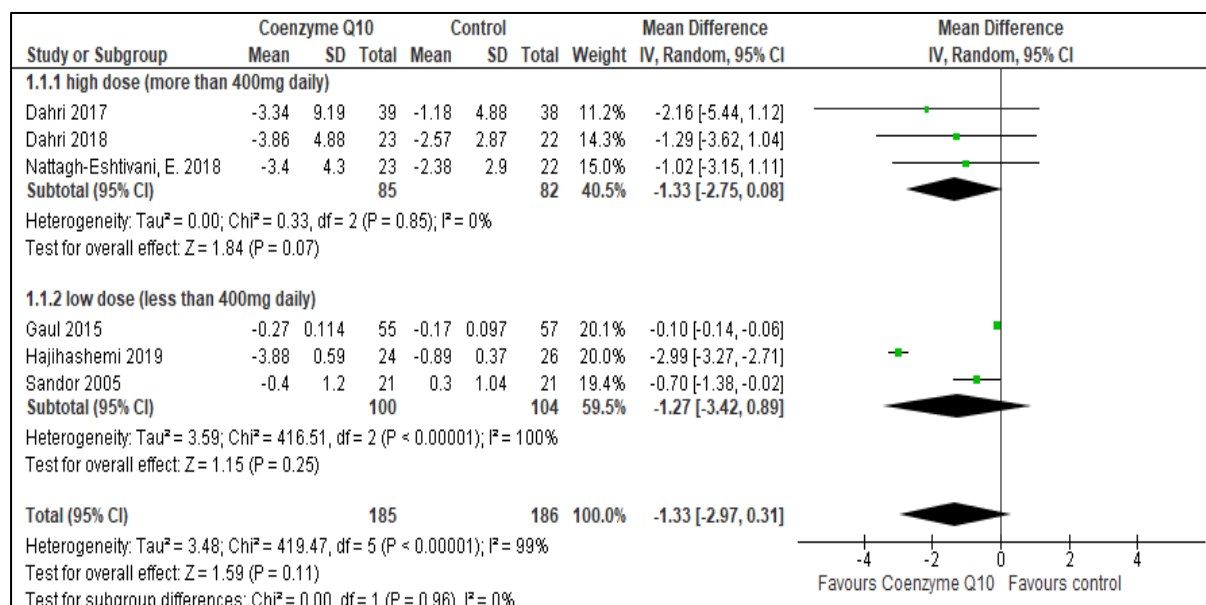


Figure 3: Forest plot of effects coenzyme Q10 versus control on severity of headache during attack

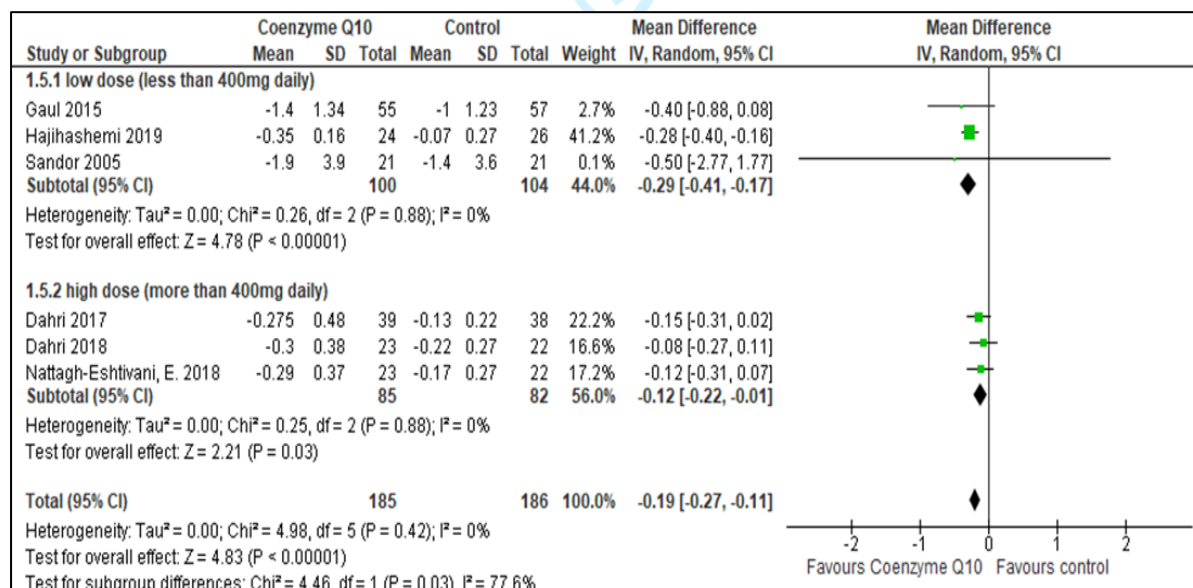


Figure 4: Forest plot of effects coenzyme Q10 versus control on duration of headache attacks per month

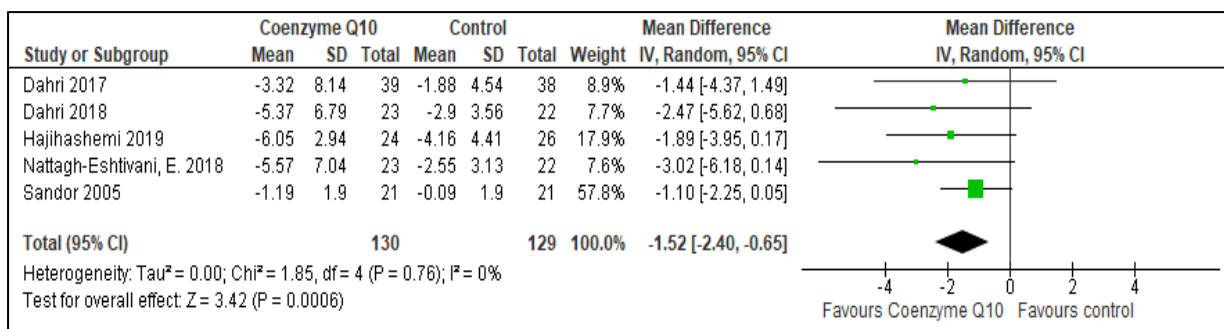


Figure 5: Forest plot of effects coenzyme Q10 versus control on frequency of migraine headache per month

For peer review only

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

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039358.R2
Article Type:	Original research
Date Submitted by the Author:	25-Nov-2020
Complete List of Authors:	Sazali, Suhairul; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Badrin, Salziyan; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Norhayati, Mohd Noor; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine Idris, Nur Suhaila; Universiti Sains Malaysia - Kampus Kesihatan, Department of Family Medicine
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Complementary medicine
Keywords:	Migraine < NEUROLOGY, COMPLEMENTARY MEDICINE, Neurology < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **Title: COENZYME Q10 SUPPLEMENTATION FOR PROPHYLAXIS IN ADULT**
4
5 **PATIENTS WITH MIGRAINE –A META-ANALYSIS**
6
7

8
9 Suhairul Sazali¹, Salziyan Badrin¹, Norhayati Mohd Noor¹, Nur Suhaila Idris¹
10

11 ¹ Department of Family Medicine, School of Medical Sciences, Universiti Sains Malaysia,
12 16150 Kubang Kerian, Kelantan, Malaysia
13

14
15 **Authors:**

16 1. Suhairul Sazali

17 MD

18 Department of Family Medicine

19 School of Medical Sciences

20 Universiti Sains Malaysia

21 16150 Kubang Kerian

22 Kelantan, Malaysia

23 Email: suhairul_sazali@yahoo.com
24
25

26 2. Salziyan Badrin (**Corresponding author**)

27 MD, MMed (Family Medicine)

28 Department of Family Medicine

29 School of Medical Sciences

30 Universiti Sains Malaysia

31 16150 Kubang Kerian

32 Kelantan, Malaysia

33 Email: salziyan@usm.my

34 Telephone number: +609-7676608

35 Fax number: +609-7653370
36
37
38

39 3. Norhayati Mohd Noor

40 MBBS, M.Comm.Med, Ph.D

41 Department of Family Medicine

42 School of Medical Sciences

43 Universiti Sains Malaysia

44 16150 Kubang Kerian

45 Kelantan, Malaysia

46 Email: hayatikk@usm.my
47
48

49 4. Nur Suhaila Idris

50 MD, MMed (Family Medicine)

51 Department of Family Medicine

52 School of Medical Sciences

53 Universiti Sains Malaysia

54 16150 Kubang Kerian

55 Kelantan, Malaysia

56 Email: nursuhaila@usm.my
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Keyword: Coenzyme Q10, Migraine, Supplementation

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

For peer review only

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

1
2
3 the control group (MD -1.52, 95% CI -2.40 to -0.65; random effects; I² statistic = 0%; P =
4
5 <0.001).
6
7

8 **Conclusion** CoQ10 appears to have beneficial effects in reducing duration and frequency of
9
10 migraine attack.
11
12

13 **PROSPERO registration number** CRD42019126127
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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/prospere>.

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

1
2
3 full-text articles when they appear to meet the eligibility criteria, or when there was insufficient
4 information to assess the eligibility. We assessed the eligibility of the trials independently and
5
6 documented all the reasons for exclusion. We resolved any disagreements between the review
7
8 authors by discussion. We contacted the authors if clarification is needed.
9
10

11 12 13 ***Data Collection and analysis*** 14

15
16 Three authors extracted data independently. We extracted data on the dosage and frequency of
17
18 CoQ10 supplementation, criteria for diagnosis of migraine, age, sex, ethnicity, and the
19
20 outcomes of each trials which include severity of the headache attacks using the visual
21
22 analogue scale (VAS), duration of headache in migraine attacks in hour per month, frequency
23
24 of migraine attacks in a month, numbers of days with nausea, numbers of analgesic used during
25
26 headache attacks, numbers of acute migraine medication used, quality of life and adverse
27
28 effects of CoQ10 using data extraction form. Disagreements between the review authors were
29
30 resolved by discussion with the fourth author.
31
32
33

34
35 The Cochrane Collaboration's risk-of-bias tools was used to assess the risk of bias in of the
36
37 included studies(9). Three authors assessed each trial's risk of bias independently. We assessed
38
39 selection bias (randomisation, allocation concealment), performance bias (blinding of
40
41 participant and health personnel), detection bias (blinding of outcome assessment), attrition
42
43 bias (incomplete outcome data), reporting bias (selective reporting) and other bias (recall bias,
44
45 transfer bias and etc). We resolved any disagreements by the discussion with the fourth author.
46
47
48 We assessed the quality of evidence for primary and secondary outcomes, according to the
49
50 GRADE methodology for risk of bias, inconsistency, indirectness, imprecision, and publication
51
52 bias; classified as very low, low, moderate, or high(10).
53
54
55

56 We analysed data using Review Manager 5.3 software(11). We used random-effects model to
57
58 pool data. We assessed the presence of heterogeneity in two steps. First, we assessed obvious
59
60

1
2
3 heterogeneity at face value by comparing populations, settings, interventions and outcomes.
4
5 Then, we assessed statistical heterogeneity by means of the I^2 statistic. We interpreted the
6
7 heterogeneity as; 0% to 40% represent might not be important, 30% to 60% may represent
8
9 moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100%
10
11 would be considerable heterogeneity(9).
12
13

14
15 We measured the treatment effect using risk ratios (RRs) and risk difference (RD) for
16
17 dichotomous outcomes and mean differences (MDs) or standardized mean difference (SMD);
18
19 both with 95% confidence intervals (CIs) for continuous outcomes. We conducted subgroup
20
21 analyses based on the different dosage of CoQ10 and if CoQ10 is combined with another
22
23 supplementation. We explored the potential sources of heterogeneity when it is present. We
24
25 checked all included trials for unit of analysis errors. Unit of analysis errors can occur when
26
27 trials randomize participants to intervention or control groups in clusters, but analysed the
28
29 results using the total number of individual participants. We adjusted results from trials showed
30
31 unit of analysis errors based on the mean cluster size and intraclass correlation coefficient(9).
32
33 We contacted the original trial's authors to request missing or inadequately reported data. We
34
35 performed analyses on the available data if missing data are not available. We performed
36
37 sensitivity analysis to investigate the impact of risk of bias for sequence generation and
38
39 allocation concealment of included studies.
40
41
42
43
44
45

46 **Results**

47
48 We retrieved 65 records from the search of the electronic databases and one record from other
49
50 sources (Supplementary file 2, Figure 1). We screened a total of 60 records. We reviewed full
51
52 text of 16 studies and excluded another 10 studies because all of the studies were non-
53
54 randomized controlled trials(3, 12-20). Therefore, we included only six studies in this review.
55
56
57
58
59
60

1
2
3 We included six studies with a total of 371 participants(21-26). In all the trials, diagnosis of
4 migraine was done based on International Headache Society criteria. Two out of six studies
5
6 (and one study that contributed to the primary outcome) declared funding from drug
7
8 manufacturers(23, 26). Two out of six studies were multicentre trials in high-income
9
10 countries(23, 26). All included trials used International Headache Society criteria (IHS) for
11
12 diagnosis of migraine. Three studies involved a total of 167 female gender only as
13
14 participants(21, 22, 25) and another three studies involved on both genders and a total of 204
15
16 participants(23, 24, 26). All the participants in the included studies were randomised into
17
18 intervention and control groups. Three studies reported using CoQ10 with other elements such
19
20 as multivitamin(23), L-carnitine(24) and preventive medication in the intervention group(21).
21
22 One study used the medication in liquid formulation of water dispersed into nanoparticles (26),
23
24 five studies used the medication in a capsule formulation(21-25). Different dosages of CoQ10
25
26 were administered in the studies: minimum of 30 mg per day(24), 300 mg per day(26), 400 mg
27
28 per day(22), 600 mg per day(23), and 800 mg per day(21, 25). All six trials excluded any
29
30 participants who on migraine preventive drugs in the last six months, who have history of using
31
32 CoQ10 or other antioxidants supplementation for at least three months prior to the
33
34 enrolment(21-26). One trial also excluded participants who failed to respond to the usage of
35
36 more than two different prophylactic agents in the past or any patients who were resistant to
37
38 all acute migraine drugs(23). All six included studies used placebo(21-26) and there was only
39
40 one trial added the preventive migraine medication to the placebo(21); however, the preventive
41
42 medication was used for both the intervention and control groups in this trial(21). Duration of
43
44 CoQ10 treatment differs among the trials and was reported at 8 weeks in one study(24), and at
45
46 3 months in five other studies(21-23, 25, 26). Table 1 summarised the characteristics of the
47
48 included trials.
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 All six included trials followed-up the participants for a minimum of six weeks(21-26). Six
4 studies were included in analyses of the primary outcomes(21-26). We also analysed according
5 to subgroup by dosage of more and less than 400 mg of CoQ10. Secondary outcomes reported
6 in the three trials(21, 23, 26). One study reported using several questionnaires for assessing
7 quality of life affected by migraine(21), which were headache impact test (HIT-6) and migraine
8 specific quality of life (MSQ) questionnaires to assess wellbeing and daily functioning;
9 meanwhile migraine disability assessment (MIDAS) questionnaire to assess disability caused
10 by migraine. The HIT-6 used scoring of 36–49 with higher scores indicate more severe effect
11 of migraine, the MSQ reported the scores between zero and 100 with higher scores indicate
12 better quality of life and the MIDAS reported the scores between zero and 35 with higher scores
13 indicate severe disability(21). We excluded 10 studies and all of the studies are non-
14 randomized controlled trials(3, 12-20).

31 ***Risk of bias***

32
33 Assessment risk of bias is shown in Figure 2a and Figure 2b (Refer Supplementary file 3,
34 Figure 2a and Figure 2b). The proportion of studies assessed as low, high or unclear risk of
35 bias for each risk of bias domain is presented in Figure 2a (Refer Supplementary file 3, Figure
36 2a). Detection bias domain had 50% of low risk with attrition and reporting bias domains
37 around 80% of low risk. The risk of bias summary for individual studies is showed in Figure
38 2b (Refer Supplementary file 3, Figure 2b). Three studies had unclear risk for detection bias
39 (21, 25, 26) and for attrition and reporting bias, only one trial had high risk of bias(23).

40
41 All six studies described the method of randomisation used and randomised the participants
42 according to block randomization(21-26). Allocation concealment was mentioned in all six
43 included studies(21-26). All six studies mentioned about blinding the personnel and the
44 participants(21-26). All six studies had less than 20% lost to follow-up and the reasons such as
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 major protocol violation(23), refused to continue the study(25, 26), failed to return to clinic(21,
4
5 22), pregnancy(21, 22, 24) and failed to keep diary(21, 22) and there were balanced between
6
7 both groups. Only one study carried out an intention-to-treat analysis in which the participants
8
9 were analysed according to the groups that they were initially assigned(21). All six studies
10
11 reported the outcomes as specified in their methods section(21-26). We detected no other
12
13 potential sources of bias.
14
15

16 17 18 ***Effects of interventions***

19
20 All six studies measured the primary outcomes and assessed at three months post
21
22 intervention(21-26). Three studies measured the secondary outcomes(21, 23, 26). Three studies
23
24 did not state on the assessment of outcomes(21, 25, 26).
25
26

27 28 ***Primary outcomes***

29
30 All six included studies reported severity of headache during migraine attack using the visual
31
32 analogue scale (VAS) after taking CoQ10 for at least six weeks(21-26). The meta-analysis
33
34 found no significant reduction in severity of headache with CoQ10 (MD -1.33, 95% CI: -2.97
35
36 to 0.31; I² statistic = 99%; P = 0.110; 6 trials; 371 participants) (Refer Supplementary file 3,
37
38 Figure 3). With more than 400 mg (MD -1.33, 95% CI -2.75 to 0.08, random effects; I² statistic
39
40 = 0%; P = 0.07; 3 trials; 167 participants) or less than 400 mg per day of CoQ10 (MD -1.27;
41
42 95% CI -3.42 to 0.89; random effects; I² statistic = 100%; P = 0.25; 3 trials; 204 participants),
43
44 there is no difference in the severity of headache compared to the control group.
45
46
47

48
49 All six studies reported on the duration of headache attacks in hour per month(21-26). There
50
51 was significant reduction of duration of headache attacks with CoQ10 as compared to the
52
53 control group (MD -0.19 hours, 95% CI -0.27 to -0.11; random effects; I² statistic = 0%; P <
54
55 0.00001; 6 trials, 371 participants) (Refer Supplementary file 3, Figure 4).
56
57
58
59
60

1
2
3 Five studies reported on the frequency of migraine headache attack per month(21, 22, 24-26).
4
5 There was significant reduction in the frequency of migraine headache with the CoQ10 as
6
7 compared to the control group (MD -1.52 times per month, 95% CI -2.40 to -0.65; random
8
9 effects; I² statistic = 0%; P = <0.001; 5 trials, 259 participants) (Refer Supplementary file 3,
10
11 Figure 5).
12
13

14
15 *a) Secondary outcomes*
16

17
18 One study reported on the number of days with nausea due to migraine headache during the
19
20 study period(26). The CoQ10 supplementation reduced the number of days with nausea due to
21
22 migraine headache (MD -1.70; 95% CI -2.92 to -0.48; P = 0.006; 1 trial, 42 participants). No
23
24 other study reported on this outcome. The same study reported the number of acute migraine
25
26 medications usage during the study period(26). The CoQ10 supplementation reduced the
27
28 number of acute migraine medications usage (MD 0.02; 95% CI -0.42 to 0.46; P = 0.91; 1
29
30 trial, 42 participants)(26).
31
32
33

34
35 Only one trial measured the quality of life among patients with migraine headache(21). Three
36
37 types of questionnaire including Migraine-specific quality of life (MSQ), The Headache Impact
38
39 Test (HIT-6) score and Migraine Disability Assessment (MIDAS) score were used to measure
40
41 the impact of the treatment on migraine headache on quality of life(21). Migraine-specific
42
43 quality of life (MSQ) questionnaire reported on role restrictive, role preventive and emotional
44
45 functioning. There were no significant improvements in MSQ questionnaire on role restrictive
46
47 (MD 17.85; 95% CI 9.59 to 26.11; P < 0.0001; 1 trial, 77 participants), role preventive (MD
48
49 17.16; 95% CI 8.75 to 25.57; P < 0.0001; 1 trial, 77 participants) and emotional functioning
50
51 (MD 16.68, 95% CI 6.70 to 26.66; P = 0.001; 1 trial, 77 participants) with the CoQ10
52
53 supplementation. The CoQ10 supplementation showed improvement in The Headache Impact
54
55 Test (HIT-6) score (MD -4.29; 95% CI -7.19 to -1.39; P = 0.004; 1 trial: 77 participants) and
56
57
58
59
60

1
2
3 improvement in Migraine Disability Assessment (MIDAS) score (MD -6.00; 95% CI -9.93 to
4 -2.07; P = 0.003; 1 trial: 77 participants). One trial reported on the adverse effects outcome on
5 diarrhoea (OR 4.44; 95% CI 0.90 to 21.79; P = 0.07) and chromaturia (OR 19.45; 95% CI 1.10
6 to 344.70; P = 0.04)(23) and they not different in the CoQ10 group.
7
8
9
10
11
12

13 **DISCUSSION**

14 15 16 **Summary of main results**

17
18
19 This review was designed to include all RCTs addressing the effectiveness of CoQ10 as one of
20 the alternative medications for migraine prophylaxis. There was significant reduction in the
21 duration by 0.19 hours of headache during attack per month and reduction in the frequency of
22 migraine by 1.52 times per month. Meanwhile, there was no significant reduction in severity
23 of headache during attack even by subgroup analysis according to the different dosages of the
24 CoQ10. Nausea event caused by migraine improved with CoQ10 but there was limited in the
25 number of the trials. Report on adverse events was limited to the minor side effects, which
26 include episodes of diarrhoea and chromaturia and showed no difference with CoQ10.
27
28
29
30
31
32
33
34
35
36
37
38

39 **Overall completeness and applicability of evidence**

40
41 We performed a comprehensive and extensive literature review to assess the effectiveness of
42 CoQ10 supplement as prevention for migraine. The numbers of female participants higher than
43 males in all of the included studies as the highest population diagnosed with migraine is
44 female(27, 28). On this review, we limited the participants to adult population because there
45 was limited number of studies done in paediatric population and a few of the studies done
46 involved other supplements such as riboflavin in paediatric population(29). All the included
47 studies had small number of participants and this limit the applicability of CoQ10 thus the
48 larger samples size is needed for a better result. The information on adverse events came from
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 only one trial which are diarrhoea and chromaturia. There is limited information from the trials
4
5 on other serious adverse events.
6
7

8 **Quality of the evidence**

9
10
11 Generally, there were low risk of bias in most of the included studies in the domains. There
12
13 was no evidence of selective reporting bias in all included trials. Although there was one study
14
15 with high bias, the other studies had complete protocols. This meta-analysis found that there
16
17 were a few of the studies has unclear risk of bias on blinding of the outcome assessment which
18
19 can lead to the treatment effect bias in the original study and the subsequent review. The risk
20
21 of attrition bias was present in one trial. Attrition bias in one study is due to high proportion of
22
23 sample excluded in both intervention and control study with no intention to treat analysis been
24
25 stated in the study (see Supplementary file 3, Figure 2b). We encountered low study samples
26
27 in all trials. Therefore, the overall level of evidence contributing to outcomes of this review is
28
29 low to moderate as assessed using the GRADE approach (Refer Table 2).
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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)	No 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.

1
2
3 For future research, we recommended that the quality of life with validated measurement tool
4 should be used. Data on side effects of coenzyme Q10 are limited thus, need to be explored
5
6 further. New studies should be performed on bigger samples.
7
8
9

10 **Conclusion**

11
12
13
14 CoQ10 might have beneficial effect on reduction of the headache duration during attack and
15 the frequency of migraine attack. The total number of trials on coenzyme Q10 supplementation
16 for migraine prophylaxis is still limited. Due to the small number of trials contributing to the
17 analyses and small effect sizes, the results presented should be considered with caution, thus
18 further bigger sample size and high-quality trials are needed to determine the beneficial effects
19 of the coenzyme Q10 in migraine.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

REFERENCES

1. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001;41(7):646-57.
2. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? *The journal of headache and pain*. 2018;19(1):17-.
3. Hershey AD, Powers SW, Vockell AL, Lecates SL, Ellinor PL, Segers A, et al. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. *Headache*. 2007;47(1):73-80.
4. Ashina M, Tvedskov JF, Lipka K, Bilello J, Penkowa M, Olesen J. Matrix metalloproteinases during and outside of migraine attacks without aura. *Cephalalgia : an international journal of headache*. 2010;30(3):303-10.
5. Gursoy-Ozdemir Y, Qiu J, Matsuoka N, Bolay H, Bempohl D, Jin H, et al. Cortical spreading depression activates and upregulates MMP-9. *The Journal of clinical investigation*. 2004;113(10):1447-55.
6. Sanoobar M, Eghtesadi S, Azimi A, Khalili M, Khodadadi B, Jazayeri S, et al. Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double blind, placebo, controlled randomized clinical trial. *Nutritional neuroscience*. 2015;18(4):169-76.
7. Hagen K, Brenner E, Linde M, Gravdahl GB, Tronvik EA, Engstrom M, et al. Acetyl-L-carnitine versus placebo for migraine prophylaxis: A randomized, triple-blind, crossover study. *Cephalalgia : an international journal of headache*. 2015;35(11):987-95.
8. Bhagavan HN, Chopra RK. Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free radical research*. 2006;40(5):445-53.
9. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane; 2019. Available from: Available from www.training.cochrane.org/handbook.
10. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ (Clinical research ed)*. 2008;336(7651):995-8.
11. The Nordic Cochrane Centre TCC. *Review Manager (RevMan)*. Version 5.3.: Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
12. Airola G, Allais G, Castagnoli Gabellari I, Rolando S, Mana O, Benedetto C. Non-pharmacological management of migraine during pregnancy. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2010;31 Suppl 1:S63-5.
13. Bianchi A, Salomone S, Caraci F, Pizza V, Bernardini R, D'Amato CC. Role of magnesium, coenzyme Q10, riboflavin, and vitamin B12 in migraine prophylaxis. *Vitamins and hormones*. 2004;69:297-312.
14. Carotenuto M, Esposito M. Nutraceuticals safety and efficacy in migraine without aura in a population of children affected by neurofibromatosis type I. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2013;34(11):1905-9.
15. Dalla Volta G, Carli D, Zavarise P, Ngonga G, Vollaro S. P026. Pilot study on the use of coenzyme Q10 in a group of patients with episodic migraine without aura. *Journal of headache and pain (varpagings)*. 2015;16(no pagination).
16. Daniel O, Mauskop A. Nutraceuticals in Acute and Prophylactic Treatment of Migraine. *Current treatment options in neurology*. 2016;18(4):14.
17. Di Lorenzo C. The use of a phytotherapeutic compound containing Tanacetum Parthenium and Andrographis, in combination with CoQ10 and Riboflavin, for migraine prophylaxis: a randomized double blind versus placebo clinical trial. *Journal of headache and pain Conference: 12th european*

- 1
2
3 headache federation congress and the 32nd national congress of the italian society for the study of
4 headaches Italy. 2018;19.
- 5 18. Esposito M, Carotenuto M. Ginkgolide B complex efficacy for brief prophylaxis of migraine in
6 school-aged children: an open-label study. *Neurological sciences : official journal of the Italian*
7 *Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2011;32(1):79-81.
- 8 19. Gaul C, Danesch U, Diener H. A proprietary supplement containing riboflavin, magnesium
9 and Q10 improves migraine symptoms in a randomized placebo-controlled double-blind trial.
10 *Cephalalgia : an international journal of headache*. 2015;35(6 SUPPL. 1):45.
- 11 20. Rozen TD, Oshinsky ML, Gebeline CA, Bradley KC, Young WB, Shechter AL, et al. Open label
12 trial of coenzyme Q10 as a migraine preventive. *Cephalalgia*. 2002;22(2):137-41.
- 13 21. Dahri M, Hashemilar M, Asghari-Jafarabadi M, Tarighat-Esfanjan A. Efficacy of coenzyme
14 Q10 for the prevention of migraine in women: a randomized, double-blind, placebo-controlled
15 study. *European Journal Of Integrative Medicine*. 2017;16:8-14.
- 16 22. Dahri M, Tarighat-Esfanjan A, Asghari-Jafarabadi M, Hashemilar M. Oral coenzyme Q10
17 supplementation in patients with migraine: effects on clinical features and inflammatory markers.
18 *Nutritional Neuroscience*. 2018:1-9.
- 19 23. Gaul C, Diener HC, Danesch U. Improvement of migraine symptoms with a proprietary
20 supplement containing riboflavin, magnesium and Q10: a randomized, placebo-controlled, double-
21 blind, multicenter trial. *Journal Of Headache And Pain*. 2015;16:516.
- 22 24. Hajhashemi P, Askari G, Khorvash F, Reza Maracy M, Nourian M. The effects of concurrent
23 Coenzyme Q10, L-carnitine supplementation in migraine prophylaxis: A randomized, placebo-
24 controlled, double-blind trial. *Cephalalgia*. 2019:333102418821661.
- 25 25. Nattagh-Eshivani E, Dahri M, Hashemilar M, Tarighat-Esfanjan A. The effect of Coenzyme
26 Q10 supplementation on serum levels of lactate, pyruvate, matrix metalloproteinase 9 and nitric
27 oxide in women with migraine. A double blind, placebo, controlled randomized clinical trial.
28 *European Journal Of Integrative Medicine*. 2018;21:70-6.
- 29 26. Sandor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, et al. Efficacy of
30 coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology*. 2005;64(4):713-5.
- 31 27. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence,
32 disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5):343-9.
- 33 28. Manzoni GC, Torelli P. Epidemiology of migraine. *The Journal of Headache and Pain*.
34 2003;4(Suppl 1):s18-s22.
- 35 29. Talebian A, Soltani B, Banafshe HR, Moosavi GA, Talebian M, Soltani S. Prophylactic effect of
36 riboflavin on pediatric migraine: a randomized, double-blind, placebo-controlled trial. *Electron*
37 *Physician*. 2018;10(2):6279-85.
- 38 30. Okoli GN, Rabbani R, Kashani HH, Wierzbowski AK, Neilson C, Mansouri B, et al. Vitamins and
39 Minerals for Migraine Prophylaxis: A Systematic Review and Meta-analysis. *Can J Neurol Sci*.
40 2019;46(2):224-33.
- 41 31. Parohan M, Sarraf P, Javanbakht MH, Ranji-Burachaloo S, Djalali M. Effect of coenzyme Q10
42 supplementation on clinical features of migraine: a systematic review and dose-response meta-
43 analysis of randomized controlled trials. *Nutr Neurosci*. 2019:1-8.
- 44 32. Khorvash F, Bagheri L, Ghasemi M, Ghaed-Amini A, Maracy MR. Coenzyme q10 in migraine
45 prophylaxis: a randomized, double-blind, placebo-controlled clinical trial. *Journal of isfahan medical*
46 *school*. 2016;33(358):1904-11.
- 47 33. Slater SK, Nelson TD, Kabbouche MA, LeCates SL, Horn P, Segers A, et al. A randomized,
48 double-blinded, placebo-controlled, crossover, add-on study of CoEnzyme Q10 in the prevention of
49 pediatric and adolescent migraine. *Cephalalgia*. 2011;31(8):897-905.
- 50 34. Shoeibi A, Olfati N, Soltani Sabi M, Salehi M, Mali S, Akbari Oryani M. Effectiveness of
51 coenzyme Q10 in prophylactic treatment of migraine headache: an open-label, add-on, controlled
52 trial. *Acta Neurologica Belgica*. 2017;117(1):103-9.
- 53
54
55
56
57
58
59
60

1
2
3 **Supplementary file 1: DETAILED SEARCH STRATEGY**
4
5
6
7

8 **MEDLINE search strategy**
9

10 Pubmed - (migraine[Title/Abstract]) AND coenzyme q10[Title/Abstract]
11
12

13 MeSH data based"coenzyme Q10"[All Fields] OR coenzyme q10[Text Word]
14
15

16 migraine[Title/Abstract] AND q10[Title/Abstract]
17
18

19 migraine[Title/Abstract] AND ubiquinone[Title/Abstract]
20
21
22
23
24

25 **CENTRAL search strategy**
26
27

28 migraine in Title Abstract Keyword AND coenzyme q10 in Title Abstract Keyword
29
30

31 migraine in Title Abstract Keyword AND ubiquinone in Title Abstract Keyword
32
33

34 migraine in Title Abstract Keyword AND q10 in Title Abstract Keyword
35
36

37 MeSH data based"coenzyme Q10"[All Fields] OR coenzyme q10[Text Word]
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Supplementary file 2: PRISMA FLOWCHART

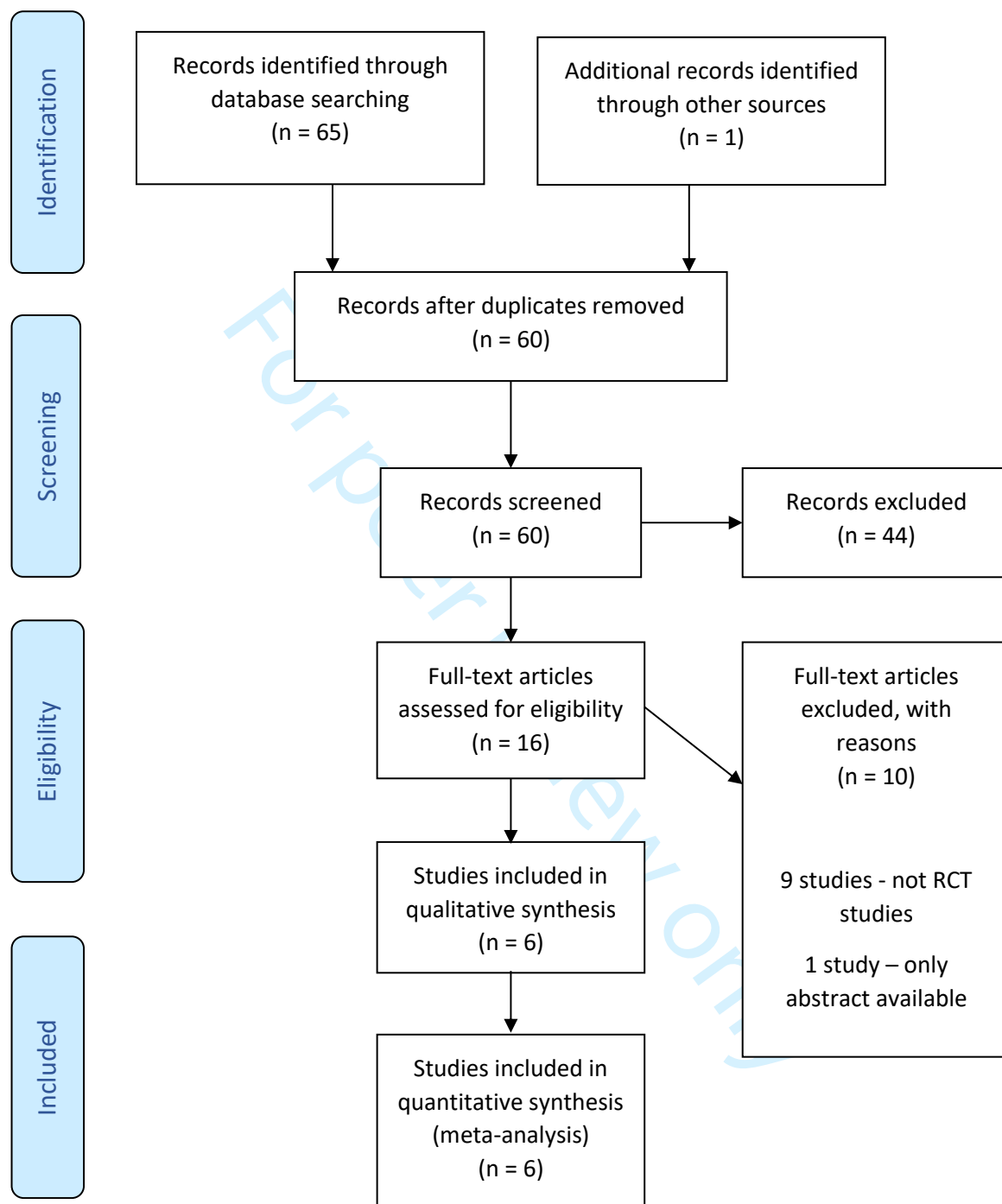


Figure 1: PRISMA Study flow diagram

Supplementary file 3: RISK OF BIAS ASSESSMENT

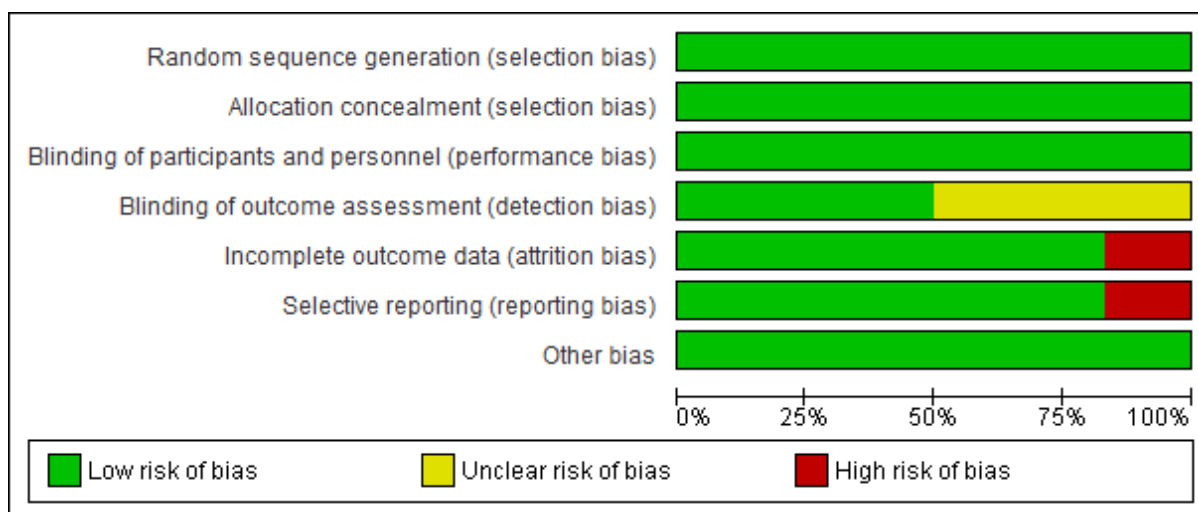


Figure 2a: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

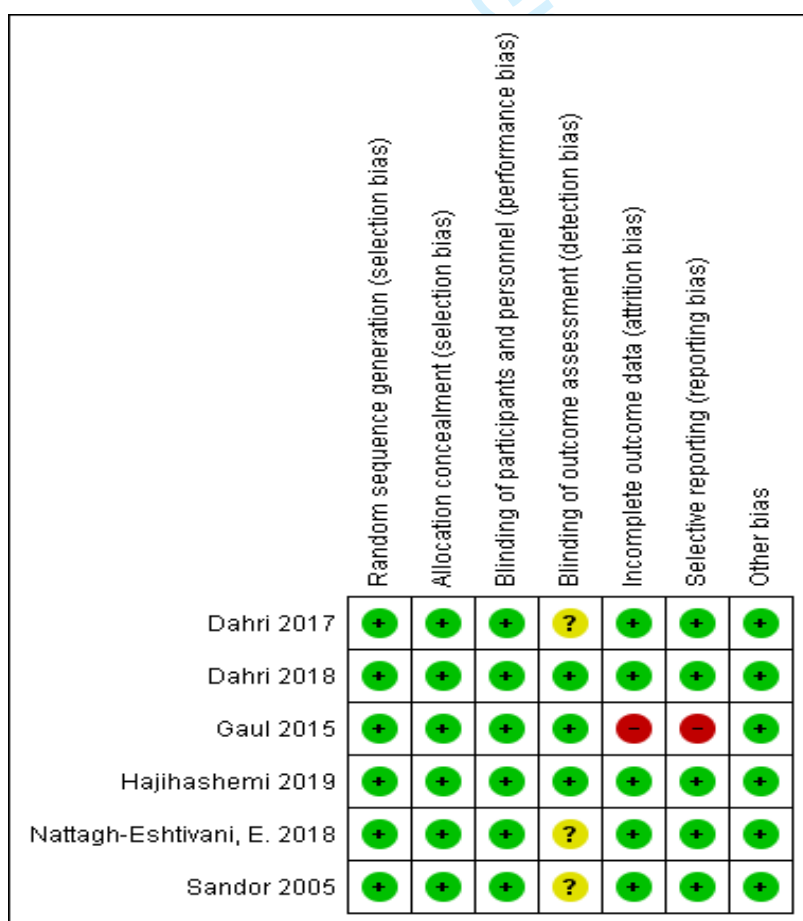


Figure 2b: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Supplementary file 4: FOREST PLOT OF PRIMARY OUTCOMES

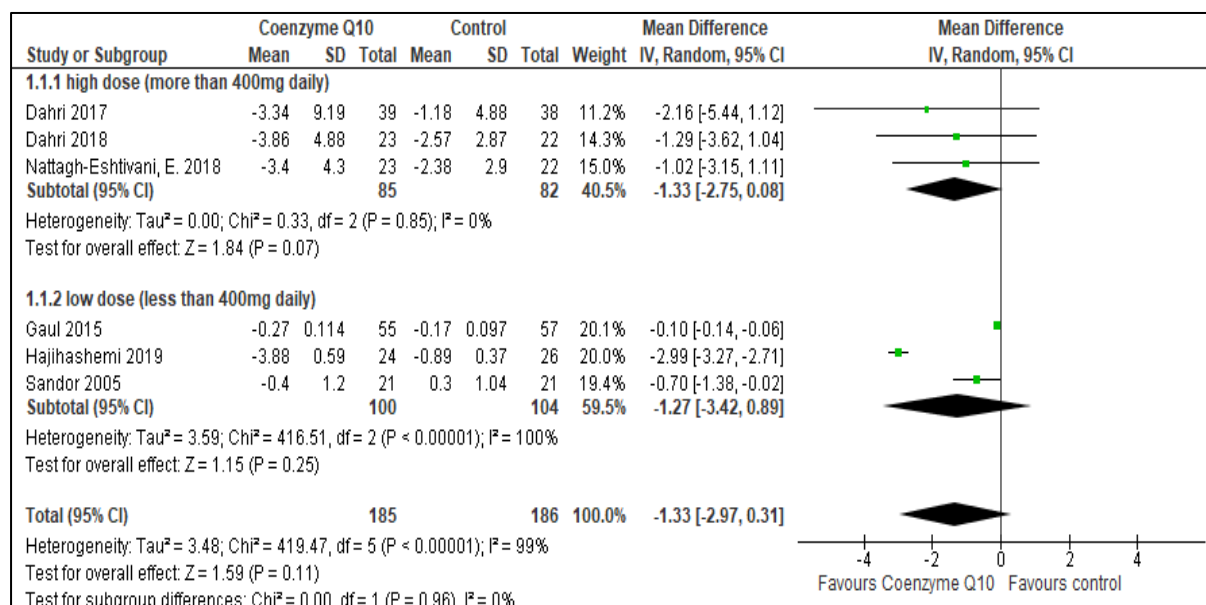


Figure 3: Forest plot of effects coenzyme Q10 versus control on severity of headache during attack

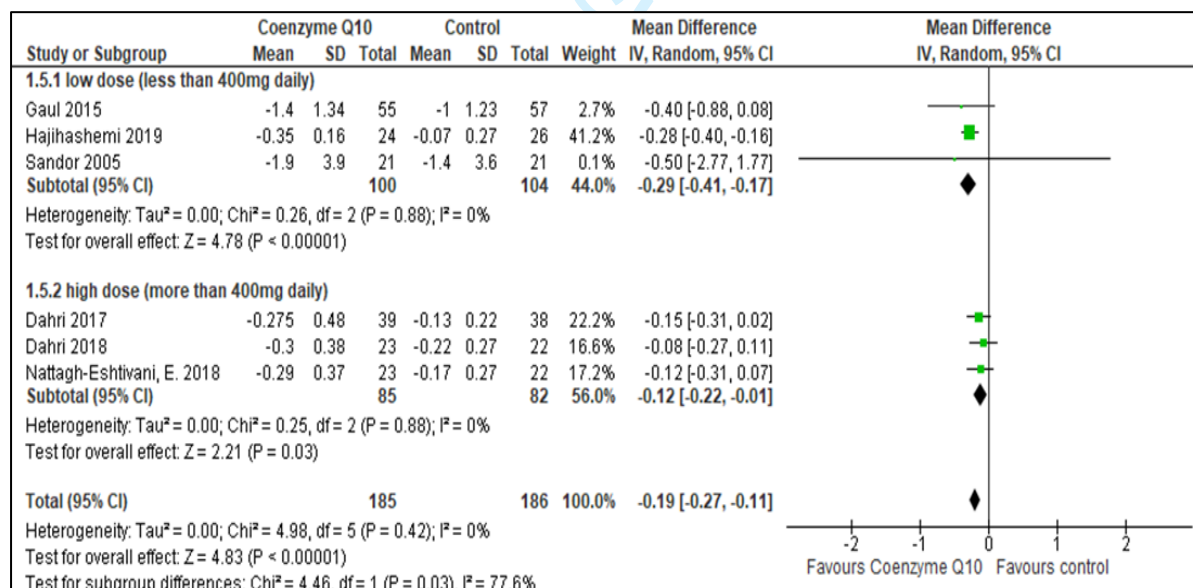


Figure 4: Forest plot of effects coenzyme Q10 versus control on duration of headache attacks per month

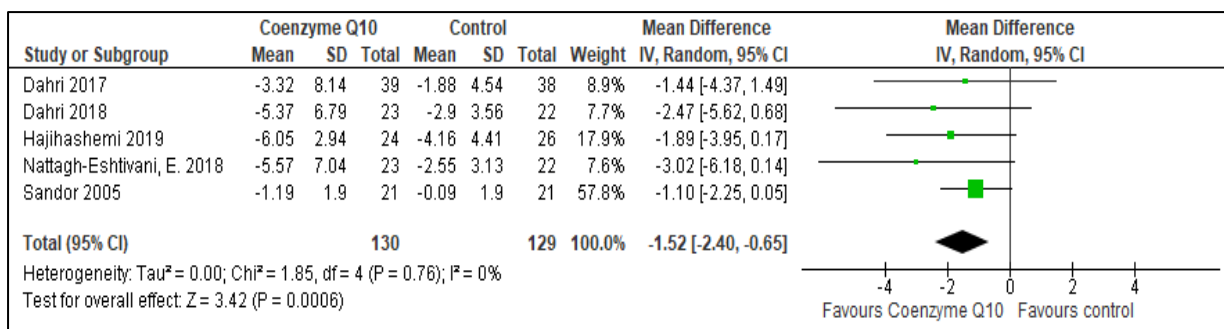


Figure 5: Forest plot of effects coenzyme Q10 versus control on frequency of migraine headache per month

For peer review only

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