

# BMJ Open Coenzyme Q10 supplementation for prophylaxis in adult patients with migraine – a meta-analysis

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## ABSTRACT

**Objective** To determine the effects of coenzyme Q10 (CoQ10) for reduction in 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 randomised control trials comparing CoQ10 with placebo or used as an adjunct treatment included in this meta-analysis. Cross-over designs and controlled clinical trials 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 and risk difference, and for continuous outcomes, mean differences (MDs) or standardised mean difference; both with 95% 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 the 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 with the control group (MD:  $-0.19$ ; 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 with the control group (MD:  $-1.52$ ; 95% CI:  $-2.40$  to  $-0.65$ ; random effects;  $I^2$  statistic=0%;  $p<0.001$ ).

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

**PROSPERO registration number** CRD42019126127.

## 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.<sup>1</sup> Migraine is a debilitating brain

## Strengths and limitations of this study

- The meta-analysis included randomised controlled trials only.
- The overall level of evidences was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.
- Subgroup analysis and potential sources of heterogeneity were explored.
- Small numbers of the included studies was a limitation.

disorder with serious social and financial consequences for the individual and the society.<sup>2</sup> Migraine medications usually aim to reduce the frequency and intensity of headache attacks and few of the medications act as preventive medication.

Low levels of the micronutrients such as riboflavin, magnesium and coenzyme in plasma and in the brain are reported in patients with migraine.<sup>3</sup> A deficit of these nutrients is thought to cause the migraine attacks. The cortical spreading depression is hypothesised to cause the elevation level of Matrix metalloproteinase 9 (MMP-9) is associated with blood–brain barrier dysfunction and inflammation of nerves exacerbates migraine attacks.<sup>4 5</sup> The coenzyme Q10 (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.<sup>6</sup> CoQ10 is a vitamin-like compound, which can be synthesised 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.<sup>3</sup> It acts as an important factor in the electron transport chain of mitochondria, which helps in energy metabolism and oxygen utilisation in the brain and muscles.<sup>7</sup> CoQ10 can be administered orally or parenterally. Peak blood levels occur 5–10

hours after oral administration. Elimination half-life is 33.19 hours.<sup>8</sup> 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 randomised 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. Cross-over designs and controlled clinical trials were excluded. We included the adult participants aged 18 to 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 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 were 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 online supplemental 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 WHO International Clinical Trials Registry Platform (ICTRP), <https://www.who.int/ictrp/en/> and [www.clinicaltrials.gov](http://www.clinicaltrials.gov). We excluded trials published other than the English language. We scanned the titles and abstracts from the searches and obtain full-text articles when they appear to meet the eligibility criteria, or when there was insufficient information to assess the eligibility. We assessed the eligibility of the trials independently and documented all the reasons for exclusion. We resolved any disagreements between the review authors by discussion. We contacted the authors if clarification was needed.

### Data collection and analysis

Three authors extracted data independently. We extracted data on the dosage and frequency of CoQ10

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

The Cochrane Collaboration's risk-of-bias tools was used to assess the risk of bias in one of the included studies.<sup>9</sup> 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, etc). We resolved any disagreements by the discussion with the fourth author. We assessed the quality of evidence for primary and secondary outcomes, according to the GRADE methodology for risk of bias, inconsistency, indirectness, imprecision and publication bias; classified as very low, low, moderate or high.<sup>10</sup>

We analysed data using Review Manager V.5.3 software.<sup>11</sup> We used random-effects model to pool data. We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by comparing populations, settings, interventions and outcomes. Then, we assessed statistical heterogeneity by means of the  $I^2$  statistic. We interpreted the heterogeneity as 0% to 40% represent might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% would be considerable heterogeneity.<sup>9</sup>

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

## RESULTS

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

We included six studies with a total of 371 participants.<sup>21–26</sup> In all the trials, diagnosis of migraine was done based on International Headache Society criteria. Two out of six studies (and one study that contributed to the primary outcome) declared funding from drug manufacturers.<sup>23 26</sup> Two out of six studies were multicentre trials in high-income countries.<sup>23 26</sup> All included trials used IHS for diagnosis of migraine. Three studies involved a total of 167 female gender only as participants<sup>21 22 25</sup> and another three studies involved on both genders and a total of 204 participants.<sup>23 24 26</sup> All the participants in the included studies were randomised into intervention and control groups. Three studies reported using CoQ10 with other elements such as multivitamin,<sup>23</sup> L-carnitine<sup>24</sup> and preventive medication in the intervention group.<sup>21</sup> One study used the medication in liquid formulation of water dispersed into nanoparticles<sup>26</sup> and five studies used the medication in a capsule formulation.<sup>21–25</sup> Different dosages of CoQ10 were administered in the studies: minimum of 30 mg per day,<sup>24</sup> 300 mg per day,<sup>26</sup> 400 mg per day,<sup>22</sup> 600 mg per day<sup>23</sup> and 800 mg per day.<sup>21 25</sup> All six trials excluded any participants who were on migraine preventive drugs in the last 6 months, who have history of using CoQ10 or other antioxidants supplementation for at least 3 months prior to the enrolment.<sup>21–26</sup> One trial also excluded participants who failed to respond to the usage of more than two

different prophylactic agents in the past or any patients who were resistant to all acute migraine drugs.<sup>23</sup> All six included studies used placebo<sup>21–26</sup> and there was only one trial that added the preventive migraine medication to the placebo<sup>21</sup>; however, the preventive medication was used for both the intervention and control groups in this trial.<sup>21</sup> Duration of CoQ10 treatment differs among the trials and was reported at 8 weeks in one study,<sup>24</sup> and at 3 months in five other studies.<sup>21–23 25 26</sup> Table 1 summarises the characteristics of the included trials.

All six included trials followed up the participants for a minimum of 6 weeks.<sup>21–26</sup> Six studies were included in analyses of the primary outcomes.<sup>21–26</sup> We also analysed according to subgroup by dosage of more and less than 400 mg of CoQ10. Secondary outcomes were reported in three trials.<sup>21 23 26</sup> One study reported using several questionnaires for assessing quality of life affected by migraine,<sup>21</sup> which were headache impact test (HIT-6) and migraine-specific quality of life (MSQ) questionnaires to assess well-being and daily functioning; meanwhile migraine disability assessment (MIDAS) questionnaire to assess disability caused by migraine. The HIT-6 used scoring of 36–49 with higher scores indicating more severe effect of migraine, the MSQ reported the scores between 0 and 100 with higher scores indicating better quality of life and the MIDAS reported the scores between 0 and 35 with higher scores indicating severe disability.<sup>21</sup> We excluded 10 studies and all were non-randomised controlled trials.<sup>3 12–20</sup>

### Risk of bias

Assessment risk of bias is shown in figure 2a and figure 2b of the online supplemental file 3. The proportion of studies assessed as low, high or unclear risk of bias for

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

Studies	Size, n	Mean age, years	Female, %	BMI, kg/m <sup>2</sup>	Interventions	CoQ10 maximum dose per day (mg)
Sándor <i>et al</i> <sup>26</sup>	42	38.65	80.9	Not mention	Intervention: CoQ10 liquid formulation of water dispersed nanoparticles Control: Placebo	100
Nattagh-Eshtivani <i>et al</i> <sup>25</sup>	45	32.7	100.0	25.16	Intervention: CoQ10 capsule Control: Placebo	800
Dahri <i>et al</i> <sup>22</sup>	45	32.36	100.0	25.55	Intervention: CoQ10 capsule Control: Placebo	400
Hajihashemi <i>et al</i> <sup>24</sup>	50	32.44	87.5	24.47	Intervention: CoQ10 capsule and L-carnitine Control: Placebo	30
Gaul <i>et al</i> <sup>19</sup>	112	38.4	86.6	38.4	Intervention: CoQ10 with multivitamins combination Control: Placebo	600
Dahri <i>et al</i> <sup>21</sup>	77	33.71	100.0	25.43	Intervention: CoQ10 capsule plus preventive drugs Control: Placebo plus preventive drugs	400

BMI, body mass index; CoQ10, coenzyme Q10.

each risk of bias domain is presented in figure 2a of the online supplemental file 3. Detection bias domain had 50% of low risk with attrition and reporting bias domains around 80% of low risk. The risk of bias summary for individual studies is shown in figure 2b of online supplemental file 3. Three studies had unclear risk for detection bias<sup>21 25 26</sup> and for attrition and reporting bias, only one trial had high risk of bias.<sup>23</sup>

All six studies described the method of randomisation used and randomised the participants according to block randomisation.<sup>21-26</sup> Allocation concealment was mentioned in all six included studies.<sup>21-26</sup> All six studies mentioned about blinding the personnel and the participants.<sup>21-26</sup> All six studies had less than 20% lost to follow-up and the reasons such as major protocol violation,<sup>23</sup> refused to continue the study,<sup>25 26</sup> failed to return to clinic,<sup>21 22</sup> pregnancy<sup>21 22 24</sup> and failed to keep diary,<sup>21 22</sup> and they were balanced between both groups. Only one study carried out an intention-to-treat analysis in which the participants were analysed according to the groups that they were initially assigned.<sup>21</sup> All six studies reported the outcomes as specified in their methods section.<sup>21-26</sup> We detected no other potential sources of bias.

### Effects of interventions

All six studies measured the primary outcomes and assessed at 3 months postintervention.<sup>21-26</sup> Three studies measured the secondary outcomes.<sup>21 23 26</sup> Three studies did not state on the assessment of outcomes.<sup>21 25 26</sup>

### Primary outcomes

All six included studies reported severity of headache during migraine attack using the VAS after taking CoQ10 for at least 6 weeks.<sup>21-26</sup> The meta-analysis found no significant reduction in severity of headache with CoQ10 (MD: -1.33; 95% CI: -2.97 to 0.31; I<sup>2</sup> statistic=99%; p=0.110; six trials; 371 participants, refer figure 3 of online supplemental file 4). With more than 400 mg (MD: -1.33; 95% CI: -2.75 to 0.08, random effects; I<sup>2</sup> statistic=0%; p=0.07; three trials; 167 participants) or less than 400 mg per day of CoQ10 (MD: -1.27; 95% CI: -3.42 to 0.89; random effects; I<sup>2</sup> statistic=100%; p=0.25; three trials; 204 participants), there is no difference in the severity of headache compared with the control group.

All six studies reported on the duration of headache attacks in hour per month.<sup>21-26</sup> There was significant reduction of duration of headache attacks with CoQ10 as compared with the control group (MD: -0.19 hour; 95% CI: -0.27 to -0.11; random effects; I<sup>2</sup> statistic=0%; p<0.00001; six trials, 371 participants, refer figure 4 of the online supplemental file 4).

Five studies reported on the frequency of migraine headache attack per month.<sup>21 22 24-26</sup> There was significant reduction in the frequency of migraine headache with the CoQ10 as compared with the control group (MD: -1.52 times per month; 95% CI: -2.40 to -0.65; random effects; I<sup>2</sup> statistic=0%; p<0.001; five trials, 259 participants, refer figure 5 of the online supplemental file 4).

### Secondary outcomes

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

Only one trial measured the quality of life among patients with migraine headache.<sup>21</sup> Three types of questionnaires including MSQ, HIT-6 score and MIDAS score were used to measure the impact of the treatment for migraine headache on quality of life.<sup>21</sup> MSQ questionnaire reported on role restrictive, role preventive and emotional functioning. There were no significant improvements in MSQ questionnaire on role restrictive (MD: 17.85; 95% CI: 9.59 to 26.11; p<0.0001; one trial; 77 participants), role preventive (MD: 17.16; 95% CI: 8.75 to 25.57; p<0.0001; one trial; 77 participants) and emotional functioning (MD: 16.68; 95% CI: 6.70 to 26.66; p=0.001; one trial; 77 participants) with the CoQ10 supplementation. The CoQ10 supplementation showed improvement in the HIT-6 score (MD: -4.29; 95% CI: -7.19 to -1.39; p=0.004; one trial; 77 participants) and improvement in MIDAS score (MD: -6.00; 95% CI: -9.93 to -2.07; p=0.003; one trial; 77 participants). One trial reported on the adverse effects outcome on diarrhoea (OR: 4.44; 95% CI: 0.90 to 21.79; p=0.07) and chromaturia (OR: 19.45; 95% CI: 1.10 to 344.70; p=0.04)<sup>23</sup> and showed no difference with the CoQ10 group.

## DISCUSSION

### Summary of main results

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

### Overall completeness and applicability of evidence

We performed a comprehensive and extensive literature review to assess the effectiveness of CoQ10 supplement as prevention for migraine. The numbers of female participants higher than males in all of the included studies

as the highest population diagnosed with migraine is female.<sup>27,28</sup> On this review, we limited the participants to adult population because there was limited number of studies done in paediatric population and a few of the studies done involved other supplements such as riboflavin in paediatric population.<sup>29</sup> All the included studies had small number of participants and this limit the applicability of CoQ10 thus the larger samples size is needed for a better result. The information on adverse events came from only one trial which are diarrhoea and chromaturia. There is limited information from the trials on other serious adverse events.

### Quality of the evidence

Generally, there were low risk of bias in most of the included studies in the domains. There was no evidence of selective reporting bias in all included trials. Although there was one study with high bias, the other studies had complete protocols. This meta-analysis found that there were few studies with 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 figure 2b of the online supplemental file 3). 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).

### 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 all the included studies 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.

**Table 2** The GRADE quality assessment for CoQ10

Summary of findings					
CoQ10 compared to control for migraine prophylaxis					
Patient or population: adult patients with migraine					
Setting: Healthcare centres					
Intervention: CoQ10					
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 CoQ10			
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†
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‡
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‡

GRADE Working Group grades of evidence: High certainty indicates we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty indicates 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 indicates our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect.

Very low certainty indicates we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect.

⊕⊕⊕○ refers to Quality of the evidence (GRADE)

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

†There is presence of the statistical heterogeneity, inconsistency and imprecision existed.

‡Downgraded due to large CIs from small sample size and small number of included studies.

CoQ10, coenzyme Q10; MD, mean difference; ; RCTs, randomised control trials.



## 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*<sup>30 31</sup>. Okoli *et al* evaluated the efficacy of all types of vitamins including CoQ10 as migraine prophylaxis.<sup>30</sup> Three out of 18 trials included in the review evaluated CoQ10.<sup>23 26 32</sup> They found no reduction in frequency, duration and severity of migraine with CoQ10. Parohan *et al*<sup>31</sup> performed the meta-analysis regarding the effects of CoQ10 supplementation on clinical features of migraine and the study included four trials<sup>22 26 33 34</sup> in which, two of the trials were included in our meta-analysis.<sup>22 26</sup> We removed the remaining two trials because the study methods did not match our review.<sup>33 34</sup> They reported that CoQ10 reduced the frequency of migraine attack but no significant effect on severity and duration of migraine attacks. We found no other systematic reviews that reported on our other prespecified secondary outcomes.

For future research, we recommended that the quality of life with validated measurement tool should be used. Data on side effects of CoQ10 are limited thus, and need to be explored further. New studies should be performed on bigger samples.

## CONCLUSION

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

**Contributors** 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. MNN was involved in coordinating 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 coordinating the flow of the review process, gave input in designing the review, carried out data extraction and gave input for writing the discussion.

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