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L-carnitine for cognitive enhancement in people without cognitive impairment (Review)

Chen N, Yang M, Zhou M, Xiao J, Guo J, He L

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[Intervention Review]

L-carnitine for cognitive enhancement in people without cognitive impairment

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A B S T R A C T

Background

Safe interventions to enhance cognitive function in cognitively healthy people would be very valuable for several reasons, including a better quality of life and professional success. While L-carnitine has been reported to enhance cognitive function in some conditions, its efficacy is disputed. The evidence of its efficacy for cognitively healthy people has not previously been systematically reviewed.

Objectives

To assess the efficacy and safety of L-carnitine for the enhancement of cognitive function in people without cognitive impairment.

Search methods

We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group's Specialized Register, on 4 November 2016. We used the search terms 'L-carnitine' or 'acetyl-L-carnitine' or 'propionyl-L-carnitine' or 'ALC' or 'PLC' or 'ALCAR' or 'ALPAR'. We ran additional separate searches in several other sources to ensure that we retrieved the most up-to-date results. We also reviewed the bibliographies of the randomised controlled trials identified and contacted the authors and known experts in the field and pharmaceutical companies to identify additional published or unpublished data.

Selection criteria

Eligible trials were randomised controlled trials (RCTs) or quasi-RCTs, parallel-group or cross-over, that compared L-carnitine or its derivatives, acetyl-L-carnitine or propionyl-L-carnitine, at any dose and for any length of treatment, with placebo or no treatment in cognitively healthy people of any age and either gender.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Two review authors independently selected trials and evaluated the methodological quality, then extracted and analysed data from the included trials.

Main results

Only two RCTs were eligible. One was a cross-over trial with 18 participants. The other randomised 400 participants to one of four treatments, of which two (L-carnitine and placebo) were relevant to this review, but the exact numbers of participants in these two treatment groups was not reported. All participants were young adults. Methodological details were poorly reported, and we considered the risk of bias in both studies to be unclear. The trials assessed different cognitive outcomes. We could extract cognitive data on approximately 200 participants from one trial. We found no evidence that L-carnitine has any effect on reaction time, vigilance, immediate memory, or delayed recall after three days of treatment. This trial report stated that there was a small number of adverse effects, none of

which were serious. The small cross-over trial also reported no effect of L-carnitine on cognition, but did not provide data; no information was provided on adverse effects. We considered the available evidence to be of very low quality for all reported outcomes.

Authors' conclusions

Due to the limited number of included trials, short-term treatment, and inadequate reporting, we were unable to draw any conclusions about the efficacy or safety of L-carnitine for cognitive enhancement in healthy adults. Well-designed, randomised, placebo-controlled trials of L-carnitine for cognition enhancement in cognitively healthy people, with large samples and relatively long-term follow-up, are still needed.

PLAIN LANGUAGE SUMMARY

L-carnitine for cognitive enhancement in people without cognitive impairment

Background

Cognition (or cognitive function) is a term used to describe thinking skills, including attention, memory, and reasoning. Supplements and drugs are sometimes used by healthy people to try to improve cognitive function and perform better at work or while studying. These supplements and drugs are known as cognitive enhancers. L-carnitine, which is found naturally in the diet, especially in meat, but can also be produced in the body, has been suggested as a possible cognitive enhancer. It is sold on its own as a dietary supplement and is found in some mixed supplements or 'energy drinks'. In this review, we searched for clinical trials in which healthy people taking L-carnitine were compared with similar people taking a dummy pill (placebo). We hoped to learn whether or not L-carnitine improves cognitive function and whether it is associated with side effects.

Results

We found only two trials to include in the review. One trial treated approximately 200 participants with L-carnitine or placebo for three days; the other trial treated only 18 participants with only a single dose of L-carnitine. Both trials included healthy young people with an average age of about 21. The trials measured different aspects of cognition using different tests. The smaller trial was only reported as an abstract, and there was no usable data, although the authors said that they found no evidence of an effect of L-carnitine on cognitive function. Important information was missing from the paper describing the other trial, but we found no evidence that L-carnitine had any effect on any of the aspects of cognition that were measured. Only the report of the larger trial mentioned adverse effects of treatment, which were all described as minor and occurring equally among those receiving L-carnitine and those receiving placebo.

Quality of the evidence

It was difficult to properly assess the quality of the included trials because of poor reporting. We considered there to be a serious risk of bias due to poor study methods, and further uncertainty about the results because the studies were so small. We also considered the studies to be too short to adequately address our research question. Due to these factors, we considered the quality of the evidence to be very low.

Conclusions

Given the limited amount of evidence of very low quality, we were not able to draw any conclusions about the effect of L-carnitine on cognitive function or its safety in healthy people. Larger, better-quality studies conducted over a longer period of time are needed to answer our review question.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. L-carnitine compared to placebo for cognitive enhancement in people without cognitive impairment

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L-carnitine compared to placebo for cognitive enhancement in people without cognitive impairment

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Patient or population: healthy young women
Setting: community
Intervention: L-carnitine
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with L-carnitine			
Reaction time (8 lamps) Assessed with: reaction time task with 8 potentially illuminated lamps Follow-up: mean 3 days	The mean reaction time (8 lamps) was 416 milliseconds	MD 5 milliseconds fewer (23.18 fewer to 13.18 more)	200 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1] [2] [3]	The number of participants was an approximation, since the report did not specify the actual numbers of participants in each study group.
Vigilance Assessed with: rapid information-processing task Follow-up: mean 3 days	The mean vigilance was 23.5 digits	MD 1.2 digits fewer (3.06 fewer to 0.66 more)	200 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1] [2] [3]	
Immediate memory Assessed with: recall of word list Scale from: 0 to 30 Follow-up: mean 3 days	The mean immediate memory was 11.6 words	MD 1 words fewer (2.07 fewer to 0.07 more)	200 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1] [2] [3]	
Delayed memory Assessed with: recall of word list Scale from: 0 to 30 Follow-up: mean 3 days	The mean delayed memory was 8.9 words	MD 0.9 words fewer (1.97 fewer to 0.17 more)	200 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1] [2] [3]	
Adverse effects - not reported	It stated that 92% of participants reported no side effects and that the numbers of participants who had some minor reaction were similar among the experimental groups, but the actual number of participants reporting any adverse effect in each group is unknown.		—	⊕⊖⊖⊖ VERY LOW [1] [2] [3]	

***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).

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level due to study limitations. Most of the 'Risk of bias' judgements were 'unclear', so we considered there to be a serious concern about risk of bias.
[2]Downgraded one level due to indirectness. The follow-up period to observe the change in cognitive function in people without cognitive impairment was very short.
[3]Downgraded one level due to imprecision. The results came from a single, small study.

L-carnitine for cognitive enhancement in people without cognitive impairment (Review)

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BACKGROUND

Description of the condition

Cognitive functions, such as attention, perception, memory, and language, are crucial for human functioning. These capacities are used to process information, including acquiring, selecting, representing, and retaining relevant data, and to guide behaviours (Sandberg 2006). Evidence from long-term follow-up studies and systematic reviews suggests an inverse association between early-life cognitive function and adult risk of unintentional injury and mortality (Calvin 2011; Osler 2007). With the continuous development of society, better cognition is also considered to mean stronger social adaptability and higher quality of life (Clark 2014; Eickenhorst 2012; Franke 2011). The maintenance and improvement of cognitive function has therefore been gradually gaining attention, with interest in dietary supplements or drugs that might enhance cognition (Clark 2014; Deline 2014; Eickenhorst 2012).

Cognitive enhancement has been defined as the amplification or extension of one or more core capacities of the mind, thus improving a person's information processing systems and allowing them to achieve better performance in their daily life (McKendrick 2014; Sandberg 2006). Safe interventions that enhance cognitive function would be very valuable.

Description of the intervention

L-carnitine (the enantiomeric form of carnitine) is a quaternary ammonium compound synthesised from the amino acids lysine or methionine. It is an important contributor to cellular energy metabolism. Although the substance was discovered in 1905, its crucial role in metabolism was not elucidated until 1955, and its deficiency was not described until 1972 (Bhattacharyya 1995; Kelly 1998). The most significant source of L-carnitine in the human diet is meat; humans also can synthesise L-carnitine from dietary amino acids. L-carnitine is produced in the liver and kidneys and stored mainly in the most active metabolic tissue such as the skeletal muscles, heart, brain, and sperm. The plasma concentration of L-carnitine varies with age, increasing until a person is nearly 70 years old, then tending to diminish in parallel with the reduction in body mass index and muscle mass (Malaguarnera 1999). Acetyl-L-carnitine (ALC) and propionyl-L-carnitine (PLC) are the most important naturally occurring carnitine derivatives. The body can convert L-carnitine to ALC or PLC, and vice versa. L-carnitine and its natural derivatives may therefore theoretically play similar roles in the body, but due to their chemical structures they appear to be present in different strengths in some tissues (Malaguarnera 2012; Mingorance 2011).

Although L-carnitine is supplied exogenously and can be synthesised endogenously, both primary and secondary deficiencies do occur. Carnitine deficiency can be acquired or result from inborn errors of metabolism (Stanley 2004). Preterm infants are at risk for carnitine deficiency due to impaired synthesis and insufficient renal tubular resorption (Evangeliou 2003). Secondary carnitine deficiency is more common and is usually associated with dialysis in chronic renal failure, although it can also be induced by intestinal resection, severe infection, and liver disease.

Besides being found in certain foods (e.g. meats, dairy products, and some plants), L-carnitine is also available in the form of supplements or included in some mixed products, such as energy drinks and vitamin mixtures. At least four formulations of L-carnitine supplements are currently available, that is liquid, tablet, capsule, and powder, and it is sometimes supplied as one component in a multicomponent preparation or a dietary intervention (L-Carnitine 2015). Oral supplementation of L-carnitine in individual dosages greater than 2 g appears to offer no advantage, since the mucosal absorption of carnitine appears to be saturated at about a 2 g dose (Harper 1988). Maximum blood concentration is reached approximately 3.5 hours after an oral dose and slowly decreases, with a half-life of about 15 hours (Bach 1983). Elimination of carnitine occurs primarily through the kidneys (Bach 1983).

Reported side effects of L-carnitine include agitation, headache, diarrhoea, nausea, vomiting, anorexia, and abdominal discomfort, mostly of mild or moderate severity (Hudson 2003; Montgomery 2003; Wang 2014).

L-carnitine and its derivatives have been proposed as a treatment, or as an adjunct to conventional medicine, for many conditions, including stable angina, intermittent claudication, diabetic neuropathy, kidney disease and dialysis, hyperthyroidism, male infertility, erectile dysfunction, chronic fatigue syndrome, Alzheimer's disease, and memory impairment (Hudson 2003; Montgomery 2003; Ribas 2014; Shang 2014; Wang 2014). Acetyl-L-carnitine is thought to traverse the blood-brain barrier more readily and may have a preferential effect on the central nervous system, whereas PLC may have better bioavailability and specifically target skeletal and cardiac muscle (Malaguarnera 2012; Mingorance 2011).

How the intervention might work

L-carnitine is involved in energy production

L-carnitine is a cofactor required for transformation of free long-chain fatty acids into acylcarnitines, and for their subsequent transport into the mitochondrial matrix, where they are oxidised to produce energy. Increasing L-carnitine content might increase the rate of fatty acid oxidation, permitting a reduction of glucose use, preserving muscle glycogen content, and ensuring maximal rates of oxidative adenosine triphosphate (ATP) production (Brass 1994a; Brass 1994b; Brass 1994c).

Improvement of cognitive function may be connected to processes influenced by the brain's energy production

In brain tissue, the L-carnitine shuttle mediates translocation of the acetyl moiety from mitochondria into the cytosol and thus contributes to the synthesis of acetylcholine and acetylcarnitine (Montgomery 2003; Nalecz 1996). Acetyl-L-carnitine can traverse the blood-brain barrier and modulate phospholipid metabolism, synaptic morphology, and synaptic transmission, and can enhance the synthesis and release of macromolecules such as neurotrophic factors, neurohormones, and multiple neurotransmitters (Benton 2004; Pettegrew 2000; Virmani 2004). These actions have stimulated interest in its effects on cognition.

Why it is important to do this review

People are interested in maintaining and improving cognitive function for several reasons, including a better quality of life and professional success. L-carnitine has been assessed as a cognitive-enhancing agent that can be supplied as a nutritional aid. Its

use in cognitively impaired people has been reviewed (Hudson 2003; Montgomery 2003; Spagnoli 1991). This systematic review of efficacy and safety aimed to carefully examine the evidence and establish whether it is acceptable for use in people without cognitive impairment for cognitive enhancement.

OBJECTIVES

To assess the efficacy and safety of L-carnitine for the enhancement of cognitive function in people without cognitive impairment.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) or quasi-RCTs in which L-carnitine or its derivatives (acetyl-L-carnitine (ALC) or propionyl-L-carnitine (PLC)) were given with the intention of enhancing cognitive function and were compared with a placebo or no-treatment control group. Trials could have a parallel-group or cross-over design.

Types of participants

People with intact cognition of any age and either gender were eligible. All participants had no self reported history or evidence of neurologic and psychiatric disorders, and they achieved normal scores when assessed by any acceptable cognitive tests.

We excluded people with a diagnosis of mild cognitive impairment or dementia caused by any kind of disorder (e.g. Alzheimer's disease) or other significant illnesses associated with cognitive impairment (such as schizophrenia, depression, or generalised anxiety disorder). People with known carnitine deficiency were also excluded. However, people with illnesses or disorders of other systems (e.g. diabetes mellitus, hypertension) but without existing cognitive impairment were included.

Types of interventions

Active intervention: L-carnitine and its derivative, ALC or PLC, irrespective of formulation, dose, or duration of treatment. We did not include trials assessing a multicomponent preparation or dietary supplement containing L-carnitine or its derivatives.

Control intervention: placebo or no treatment.

Types of outcome measures

Primary outcomes

1. Cognitive function as measured by psychometric tests. These should be validated for use in healthy populations and may include comprehensive neuropsychological test batteries or tests of individual cognitive domains (e.g. memory functions including verbal memory, visual memory, immediate or delayed recall, executive function, attention, etc.).
2. Incidence and severity of adverse effects.

Search methods for identification of studies

We searched for all RCTs and quasi-RCTs of L-carnitine for cognitive enhancement, without language restrictions.

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group's Specialized Register. We used the search terms 'L-carnitine' or 'acetyl-L-carnitine' or 'propionyl-L-carnitine' or 'ALC' or 'PLC' or 'ALCAR' or 'ALPAR'.

ALOIS is maintained by the Information Specialists of the Cochrane Dementia and Cognitive Improvement Group and contains dementia and cognitive improvement studies identified from:

1. monthly searches of a number of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO, and LILACS;
2. monthly searches of a number of trial registers: metaRegister of Controlled Trials, UMIN Japan Trial Register, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (which covers ClinicalTrials.gov, ISRCTN, Chinese Clinical Trials Register, German Clinical Trials Register, Iranian Registry of Clinical Trials, and the Netherlands National Trials Register, as well as others);
3. quarterly search of the Cochrane Central Register of Controlled Trials (CENTRAL);
4. six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings, Index to Theses, Australasian Digital Theses.

To view a list of all sources searched for ALOIS, see 'About ALOIS' on the ALOIS website.

We ran additional separate searches in many of the above sources to ensure that we identified studies involving participants without cognitive impairment and that we retrieved the most up-to-date results. The search strategies can be found in Appendix 1.

Searching other resources

We checked the references of published studies to identify additional trials. We also reviewed the bibliographies of the RCTs identified and contacted the authors to identify additional published or unpublished data where possible.

Data collection and analysis

Selection of studies

Two review authors (MZ and NC) independently evaluated the titles and abstracts identified from the register search. The full text of all potentially relevant studies were retrieved for assessment, and the same two review authors independently determined which trials fit the inclusion criteria. Any disagreements were resolved by discussion or by consulting a third review author (LH) if necessary.

Data extraction and management

Two review authors (MZ and NC) independently extracted data from the trials onto a data extraction form. The form included the study name, type of design, study population size, duration, number of participant withdrawals, participants analysed in the different treatment groups, inclusion and exclusion criteria, intervention (route and dosage), and outcomes. One review author (MZ) entered the data into Review Manager 5 software, and a second review author (NC) checked the data entry (RevMan 5).

Assessment of risk of bias in included studies

We assessed the risk of bias in included studies considering the method of random sequence generation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and any other potential sources of bias. Two review authors (NC and MZ) performed this assessment independently using the Cochrane 'Risk of bias' tool (Higgins 2011a). We then judged all trials on each domain and categorised them as follows:

- low risk of bias for all key domains: low risk of bias;
- unclear risk of bias for one or more key domains: unclear risk of bias;
- high risk of bias for one or more key domains: high risk of bias.

We evaluated the following items for included cross-over trials according to the method of assessing risk of bias in cross-over trials (Higgins 2011a):

1. whether the cross-over design was suitable;
2. whether there was a carry-over effect (the washout period should be no shorter than five half-life durations of each intervention);
3. whether only first-period data were available;
4. incorrect analysis; and
5. comparability of results with those from parallel-group trials.

Measures of treatment effect

We analysed the data using Review Manager 5 software (RevMan 5). We expressed the results as risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes and as mean differences (MDs) or standardised mean differences (SMDs) for continuous outcomes.

Unit of analysis issues

We included only studies randomising individuals. We included cross-over trials as long as either first-period data or data taking account of the cross-over design were available. If a study included repeated measures of the same outcome, then we defined several outcomes based on different periods of follow-up and performed separate analyses. If studies compared more than two intervention groups, we selected the most relevant pair of intervention groups to include in the analyses (Higgins 2011b).

Dealing with missing data

1. We contacted the original investigators to request missing data whenever possible.
2. We recorded the amount of missing data and reasons given.
3. We addressed the potential impact of missing data on the findings of the review in the Discussion section.

Assessment of heterogeneity

We planned to assess heterogeneity among trials by using the Chi^2 test, and to use I^2 values to quantify inconsistency across studies (Deeks 2011; Higgins 2002; Higgins 2003), however heterogeneity was not assessed as no meta-analysis was performed.

Assessment of reporting biases

We assessed the within-study risk of bias from selective outcome reporting for each included trial according to the standard described in the Assessment of risk of bias in included studies section. We tried to obtain the study protocol, and then compared outcomes in the protocol and published report. When the protocol was unavailable, we compared outcome measures listed in the methods section with those reported in the results section. We planned to use funnel plots to investigate the possibility of between-study publication bias if there were sufficient numbers of included studies (at least 10 included in a meta-analysis) (Sterne 2011), but as we included only two trials, we did not use a funnel plot.

Data synthesis

We described the included trials but did not perform any meta-analysis due to insufficient data and differences between the included trials.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were performed due to insufficient data.

Sensitivity analysis

No sensitivity analyses were performed due to insufficient data.

Presentation of results and 'Summary of findings' table

We rated our confidence in the evidence for each outcome based on the GRADE criteria of risk of bias, imprecision, inconsistency between studies, indirectness, and publication bias (Schünemann 2011). We presented the results for reaction time, vigilance, immediate memory, delayed memory, and adverse effects in a 'Summary of findings' table, based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

RESULTS

Description of studies

Results of the search

After a software de-duplication and first assessment by the Cochrane Dementia and Cognitive Improvement Group Information Specialist, 191 results were passed to the review authors for further assessment. We identified 22 potentially eligible records by evaluating the titles and abstracts, but excluded 20 references for 18 studies (see Characteristics of excluded studies) after screening their full text. Only two trials fulfilled the inclusion criteria (see Characteristics of included studies) (Figure 1) (Benton 2004; Muñiz-Pumares 2011).

Figure 1. Study flow diagram.
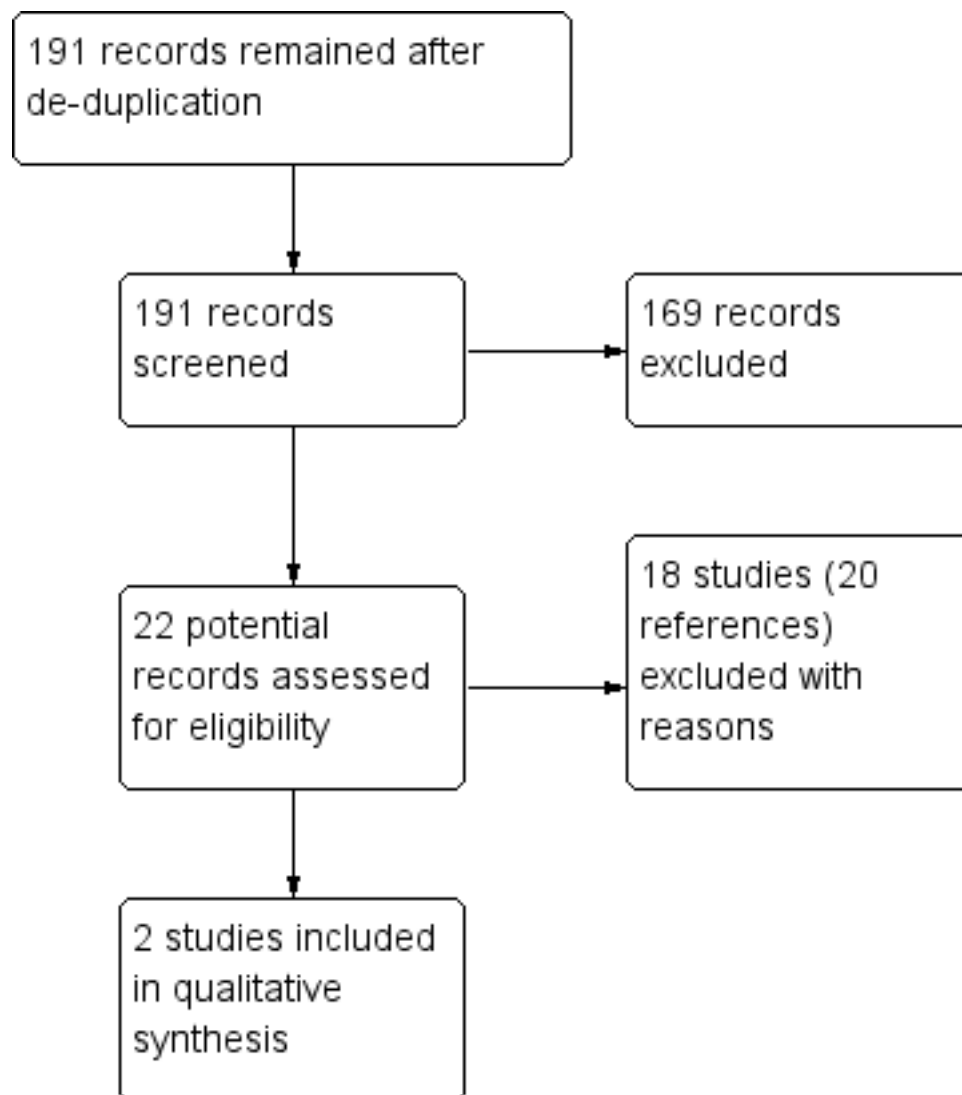
Included studies

The Benton 2004 study aimed to assess the effects of carnitine, lecithin, or their combination on cognition in healthy adult women, while the Muñiz-Pumares 2011 study evaluated the effects of acute supplementation with L-carnitine on exercise performance, cognitive function, and cortisol in healthy adults. The total number of participants in the two included trials was 418. Benton 2004 had a parallel-group design and enrolled 400 participants, but there were four intervention groups, of which only two were relevant to this review, and the actual numbers of participants randomly allocated to each group were unknown (although we can assume it was approximately 100). Muñiz-Pumares 2011 was a cross-over trial that enrolled 18 participants; it was published only as a conference abstract.

The mean age of participants in both trials was around 21 years, indicating that most of them were adolescents or young adults. The Benton 2004 study recruited only women, while the Muñiz-Pumares 2011 study enrolled participants of both sexes. The demographic characteristics were not compared between groups at baseline

in either study, but both trials included healthy volunteers only (Benton 2004; Muñiz-Pumares 2011).

Neither trial clearly described inclusion and exclusion criteria: the Benton 2004 trial recruited female undergraduates by posters, from which we could speculate that they included healthy young people. Muñiz-Pumares and colleagues performed their study among 18 healthy, active men and women, but as this study was published only in abstract form, detailed inclusion and exclusion criteria were not specified (Muñiz-Pumares 2011).

L-carnitine was administered orally in both included trials. The Benton 2004 trial had four comparison arms, treated with lecithin, carnitine, lecithin plus carnitine, or placebo, respectively. We extracted data from the carnitine and placebo groups for the present review. Muñiz-Pumares 2011 compared rhodiola rosea beverage with and without L-carnitine. The Muñiz-Pumares 2011 trial gave participants a single dose of 500 mg of L-carnitine, while Benton and colleagues gave their participants 500 mg of carnitine a day, in two divided doses, for three continuous days (Benton 2004).

Neither trial report mentioned participant withdrawal or loss to follow-up.

Our primary efficacy outcome was cognitive function. Both included studies evaluated cognitive function, but the instruments used to evaluate it varied. The Benton 2004 study used recall of word list, reaction times, and an information-processing task. The Muñiz-Pumares 2011 study assessed cognition using Rapid Visual Information Processing (RVP), Visual Recognition Memory (VRM), and the Stroop Colour-Word Test.

Only one of the included trials referred to side effects associated with L-carnitine (Benton 2004).

Excluded studies

We excluded 18 potentially relevant studies for the following reasons: not an RCT or a quasi-RCT according to the full text (Salvioli 1994; Vecchi 1990); enrolled participants with cognitive dysfunction or illnesses associated with cognitive impairment (Bonavita 1986; Cipolli 1990; Malaguarnera 2007; Malaguarnera 2008; Malaguarnera 2014; Mantero 1989; Martinotti 2011; Pueschel 2006; Vecchi 1990; Warner 1997); included participants with known carnitine deficiency (Cruciani 2009); used interventions other than L-carnitine or its derivatives alone (Chan 2010; Hakkou 1990; Hoffman 2010; Yonei 2008); did not evaluate any of the outcome measures specified in our protocol (Cavallini 2004; Martinotti 2011; Sugino 2007).

Risk of bias in included studies

Both trials reported little or no information to allow accurate assessment of the risk of bias (see Characteristics of included studies; Figure 2) (Higgins 2011a).

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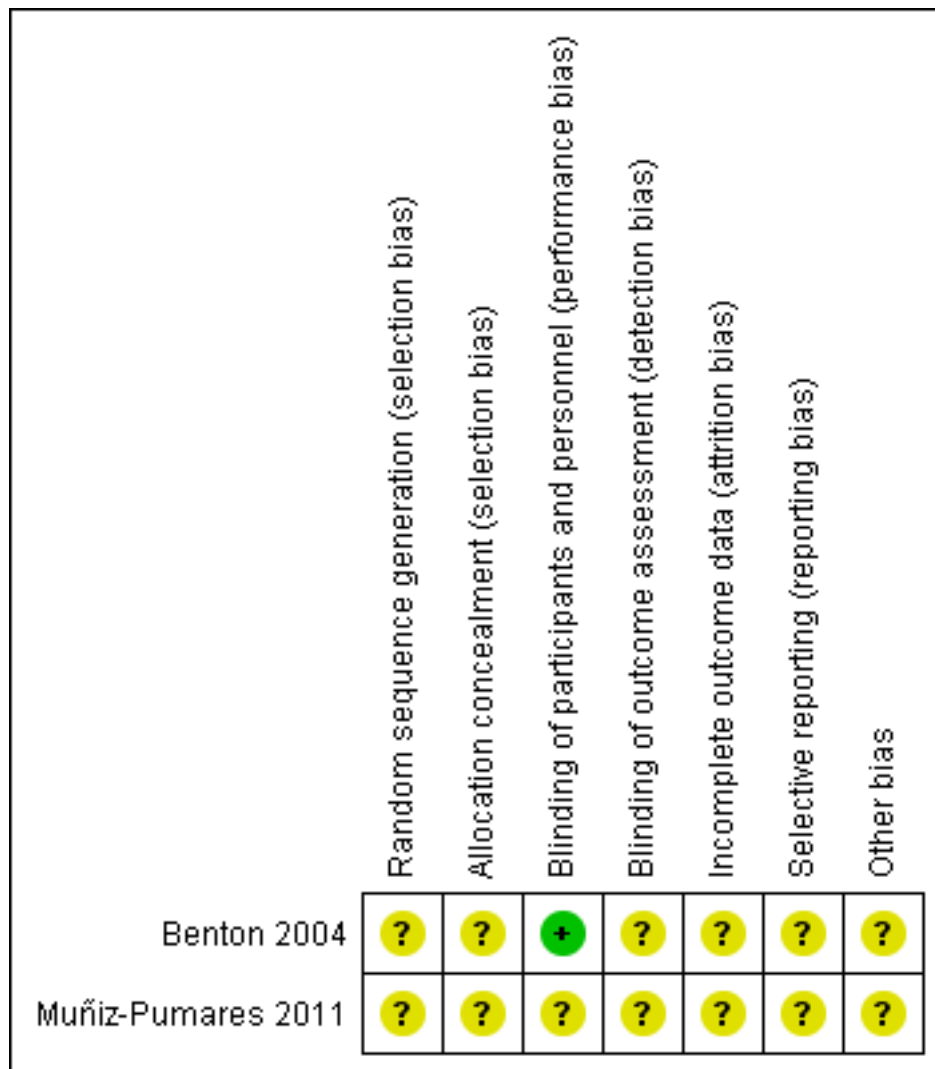
Allocation

Benton 2004 had a parallel-group design and stated that participants were allocated randomly to one of the four intervention groups. Muñiz-Pumares 2011 had a cross-over design and stated that the interventions were given to each participant in random order. However, neither study provided sufficient

information about the methods used for random sequence generation or allocation concealment.

Blinding

Both trials stated they were double-blind, but we could not judge who was blinded in practice (participants, personnel involved in treatment, or efficacy evaluators) according to the study reports. We could only speculate that the participants and treatment implementers may have been blinded to the interventions administered to participants in the Benton 2004 trial, because placebos or active supplements were contained in similar capsules, and all participants were asked to guess what kind of ingredients had been consumed at the end of the study; whether the efficacy evaluators were also blinded was not specified. The Muñiz-Pumares 2011 study only briefly referred to blinding in broad terms as "double-blind", with no other relevant information available specifying who was blinded.

Incomplete outcome data

In both trials the study duration was very short (one day in Muñiz-Pumares 2011 and three days in Benton 2004). Such a short study duration is likely to imply small numbers of participants lost to follow-up. However, the reports did not mention missing data or the use of intention-to-treat analysis. We considered that there was insufficient information to judge the risk of attrition bias due to incomplete outcome data.

Selective reporting

Protocols were not available for either trial. Both trials used multiple measures of cognitive function, but neither specified primary and secondary outcomes. We considered the risk of bias due to selective reporting to be unclear for both studies. We did not perform funnel plots to investigate the possibility of publication bias because only two trials were included.

Other potential sources of bias

We considered another potential source of bias for both trials, that is participants' demographic characteristics and their cognitive functional state were not compared at baseline, therefore we were unsure about the comparability between groups. In the cross-over study (Muñiz-Pumares 2011), there was no discussion of an appropriate washout period or of possible carry-over effects.

Effects of interventions

See: **Summary of findings for the main comparison** L-carnitine compared to placebo for cognitive enhancement in people without cognitive impairment

Primary outcomes

Cognitive function

Both included trials assessed cognitive function as one of the primary efficacy outcomes, but the instruments used and the types of data differed between trials. Benton and colleagues evaluated several domains of cognitive function, including reaction times, attention, and short-term memory, using a battery of tests. Means and standard deviations for each outcome measure were listed, but the report did not specify the numbers of participants in each experimental group, and our attempt to obtain this information from the trial authors failed (although we can assume the number

of participants receiving L-carnitine or placebo was approximately 200). From the reported data, we calculated the MD and 95% CI for each efficacy outcome. We found no evidence that three days of carnitine (500 mg daily) administration had any effect on the above cognitive functions compared to placebo (reaction time task with one, two, four, or eight potentially illuminated lamps, respectively (Benton 2004; Jensen 1987): MD -6.00, 95% CI -18.00 to 6.00, P = 0.33; MD -2.00, 95% CI -13.02 to 9.02, P = 0.72; MD 0.00, 95% CI -11.95 to 11.95, P = 1.00; MD -5.00, 95% CI -23.18 to 13.18, P = 0.59; vigilance test: MD -1.20, 95% CI -3.06 to 0.66, P = 0.21; immediate memory: MD -1.00, 95% CI -2.07 to 0.07, P = 0.07; delayed memory: MD -0.90, 95% CI -1.97 to 0.17, P = 0.10) (Summary of findings for the main comparison) (Benton 2004).

The other trial was only reported as an abstract (Muñiz-Pumares 2011). Its authors stated that they found no significant differences in the cognitive variables they measured between L-carnitine and placebo treatment periods (P > 0.05), but the actual data were unavailable.

As most of our judgements about risk of bias were 'unclear', we considered that there was serious concern about risk of bias in these studies. In addition, because the results came from single small studies, we also considered that there was serious concern about the precision of the results. Furthermore, both trials had very short follow-up periods to observe change in cognitive function in people without cognitive impairment, therefore we also had serious doubts about the directness of the evidence to answer the healthcare questions of the present review. Finally, as only two trials were included, both of which were published in English, we were unable to exclude the possibility of publication bias. Hence, we judged all of the available evidence to be of very low quality according to GRADE criteria (Summary of findings for the main comparison) (Atkins 2004; Schünemann 2011), meaning that we are unable to draw any conclusions about efficacy from this evidence.

Incidence and severity of adverse effects

We planned to categorise adverse events into 'serious' or 'not serious' subtypes. Serious adverse events were those leading to death; were life-threatening; required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability; or any important medical event that might have jeopardised the participant or required intervention to prevent it. We considered all other adverse events to be non-serious (ICHEWG 1997). Only one of the included trials assessed adverse effects of L-carnitine administration (Benton 2004). Benton 2004 stated that 92% of participants reported no side effects and that the numbers of participants who had some minor reaction (e.g. tiredness, hunger, headache, or stomachache) were similar amongst the experimental groups. The other trial did not provide any relevant information (Muñiz-Pumares 2011).

We also judged this evidence to be of very low quality, based on several GRADE considerations, as mentioned above: risk of bias, imprecision, and indirectness (Summary of findings for the main comparison), therefore we can draw no conclusions about adverse effects of L-carnitine when used in cognitively healthy people.

D I S C U S S I O N

L-carnitine seemed to be a promising intervention for treating or preventing cognitive impairment based on its pharmacological

actions, but its efficacy as a cognitive enhancer for healthy people was uncertain, thus prompting the present systematic review. We have done our best to collect and extract all possible data to conduct a more complete systematic analysis, however relevant evidence was lacking.

Summary of main results

We included only two trials in the present systematic review, both of which administered L-carnitine to cognitively healthy people orally and assessed cognitive function after treatment.

Both trials reported no significant difference between L-carnitine and placebo for a variety of cognitive test scores, but no meta-analysis could be performed due to obviously different designs, methods, study periods, inconsistent outcome measures, and unavailable data.

One trial reported a small number of adverse effects, none of which was serious. The incidence of adverse effects was stated to be similar between intervention groups, but detailed data were not provided.

Overall completeness and applicability of evidence

Both studies included healthy young people. Treatment durations were very short - either a single dose, in Muñiz-Pumares 2011, or a continuous three-day treatment period, in Benton 2004 - and no follow-up after the end of treatment was performed. The studies were therefore unable to address the question of lasting cognitive effects.

Quality of the evidence

Due to inadequate reporting, we judged the risk of bias in all or almost all domains in both studies to be unclear. Overall, we considered the available evidence to be of very low quality due to potential risk of bias, imprecision, and indirectness.

Potential biases in the review process

We were unable to exclude the possibility of publication bias.

Agreements and disagreements with other studies or reviews

The purpose of treatment and the methods needed to evaluate cognitive effects in people without cognitive impairment are different from those of studies aiming to treat people who already have, or are at high risk of, cognitive impairment, but the mechanisms of the effects of L-carnitine on cognitive function

may be to some extent similar. Several studies have reported that L-carnitine can improve cognitive function or reduce the rate of cognitive deterioration in people with Alzheimer's disease/mild cognitive impairment (Montgomery 2003; Spagnoli 1991; Thal 1996), Parkinson's disease (Puca 1990), hepatic encephalopathy (Cecere 2002; Malaguarnera 2013), and chronic alcoholism (Tempesta 1990). However, other good-quality trials or meta-analyses did not find any efficacy of L-carnitine in treating people with Alzheimer's disease/mild cognitive impairment (Hudson 2003; Thal 2000).

Other trials have examined the effect of ingestion of nutritional supplements containing L-carnitine and other ingredients, and have concluded that the supplements could maintain cognitive function in healthy participants compared to placebo, but the efficacy of L-carnitine alone was not evaluated, and relevant data could not be extracted from those trials (Chan 2010; Hoffman 2010). It is therefore not possible to draw any conclusions from these studies about L-carnitine specifically.

L-carnitine has also been used as an alternative or additional treatment for some conditions besides cognitive impairment, such as heart disease, kidney disease, mood disorders in the elderly, and peripheral neuropathies. Its efficacy for these conditions is also not well supported by evidence and is controversial, but most studies have found that its use in humans is relatively well tolerated without serious adverse effects (Hudson 2003; Malaguarnera 2012; Montgomery 2003; Wang 2014).

AUTHORS' CONCLUSIONS

Implications for practice

Due to the limited number of included trials, short-term treatment, and inadequate reporting, we were unable to draw any conclusions about the efficacy or safety of L-carnitine for cognitive enhancement in healthy adults.

Implications for research

Well-designed, randomised, placebo-controlled trials of L-carnitine with longer-term follow-up are still needed to evaluate the efficacy and determine the long-term safety of L-carnitine for cognitive enhancement in cognitively healthy people.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Benton 2004

Methods	Randomised: methods of randomisation and allocation concealment were not described
	Double-blind
	Placebo and positive controlled
	Duration: 3 days
Participants	Country: UK
	Number of participants: 400 females
	Age: average 21.8 years
	Inclusion: people in good health and not taking any supplements similar to experiment interventions
	Exclusion: not specified
Interventions	There were 4 treatment groups: carnitine 500 mg per day; lecithin 1.6 g per day; carnitine 500 mg and lecithin 1.6 g per day; placebo. 4 capsules containing 1 of the above agents were given each day, 2 in the morning and 2 in the evening, for 3 days.
Outcomes	• Cognitive tests: recall of word list, reaction times, rapid information-processing task • Mood assessment • Side effects
	Each participant took the battery of cognitive tests 3 times: before and after 3-day treatment, and 30 minutes after they consumed either a placebo or glucose drink after the treatment.
Notes	
Risk of bias	

Cochrane Database of Systematic Reviews

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not described.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	It was stated as double-blind; identical capsules were used for placebo and active supplement, and at end of study all participants were asked to guess what kind of ingredients had been consumed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was stated as double-blind, but details were not provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The experimental duration was short, but the number of participants lost to the study was not specified.
Selective reporting (reporting bias)	Unclear risk	The study protocol is unavailable, so there was insufficient information to permit a clear judgement.
Other bias	Unclear risk	The inclusion and exclusion criteria were not clearly described, and the baseline conditions were not compared between groups, therefore we are unsure about the comparability of the participants.

Muñiz-Pumares 2011

Methods	Randomised cross-over design: methods of randomisation and allocation concealment were not described Double-blind Placebo controlled Duration: only a single dose was given, and the outcome measures were evaluated 45 minutes after the medical beverage ingestion and immediately after exercise
Participants	Number of participants: 18 healthy volunteers with an average age as 21 ± 6 years Inclusion: healthy, active men and women
Interventions	Experimental group: L-carnitine 500 mg + rhodiola rosea beverage (250 mg, 3% Rosavin) Control group: placebo + rhodiola rosea beverage (250 mg, 3% Rosavin) 250 mL medical beverage was given to each participant 45 min before exercise.
Outcomes	• Computerised cognitive tasks of rapid visual information processing, visual recognition memory, and Stroop Colour-Word • Expired gas and heart rate • Laboratory tests of capillary blood and saliva
Notes	We found only a conference (International Sports Science + Sports Medicine Conference) abstract. We attempted to obtain detailed information but our efforts were unsuccessful.

Muñiz-Pumares 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	We were unable to obtain detailed methods.
Allocation concealment (selection bias)	Unclear risk	We were unable to obtain detailed methods.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	We were unable to obtain detailed methods.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	We were unable to obtain detailed methods.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	We were unable to obtain details.
Selective reporting (reporting bias)	Unclear risk	We were unable to obtain details.
Other bias	Unclear risk	We were unable to obtain details.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bonavita 1986	The study included people with senile brain symptoms, which was not a specific neurological disorder but often referred to a number of neuropsychic signs and/or symptoms. According to baseline assessment of cognitive function, at least some of the participants were with cognitive dysfunction at enrolment.
Cavallini 2004	The study mainly evaluated the efficacy of carnitine and androgen for sexual dysfunction, depressed mood, and fatigue. Our evaluation of the full text found no data relevant to the cognition outcomes studied in the present review.
Chan 2010	The experimental intervention was a nutriceutical formulation containing acetyl-L-carnitine as well as other nutritional components, but the efficacy of acetyl-L-carnitine was not evaluated alone, and relevant data could not be extracted from this trial.
Cipolli 1990	The study enrolled mentally impaired elderly, although the severity was mild.
Cruciani 2009	Participants were with known carnitine deficiency.
Hakkou 1990	The intervention studied in this trial was DL-carnitine, which is not L-carnitine or its derivative, as required in our protocol.
Hoffman 2010	The experimental intervention was a multicomponent supplement containing acetyl-L-carnitine.

Study	Reason for exclusion
Malaguarnera 2007	The inclusion criteria did not refer to the level of cognitive function, but the results showed that the average Mini–Mental State Examination of participants was only about 16 points at baseline, which indicated that at least some of the participants were with obvious cognitive dysfunction.
Malaguarnera 2008	The study enrolled elderly people with a diagnosis of chronic fatigue syndrome, the criteria of which included cognitive complaints such as impaired memory or concentration.
Malaguarnera 2014	Participants were with hepatitis C virus infection, which was associated with cognitive impairment and mood disturbance.
Mantero 1989	Participants were geriatric patients with mental deterioration.
Martinotti 2011	The study was designed to evaluate the effects of acetyl-L-carnitine for alcohol-dependent participants, but the main outcome measures were anhedonia, melancholic, and negative symptoms; cognitive function was not measured. Furthermore, alcohol dependence is associated with cognitive impairment.
Pueschel 2006	The study evaluated people with Down syndrome, who had an increased risk of developing cognitive impairment.
Salvioli 1994	The study is not an RCT or a quasi-RCT according to the full text.
Sugino 2007	This trial aimed to evaluate the effects of citric acid and L-carnitine for physical fatigue; there was no mention of evaluation of any types of cognitive functions.
Vecchi 1990	The study is not an RCT or a quasi-RCT according to the description, and the participants were with mild mental impairment.
Warner 1997	All participants had a neurologic disorder, i.e. epilepsy.
Yonei 2008	The experimental intervention was a multicomponent dietary supplement containing L-carnitine.

RCT: randomised controlled trial

A P P E N D I C E S

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
1. ALOIS (www.medi-cine.ox.ac.uk/alois/) [Last searched: 4 November 2016]	l-carnitine or "acetyl-L-carnitine" or "propionyl-L-carnitine" or "ALC" or "PLC" or "ALCAR" or ''ALPAR''.	4
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1946-present (Ovid SP) [Last searched: 4 November 2016]	1. L-carnitine.ti,ab. 2. Carnitine/ 3. (ALC or PLC or ALCAR or ALPAR).ti,ab. 4. "acetyl-l-carnitine".ti,ab.	1106

(Continued)

5. "propionyl-l-carnitine".mp.

6. or/1-5

7. randomized controlled trial.pt.

8. controlled clinical trial.pt.

9. randomi?ed.ab.

10. placebo.ab.

11. drug therapy.fs.

12. randomly.ab.

13. trial.ab.

14. groups.ab.

15. or/7-14

16. (animals not (humans and animals)).sh.

17. 15 not 16

18. 6 and 17

19. (cognit* or memory or mental or brain).ti,ab.

20. dement*.ti,ab.

21. alzheimer*.ti,ab.

22. exp Dementia/

23. (healthy or older or elder* or aged).ti,ab.

24. Aged/

25. seniors.ti,ab.

26. or/19-25

27. 18 and 26

3. Embase	1. L-carnitine.ti,ab.	1322
1974-2016 December 30 (Ovid SP)	2. carnitine/	
[Last searched: 4 November 2016]	3. (ALC or PLC or ALCAR or ALPAR).ti,ab.	
	4. "acetyl-l-carnitine".ti,ab.	
	5. "propionyl-l-carnitine".mp.	
	6. or/1-5	
	7. randomized controlled trial/	
	8. controlled clinical trial/	
	9. randomi?ed.ab.	
	10. placebo.ab.	
	11. randomly.ab.	

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(Continued)

	12. trial.ab.	
	13. groups.ab.	
	14. "double-blind*".ti,ab.	
	15. or/7-14	
	16. 6 and 15	
	17. (cognit* or memory or mental or brain).ti,ab.	
	18. dement*.ti,ab.	
	19. alzheimer*.ti,ab.	
	20. exp dementia/	
	21. (healthy or older or elder* or aged).ti,ab.	
	22. aged/	
	23. seniors.ti,ab.	
	24. or/17-23	
	25. 16 and 24	
4. PsycINFO 1806-December week 4 2015 (Ovid SP) [Last searched: 4 November 2016]	1. L-carnitine.ti,ab. 2. carnitine.mp. 3. (ALC or PLC or ALCAR or ALPAR).ti,ab. 4. "acetyl-l-carnitine".ti,ab. 5. "propionyl-l-carnitine".mp. 6. or/1-5 7. Clinical Trials/ 8. randomi?ed.ab. 9. placebo.ab. 10. randomly.ab. 11. trial.ab. 12. groups.ab. 13. (RCT or CCT).ti,ab. 14. "double-blind*".ti,ab. 15. or/7-14 16. 6 and 15	320
5. CINAHL (EBSCOhost) [Last searched: 4 November 2016]	1. TX L-carnitine 2. (MH "Carnitine") 3. TX ALC OR PLC OR ALCAR OR ALPAR 4. TX "acetyl-l-carnitine"	266

(Continued)

5. TX "propionyl-l-carnitine"

6. S1 or S2 or S3 or S4 or S5

7. TX random*

8. TX placebo*

9. TX (RCT OR CCT)

10. (MH "Clinical Trials") OR (MH "Randomized Controlled Trials")

11. TX "double-blind*"

12. TX "single-blind*"

13. AB groups

14. AB trial

15. S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14

16. S6 and S15

17. TX (cognit* OR memory OR mental OR brain)

18. TX dement*

19. TX alzheimer*

20. (MH "Dementia+")

21. TX (healthy OR older OR elder* OR aged)

22. S17 or S18 or S19 or S20 or S21

23. S16 and S22

6. Web of Science and conference proceedings [Last searched: 4 November 2016]	Topic: (("l-carnitine" OR carnitine) AND (random* OR trial OR placebo OR "double blind*" OR "blinded" OR "single blind*" OR "control group*") AND cognit*) **Timespan:** All years. Search language=Auto	127
7. LILACS (BIREME) [Last searched: 4 November 2016]	"l-carnitine" OR carnitine [Words] and cognition OR cognitive [Words]	3
8. CENTRAL (the Cochrane Library) (Issue 4 of 4, 2015) [Last searched: 4 November 2016]	#1 ALC or PLC or ALCAR or ALPAR #2 "acetyl-l-carnitine" #3 "propionyl-l-carnitine" #4 L-carnitine #5 Carnitine #6 MeSH descriptor: [Carnitine] explode all trees #7 #1 or #2 or #3 or #4 or #5 or #6 in Trials #8 cognit* or memory or mental or brain	730

(Continued)

	#9 healthy or older or elder* or aged	
	#10 dement* or Alzheimer*	
	#11 #8 or #9 or #10 in Trials	
	#12 #7 and #11 in Trials	
9. ClinicalTrials.gov (www.clini-caltrials.gov) [Last searched: 4 November 2016]	Advanced search: Condition: cognition OR cognitive AND Intervention: L-carnitine	2
10. WHO ICTRP Search Portal (apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrials.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry – India; Clinical Research Information Service – Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register] [Last searched: 4 November 2016]	Advanced search: Condition: cognition OR cognitive AND Intervention: L-carnitine	0
TOTAL before de-duplication and first assess		3880
TOTAL after de-duplication and first assess		181

CONTRIBUTIONS OF AUTHORS

Ning Chen and Mi Yang: wrote the draft of the review.

Muke Zhou, Ning Chen, Jian Guo, Jing Xiao: performed data collection, methodological quality assessment, and analyses.

Li He: the corresponding author, developed the proposal, offered expert advice, reviewed and revised the draft, and is responsible for developing and updating the review.

DECLARATIONS OF INTEREST

Ning Chen: None known.
Mi Yang: None known.
Muke Zhou: None known.
Jing Xiao: None known.
Jian Guo: None known.
Li He: None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We planned to calculate a weighted treatment effect using a fixed-effect model or a random-effects model across trials, but no treatment effect across trials could be calculated because there was not enough relevant data.

For missing data, we planned to use an intention-to-treat method or include per protocol data, but neither was done because there was insufficient information.

We planned to conduct sensitivity analyses, heterogeneity assessment, and subgroup analyses, but these were not done because only two trials were included and no meta-analysis could be performed.

We planned to construct a 'Summary of findings' table and to include the results for global cognitive function, memory, executive function, and adverse effects. However, according to the available data from a single study (Benton 2004), we presented the results for reaction time, vigilance, immediate memory, delayed memory, and adverse effects in the 'Summary of findings' table.

NOTES

The protocol was first published in Issue 11, 2011 of the Cochrane Library (Yang 2011), but the title and types of participants have been changed in the updated protocol and review to make the objectives of the review clearer.

INDEX TERMS

Medical Subject Headings (MeSH)

Attention [drug effects]; Carnitine [*therapeutic use]; Cognition [*drug effects]; Memory [drug effects]; Memory, Short-Term [drug effects]; Nootropic Agents [*therapeutic use]; Publication Bias; Randomized Controlled Trials as Topic; Reaction Time [drug effects]

MeSH check words

Humans; Young Adult