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Vitamins C and E for asthma and exercise-induced bronchoconstriction (Review)

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[Intervention Review]

Vitamins C and E for asthma and exercise-induced bronchoconstriction

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ABSTRACT

Background

The association between dietary antioxidants and asthma or exercise-induced bronchoconstriction (EIB) is not fully understood. Vitamin C and vitamin E are natural antioxidants that are predominantly present in fruits and vegetables; inadequate vitamin E intake is associated with airway inflammation. It has been postulated that the combination may be more beneficial than either single antioxidant for people with asthma and exercise-induced bronchoconstriction.

Objectives

To assess the effects of supplementation of vitamins C and E versus placebo (or no vitamin C and E supplementation) on exacerbations and health-related quality of life (HRQL) in adults and children with chronic asthma. To also examine the potential effects of vitamins C and E on exercise-induced bronchoconstriction in people with asthma and in people without a diagnosis of asthma who experience symptoms only on exercise.

Search methods

Trials were identified from the Cochrane Airways Review Group Specialised Register and from trial registry websites. Searches were conducted in September 2013.

Selection criteria

We included randomised controlled trials of adults and children with a diagnosis of asthma. We separately considered trials in which participants had received a diagnosis of exercise-induced bronchoconstriction (or exercise-induced asthma). Trials comparing vitamin C and E supplementation versus placebo were included. We included trials in which asthma management for treatment and control groups included similar background therapy. Short-term use of vitamins C and E at the time of exacerbation or for cold symptoms in people with asthma is outside the scope of this review.

Data collection and analysis

Two review authors independently screened the titles and abstracts of potential studies and subsequently screened full-text study reports for inclusion. We used standard methods as expected by The Cochrane Collaboration.

Main results

It was not possible to aggregate the five included studies (214 participants). Four studies (206 participants) addressed the question of whether differences in outcomes were seen when vitamin C and E supplementation versus placebo was provided for participants with asthma, and only one of those studies (160 children) included a paediatric population; the remaining three studies included a combined total of just 46 adults. An additional study considered the question of whether differences in outcomes were noted when vitamin C and E

supplementation was compared with placebo for exercise-induced asthma; this trial included only eight participants. The randomisation process of the trials were unclear leading us to downgrade the quality of the evidence. Four of the studies were double blind while the other study was single blind.

None of these studies provided data on our two prespecified primary outcome measures: exacerbations and HRQL. Lung function data obtained from the studies were inconclusive. The only studies that provided any suggestion of an effect, and only with some outcomes, were the paediatric study, especially for children with moderate to severe asthma, and the small study on exercise-induced asthma. Even so, this evidence was judged to be at moderate/low quality. Only one study contributed data on asthma symptoms and adverse events, reporting no evidence of an effect of the intervention for symptoms and that one participant in the treatment group dropped out due to cystitis.

Authors' conclusions

It is not possible to draw firm conclusions from this review with respect to the comparison of vitamin C and E supplementation versus placebo in the management of asthma or exercise-induced bronchoconstriction. We found only one study relevant to exercise-induced bronchoconstriction; most included participants came from studies designed to assess the effect of vitamin supplementation on the impact of atmospheric pollutants (such as ozone). Evidence is lacking on the comparison of vitamin C and E supplementation versus placebo for asthma with respect to outcomes such as HRQL and exacerbations, which were not addressed by any of the included studies.

When compared with lung function tests alone, HRQL scores and exacerbation frequency are better indicators of the severity of asthma, its impact on daily activities and its response to treatment in a patient population. These end points are well recognised in good quality studies of asthma management. However, clinical studies of vitamins C and E in the management of asthma using these important end points of exacerbations and effects on quality of life are not available, and evidence is insufficient to support robust conclusions on the role of vitamin C and E supplementation in asthma and exercise-induced breathlessness.

PLAIN LANGUAGE SUMMARY

Vitamins C and E for asthma and exercise-induced breathlessness

Review question

We considered in this review whether vitamins C and E, when taken together daily, may be helpful for people with asthma or exercise-induced breathlessness.

Background

Asthma is an inflammatory lung condition characterised by narrowing of the airways; it is associated with breathlessness, chest tightness, cough and wheezing. The condition affects quality of life. It is estimated that more than 300 million people suffer from asthma, and vitamins C and E have been suggested as supplements that might help to reduce symptoms.

Study characteristics

Five studies comparing vitamins C and E versus placebo (no vitamins C and E) in 214 people with asthma or exercise-induced breathlessness were included in this review. Four studies included adults, and one included children. The very limited number of studies available for review and their different designs meant that we were only able to describe individual studies, rather than pooling their results to determine an average result. In most study reports, the design was not well described; therefore it was impossible to assess the risk of bias for most of the studies. In terms of our key outcomes, very few relevant data were provided by the trial authors.

Key results

We found no indication of benefit in the studies that considered vitamins C and E in relation to asthma. However, at this stage, it is not possible to form any clear conclusions based on these findings, as available evidence is insufficient to allow proper assessment of the use of vitamins C and E as treatment for patients with asthma. Additional well-designed research is required to answer this question.

Quality of the evidence

How patients were allocated to receive either vitamins C and E or placebo was not clearly described in any of the five included studies. This may mean that the studies were not well randomised, which can affect the results. A second concern is that the designs of the studies were different, which means that we cannot be certain that the studies were measuring the same thing. By taking this into account, we judged the evidence in this review overall to be of low to moderate quality.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Vitamin C and E supplementation compared with placebo for asthma

Patient or population: participants with asthma

Intervention: vitamin C and E supplementation

Comparison: placebo

Outcomes	Analyses in study report	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Health-related quality of life	No data available			
Asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroids	No data available			
Lung function (FEV_1, PEF) Follow-up: 12 weeks Hernandez 2009; 12 weeks Romieu 2004; and 5 weeks Trenga 2001	3 narrative reports from relevant studies. No indication of significant benefit for FEV_1 or PEF from vitamin C and E supplementation*	192 participants (3 studies)	⊕⊕⊕⊖ **moderate**[1]	No aggregation was possible *One study (Romieu 2004) however indicated benefit with respect to FEF_{25-75}
Symptoms Follow-up: 12 weeks	Authors reported 'symptom scores were compared between the vitamins C and E versus placebo groups, and there was no statistically significant difference between the two groups (P value 0.93)'	15 participants (1 study)	⊕⊕⊖⊖ **low** **1, 2**	
Adverse events Follow-up: 12 weeks	In one study, a participant in the treatment group dropped out because of the development of cystitis, which was regarded as an adverse event	15 participants (1 study)	⊕⊕⊖⊖ **low** **1, 2**	

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **FEF_{25-75}:** forced expiratory flow from 25% to 75% of vital capacity; **FEV_1:** forced expiratory volume in one second; **PEF:** peak expiratory flow; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Point deducted for risk of bias assessment in included studies with respect to randomisation (all assessed as unclear).
[2]An additional point was deducted for imprecision (data provided by a single small trial).

Summary of findings 2.

Vitamins C and E supplementation compared with placebo for exercise-induced asthma

Patient or population: participants with exercise-induced asthma

Intervention: vitamins C and E supplementation

Comparison: placebo

Outcomes	Analyses in study report	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Health-related quality of life	No data available			
Asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroids	No data available			
Lung function (FEV_1, PEF) Follow-up: 3 weeks	It is unclear in the trial report whether these differences for this outcome refer to improvement between before and after supplementation or, alternatively, between supplementation and placebo	8 participants (1 study)	⊕⊕⊖⊖ **low** **1, 2**	
Adverse events	No data available			

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **FEV_1:** forced expiratory volume in one second; **PEF,** peak expiratory flow; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Point deducted for risk of bias assessment in included studies with respect to randomisation (study assessed as unclear risk of bias) and blinding (study assessed as having high risk of bias).
[2]An additional point was deducted for imprecision (data provided by a single small trial).

BACKGROUND

Description of the condition

Globally an estimated 300 million people suffer from asthma—a figure that is predicted to increase to 400 million by 2025 (WHO 2007). Prevalence of asthma and asthma-related symptoms varies between 1% and 18% in different countries. The annual death rate from asthma is estimated to be around 250,000 (GINA 2012).

The United Kingdom (UK) has one of the highest prevalences of asthma in Europe, with 5.4 million people suffering from this condition, representing one in five households affected (Asthma UK 2013). Of this number, it is estimated that 1.1 million are children, which indicates that one in 11 UK children have asthma (Asthma UK 2013).

Asthma is associated with significant morbidity, and symptoms such as wheeze and breathlessness are more common in the UK than in other major European countries (LAIA 2006). Exercise may induce bronchoconstriction in some people without asthma (exercise-induced bronchoconstriction (EIB)), or exercise may be a trigger for some people with asthma (exercise-induced asthma (EIA)). EIB, which is a common symptom in patients with asthma, is defined as narrowing of the airways in association with exercise; it is accompanied by wheeze and breathlessness and is considered to be a marker of airway inflammation. However a proportion of people with EIB do not have a diagnosis of asthma; therefore in some, this may represent a discreet clinical entity.

Quality of life (Clayton 2005) and financial (Wu 2007) implications are involved for many people with asthma. Although no cure for asthma is known, effective treatment can control the symptoms. Uncontrolled asthma may affect school and work attendance, sleep, exercise tolerance and general quality of life. The fundamental importance of considering the impact of exacerbations (Fitzgerald 2006) and health-related quality of life (HRQL) (Wilson 2012) in relation to chronic asthma has been well appreciated for several years, and these outcomes are commonly assessed in clinical trials of participants with chronic asthma. Asthma carries a mortality risk that can be avoided if symptoms are recognised and controlled. It has been reported that asthma has been responsible for the loss of about 15 million disability-adjusted life-years (DALY) (GINA 2012). Although mortality in asthma is relatively low—with 1143 deaths from asthma reported in the UK in 2010—the UK has a higher mortality rate than other major European countries, and the rate has remained unchanged over the past 20 years despite improvements in treatment and understanding of the condition.

Worldwide, significant use of resources is due directly to the medical cost of asthma and indirectly to time lost from work (GINA 2012). It is reported that the cost of asthma in 2008 was very high in countries such as Canada, Germany, Singapore, Switzerland and the United States of American (USA) (Global asthma report 2011). The UK National Health Service reports that in this high prevalence country, almost £1 billion is spent on asthma each year, and the condition is responsible for 18,000 general practitioner (GP) consultations (Asthma UK 2013; LAIA 2006). More than 65,000 hospital admissions for asthma were recorded In the period between 2005 and 2006 in the UK (NHS 2011), and in the USA approximately 10 million people experience asthma exacerbations each year (Krishnan 2006).

Between 2001 and 2009, the number of people in the USA with asthma increased by 5 million, from 20 to 25 million (CDCP 2011); from 2008 to 2010, higher asthma prevalence rates were reported among Alaskan Native (9.4%), American Indian (also 9.4%), black (11.2%) and multiple-race (14.1%) people than among white people (7.7%), and for Asian people, the rate was 5.2% (CDCP 2011). Prevalence rates are slightly higher among children (10%) than adults (8%) in the USA (CDC 2012; CDCP 2011).

Exercise-induced bronchoconstriction is quite common, with a prevalence of about 7% to 20% in the general population. Among patients who have asthma, up to 80% are thought to have EIB (Randolph 2009). Early identification of EIB and appropriate treatment are recommended. American Thoracic Society guidelines on EIB identified two randomised trials showing that vitamin C (ascorbic acid) supplementation was associated with less decline in forced expiratory volume in one second (FEV_1) after exercise. However the evidence was not sufficiently strong to support robust conclusions, and larger trials were recommended (Parsons 2013).

Description of the intervention

The prevalence of asthma is increasing worldwide; this has largely been attributed to environmental factors (Anderson 2007). Studies have been conducted to identify the environmental triggers that may adversely affect lung function and asthma symptoms.

Some evidence suggests that a lower level of fruit consumption is associated with paediatric wheezing (Chatzi 2007; Okoko 2007). Benefits of fruit intake for adults with asthma have also been reported, suggesting that this aspect of diet may be a modifiable risk factor for asthma symptoms (Patel 2006). By implication, changes in fruit intake may be contributing to increased asthma prevalence.

In the UK, consumption of fresh fruits and vegetables declined between the 1950s and the early 1990s (Seaton 1994). In the USA, fruit and vegetable consumption remained at the same level between 1994 and 2005 (Blanck 2008), and numerous recent examples can be found of national initiatives undertaken to promote consumption of fresh fruits and vegetables both in Europe (EUFIC 2012) and worldwide (WHO 2012).

Vitamin C (ascorbic acid) and vitamin E (alpha-tocopherol) are natural antioxidants that are predominantly present in fruits and vegetables. Low levels of antioxidants in a 'Western' diet have been proposed to be involved in the increased prevalence of asthma in these societies. Consistent with this, low levels of antioxidants, including vitamin E, have been demonstrated in the diet, plasma and lungs of individuals with asthma (Kelly 1999). In addition, worse lung function and increased severity of symptoms have been associated with low levels of vitamin E in plasma (Misso 2005). Some studies have suggested that vitamin E supplements may be beneficial for individuals with asthma when exposed to air pollution (Trenga 2001), and that increasing vitamin E intake may reduce asthma severity and improve lung function (Fogarty 2012). However, another meta-analysis of observational studies found an association between asthma diagnosis and vitamin A or C, but not vitamin E (Allen 2009).

A few studies have looked at the effects of vitamin C supplementation on EIB, EIA or both. It has been proposed that the

benefit of vitamin C supplementation in preventing EIB may be due to its potential anti-inflammatory properties. Previous studies have suggested a lower decline in FEV_1 and reduced symptoms of EIB post exercise following vitamin C administration (Hemila 2013).

How the intervention might work

Dietary antioxidants in the epithelial lining and lining fluids of the lung may be beneficial in reducing oxidative damage (Arab 2002). Misso 2005 reported particularly low vitamin C intake among men with severe asthma and noted that more research is needed to assess the benefits of vitamin C supplementation in patients with severe asthma. Although the same study reported higher levels of vitamin C in women compared with men, the level of vitamin C in both sexes was still lower in people with severe asthma than in those with mild and control cases (Misso 2005).

Inadequate vitamin E intake is associated with airway inflammation (Seaton 1994). Antioxidants usually would mitigate the effects of free radicals and associated oxidative stress in inflammation, but low levels of vitamin E have been demonstrated in the lung airway lining of people with asthma (Kelly 1999), suggesting a role for this deficiency in the inflammatory process. Vitamin E could also play a crucial role in development of foetal lungs and prevention of asthma later in life. Studies looking at maternal vitamin E supplementation have been conducted to check this hypothesis (Devereux 2006). Increased dietary vitamin E intake is noted to be associated with lower immunoglobulin E (IgE) levels, suggesting a protective effect against development of asthma. Therefore vitamin E may have a role as adjunctive therapy in asthma (Fogarty 2000).

A Cochrane review of vitamin C for asthma concluded that evidence from randomised trials is insufficient to allow review authors to ascertain the role of vitamin C in asthma; this review concluded that more robust large-scale studies are required to provide clarity on this issue (Kaur 2009).

Environmental oxidants such as ozone are associated with exacerbations of airway inflammation and reduced lung function (Castillejos 1992; Romieu 1996; Romieu 1997). A growing number of studies have suggested that the combination of antioxidant vitamins C and E could reduce lipid peroxidation and thereby inflammation in lung cells in response to ozone exposure (Niki 1982; Sharma 1992). Nutritional supplement therapy, including vitamins C and E along with other minerals in adults with asthma, has been associated with better asthma control and HRQL scores (Guo 2012). Given this fact, dietary supplementation therapy may provide a cost-effective way of reducing asthma-related morbidity.

Why it is important to do this review

Uncertainties continue regarding the effects of vitamin C and vitamin E antioxidants given in combination, and whether the combination may be more beneficial than either single antioxidant for people with asthma and exercise-induced bronchoconstriction; for this reason, this review will compare the two combined therapies versus each of the single components, as well as vitamin C and vitamin E versus placebo.

OBJECTIVES

To assess the effects of supplementation of vitamins C and E versus placebo (or no vitamin C and E supplementation) on exacerbations and HRQL in adults and children with chronic asthma. To also examine the potential effects of vitamins C and E on exercise-induced bronchoconstriction in people with asthma and in people without a diagnosis of asthma who experience symptoms only on exercise.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs). We included studies reported as full text and those published as abstracts only. We planned to include unpublished data if the opportunity to do so had arisen.

Types of participants

We included adults and children with a diagnosis of asthma, exercise-induced bronchoconstriction or exercise-induced asthma. Results from these populations were reported separately.

Types of interventions

We planned to include the following comparisons.

- Vitamin C and vitamin E versus placebo.
- Vitamin C and vitamin E versus vitamin C alone.
- Vitamin C and vitamin E versus vitamin E alone.

We found no trials that addressed the last two categories.

The primary focus of the review was regular vitamin C and E supplementation to prevent exacerbations and improve HRQL. Short-term use of vitamins C and E at the time of exacerbations or for cold symptoms in people with asthma is outside the scope of this review, and clinical trials addressing these issues would have been excluded; however none were identified.

Types of outcome measures

Primary outcomes

- Health-related quality of life (measured using clinically validated tools).
- Asthma exacerbation, defined as hospital admission or treatment with a course of oral corticosteroids and/or antibiotics.

Secondary outcomes

- Measures of lung function: forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF).
- Asthma symptoms (such as wheeze, dyspnoea).
- Cost.
- Adverse events/side effects.

Reporting in the trial one or more of the outcomes listed here is not an inclusion criterion for this review.

In the separate analysis of trials involving people with a diagnosis of exercise-induced bronchoconstriction (or exercise-induced asthma), we planned to focus on measures of lung function, that is, FEV_1 and PEF.

Search methods for identification of studies

Electronic searches

We identified trials from the Specialised Register of the Cochrane Airways Review Group (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), part of *The Cochrane Library*, as well as MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and through handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). We searched all records in the CAGR using the search strategy presented in Appendix 2.

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We searched all databases from their inception to the present and imposed no restriction on language of publication. The searches were conducted in September 2013.

Searching other resources

We checked reference lists of all relevant primary studies and review articles to look for additional references.

We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and in the grey literature (e.g. through OpenGrey; http://www.opengrey.eu/).

Data collection and analysis

Selection of studies

Two review authors (MW and KS) independently screened titles and abstracts from search results to identify all potential studies for inclusion in the review and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve.' We included trials in which asthma management for both treatment and control groups consisted of similar background therapy. We retrieved the full-text study reports/publications, and two review authors (MW and KS) independently screened the full text, identified studies for inclusion and identified and recorded reasons for exclusion of ineligible studies. We resolved disagreements through discussion or, if necessary, by consulting a third review author (SJM). We identified and excluded duplicate studies and collated multiple reports of the same study, so that each study rather than each report served as the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of included studies.

Data extraction and management

We used a data collection form that had been piloted in previous reviews to document study characteristics and outcome data. Two review authors (SJM and AH) extracted the following characteristics of the included studies.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study settings, withdrawals and date of study.
- Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications and excluded medications.
- Outcomes: primary and secondary outcomes as specified and collected and time points reported.
- Notes: funding for trial and notable conflicts of interest for all trial authors.

Two review authors (SJM and AH) independently extracted outcome data from included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. We planned to resolve disagreements by reaching consensus or by involving a third review author (MW) and found that it was possible to do this entirely by reaching consensus. One review author (SJM) transferred data into the Review Manager (RevMan) file. We double-checked that results were reported correctly by comparing them against the study reports. A second review author (AH) checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (SJM and AH) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion and assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded each potential source of bias as high, low or unclear risk and provided a quote from the study report, together with a justification for our judgement, in the Risk of bias in included studies table. We summarised risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different from that associated with a participant-reported pain scale).

When considering treatment effects, we took into account the risk of bias for all studies that contributed to that outcome. The conclusions of the review accounted for the risk of bias in included studies.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and reported any deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We planned to analyse dichotomous data as odds ratios and continuous data as mean differences or standardised mean

differences and to enter data presented as a scale with a consistent direction of effect. However the opportunity for aggregation of data did not arise.

We planned to describe in narrative format skewed data reported as medians and interquartile ranges, had this issue arisen.

It was planned that when multiple trial arms were reported in a single trial, we would have included only the relevant arms; if two comparisons (e.g. high-dose supplementation vs placebo and low-dose supplementation vs placebo) were combined in the same meta-analysis, we planned to halve the control group to avoid double-counting. However these issues did not arise.

Unit of analysis issues

The unit of analysis was the participant.

Dealing with missing data

We planned to contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as an abstract only); when greater clarity was needed, we requested more information. To our protocol, we added that when this was not possible, and missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by performing a sensitivity analysis (see Sensitivity analysis); however these issues did not arise.

Assessment of heterogeneity

We planned to use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we had identified substantial heterogeneity, we planned to report this and explore possible causes through prespecified subgroup analysis (see Subgroup analysis and investigation of heterogeneity). These issues did not arise, as no opportunities were available for aggregating data from different studies.

Assessment of reporting biases

If we had been able to pool more than 10 trials, we would have created and examined a funnel plot to explore small-study biases.

Data synthesis

We planned to undertake meta-analyses only when this was meaningful (i.e. when treatments, participants and the underlying clinical question were similar enough for pooling to make sense). We planned to use a fixed-effect model and to perform a sensitivity analysis using a random-effects model. Dichotomous outcomes were to be analysed in odds ratios, and continuous data were to be evaluated as mean differences. However, when standard deviations were not reported but could be deduced, we planned to conduct the analysis using the generic inverse variance method. These issues did not arise, as no opportunities were available for aggregating data from different studies.

Summary of findings table

We planned to create a summary of findings table using the following outcomes.

- Health-related quality of life.
- Asthma exacerbation as defined by hospital admission or by treatment with a course of oral corticosteroids.
- Measures of lung function: FEV_1, PEF.
- Asthma symptoms.
- Adverse events.

However, only a small number of outcomes in the included trials were relevant to the above list. When possible, we used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it related to studies contributing to the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and used GRADEpro software. We justified all decisions to downgrade or upgrade the quality of studies by using footnotes, and we made comments to enhance the reader's understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

- Participant age (children younger than 12 years of age vs adults and adolescents).
- Severity of asthma (requirement or no requirement for regular preventive treatment).

We planned to use the following outcomes in subgroup analyses.

- Health-related quality of life.
- Asthma exacerbation as defined by hospital admission or by treatment with a course of oral corticosteroids.
- Measures of lung function: FEV_1, PEF.
- Asthma symptoms.
- Adverse events.

We also planned to use the formal test for subgroup interactions found in Review Manager (Review Manager (RevMan)).

Sensitivity analysis

We planned to carry out the following sensitivity analyses.

- Study quality as defined by standard Cochrane risk of bias criteria.
- Use of random-effects meta-analysis instead of a fixed-effect approach.

Reaching conclusions

We based our conclusions only on findings from a narrative synthesis of included studies in this review, as quantitative aggregation was not possible. We avoided making recommendations for practice, and our implications for future research outline uncertainties in the area and suggest priorities for future studies.

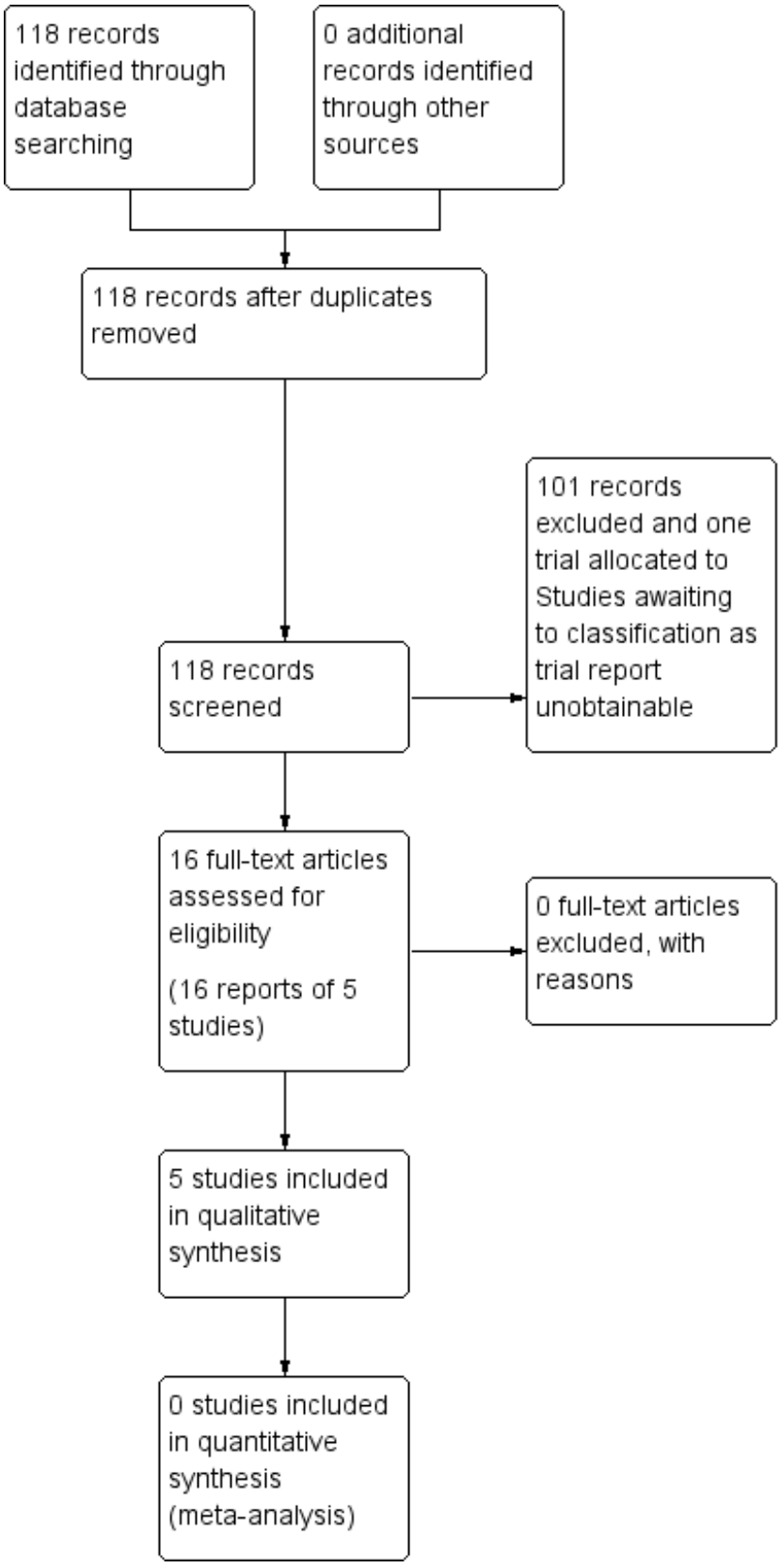
RESULTS

Description of studies

Results of the search

118 studies were identified through electronic searches in September 2013. Five were included (Characteristics of included studies), and one was allocated to Characteristics of studies awaiting classification. For the five that met our criteria for inclusion, 16 records were obtained (three for Hernandez 2009, eight for Romieu 2004 and one each for Kiss 2000; Murphy 2002 and Trenga 2001). The remaining 101 were excluded, and our reasons for exclusion are provided in Characteristics of excluded studies. See Figure 1 for the study flow diagram.

Figure 1. Study flow diagram.



Included studies

Five studies met our inclusion criteria (Hernandez 2009; Kiss 2000; Murphy 2002; Romieu 2004; Trenga 2001). Four focused on vitamins C and E for asthma (Hernandez 2009; Kiss 2000; Romieu 2004; Trenga 2001), and one provided vitamins C and E for EIB (Murphy 2002).

A total of 214 participants were described (206 for asthma and eight for exercise-induced asthma).

In four studies, the participants were adults, and only one study (Romieu 2004) focused on a paediatric group (160 children).

Considerable variation in the duration of the studies was noted: Hernandez 2009 (12 weeks); Kiss 2000 (two weeks); Murphy 2002 (three weeks); Romieu 2004 (12 weeks); and Trenga 2001 (five weeks). In Trenga 2001, participants were exposed to 0.12 ppm of ozone or to air for 45 minutes during intermittent moderate exercise; therefore only part of the study (data collected during air exposure) was of direct relevance to this review. Romieu 2004 considered vitamin C and E supplementation in the context of environmental exposure to ozone.

Study design

Two of the five studies used a parallel-group design (Hernandez 2009; Romieu 2004) (n = 175), and three used a cross-over design (Kiss 2000; Murphy 2002; Trenga 2001) (n = 39). No data were provided in the trial report of Kiss 2000 that could be added to the review, although it was clear from the trial report that lung function data had been collected.

Population

Variation among the studies was also noted in terms of severity. In the four asthma studies, this ranged from moderate to severe in Hernandez 2009 to mild in Kiss 2000. Severity was unclear in Trenga 2001, and in the paediatric trial (Romieu 2004), approximately half of the children were in the mild category; the condition of the others was moderate to severe (Table 1).

Interventions

Marked heterogeneity was observed in vitamins C and E dosage regimens used in the selected studies. The paediatric study used 250 mg (vitamin C) and 50 mg (vitamin E); in the adult studies, the daily dose of vitamin C in Hernandez 2009 was 2000 mg compared with 500 mg in Trenga 2001. See Table 1.

Excluded studies

Of the 101 excluded records, 92 (92%) were excluded because the study did not include a condition for which participants received supplementation of vitamins C and E in combination. Eight studies (8%) were excluded because the supplementation included interventions, in addition to vitamins C and E (and those additional interventions were not included in the control condition), and an additional study (1%) was excluded as the participants were pregnant women without a diagnosis of asthma, and respiratory outcomes were assessed in their infants.

Risk of bias in included studies

Full details of our risk of bias judgements can be found in Characteristics of included studies, and an overview of our judgements can be seen in Figure 2 and Figure 3.

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

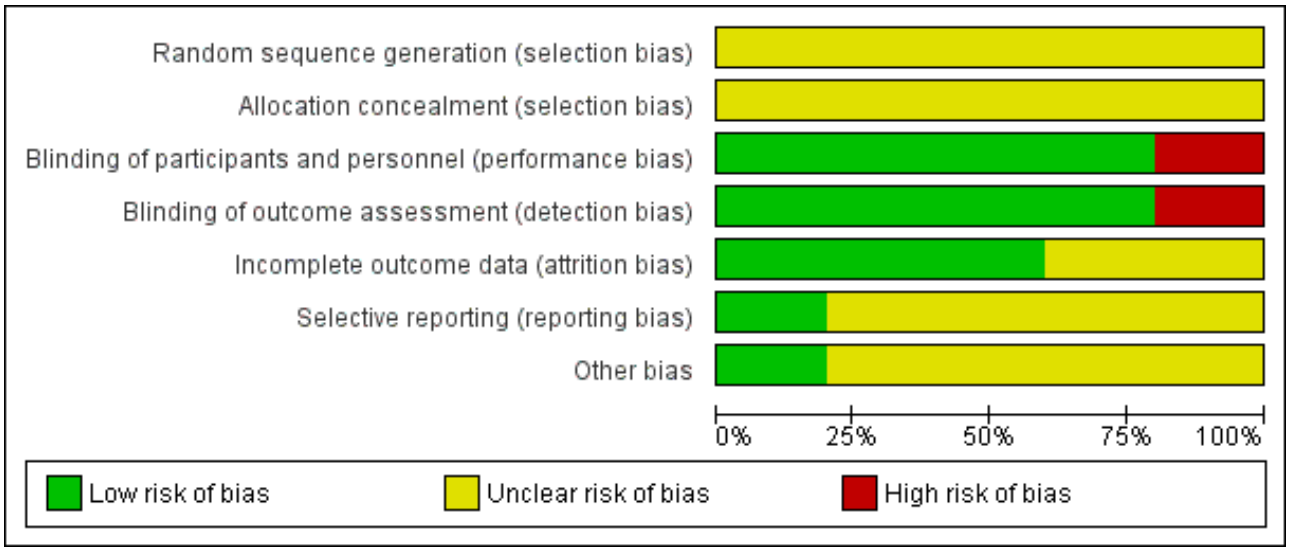
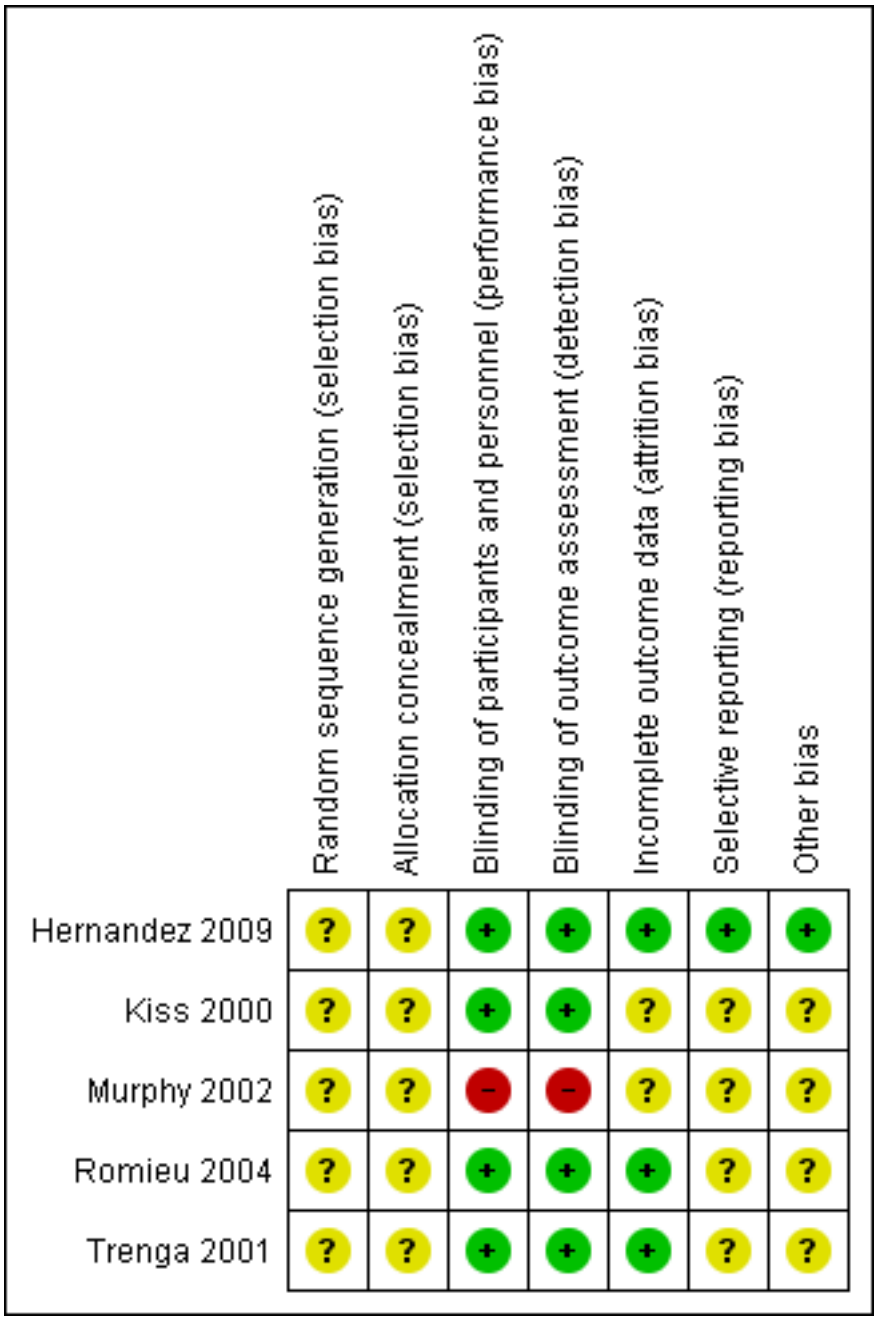


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All five trials were judged as unclear with regard to random sequence generation and allocation concealment.

Blinding

We evaluated four of the five studies as low risk with regard to performance bias (Hernandez 2009; Kiss 2000; Romieu 2004; Trenga 2001). The remaining trial was single-blind; therefore we judged it to be at high risk of bias (Murphy 2002).

Assessment of detection bias led to similar judgements. Performance bias with Hernandez 2009; Kiss 2000; Romieu 2004 and Trenga 2001 was determined to be in the low risk category, whereas Murphy 2002 was judged to be at high risk of bias in this respect.

Incomplete outcome data

We considered three trials to be at low risk of bias in terms of attrition bias (Hernandez 2009; Romieu 2004; Trenga 2001), and we were unclear about the other two trials.

Selective reporting

Only one trial (Hernandez 2009) was assessed as low risk with respect to reporting bias; the remaining four trials were judged as unclear in this respect.

Other potential sources of bias

Hernandez 2009 was assessed as low risk with respect to other bias, and the remaining four trials were judged as unclear in this respect.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

Asthma

Health-related quality of life

We found no HRQL data in the included studies.

Asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroids

We found no asthma exacerbation data in the included studies.

Measures of lung function: FEV_1, PEF

Lung function was apparently recorded but not reported in Kiss 2000, a very small cross-over study with only 14 participants, which is available as a conference abstract.

In Hernandez 2009, a very small study with just 15 participants, FEV_1 was recorded for each participant at baseline, then weekly during the remainder of the trial. Study authors reported, 'there was no significant difference in the cumulative %pred FEV_1 between the vitamins C and E versus placebo groups through to week 12 (P = 0.42).' This result was reported in a way that did not provide sufficient information for incorporation in a meta-analysis.

In Romieu 2004 (160 children), the change in lung function related to naturally occurring environmental exposure to ozone 10 ppb was reported as follows.

- Forced vital capacity (FVC) (mL/10 ppb) vitamin C and E supplement 0.67 (standard error (SE) 1.55), placebo 0.54 (SE 1.64), effect of supplement 0.49 (not significant).
- FEV_1 (mL/10 ppb) vitamin C and E supplement 0.19 (SE 1.35), placebo -0.90 (1.26), effect of supplement 1.09 (not significant).
- Forced expiratory flow 25%-75% (FEF_{25-75}) (mL-s/10 ppb) vitamin C and E supplement 1.01 (SE 2.63), placebo -5.75 (2.36), effect of supplement 6.76 (P value < 0.05).
- PEF (mL-s/10 ppb) vitamin C and E supplement 5.13 (SE 4.36), placebo 2.40 (SE 4.65), effect of supplement 2.73 (not significant).

Trenga 2001 focused on ozone-induced bronchial hyperresponsiveness. Participants were exposed to 0.12 ppm of ozone or to air for 45 minutes during intermittent moderate exercise. Following 45-minute exposures, participants were challenged with two 10-minute inhalations of sulfur dioxide (SO_2) during exercise to assess ozone (O_3)-induced bronchial hyperresponsiveness (BHR): the first at 0.10 ppm and the second at 0.25 ppm. The study was therefore of only partial relevance to this review (in the element for which participants were exposed to air). When participants were exposed to air, no significant difference in pulmonary function was noted (as measured in FVC, FEV_1, FEF_{25-75} and PEF) between vitamins C and E and placebo at the 45-minute end point. This result was reported in a way that did not provide sufficient information for incorporation in a meta-analysis.

The quality of evidence on measures of lung function (with respect to FEV_1 and PEF) as based on GRADE criteria was evaluated as moderate (Summary of findings for the main comparison).

Asthma symptoms

In Hernandez 2009, authors reported that 'symptom scores were compared between the vitamins C and E versus placebo groups, and there was no statistically significant difference between the two groups (P = 0.93).' Using GRADE criteria, we judged the quality of evidence on this outcome as low (Summary of findings for the main comparison).

Cost

We found no economic data related to this outcome in the included studies.

Adverse events

In Hernandez 2009, one participant in the treatment group dropped out following the development of cystitis, which was regarded as an adverse event. None of the other studies reported any adverse event data. The quality of evidence on this outcome as based on GRADE criteria was evaluated as low (Summary of findings for the main comparison).

Withdrawals

Little evidence of high withdrawal rates was found. In Trenga 2001, none of the 17 participants withdrew; in Hernandez 2009, one of the 15 participants withdrew; in Romieu 2004, two of the 160 children withdrew and in the remaining two studies—Kiss 2000 (14 participants) and Murphy 2002 (eight participants)—no mention is made of any withdrawals.

Exercise-induced asthma/bronchoconstriction

Health-related quality of life

We found no HRQL data in Murphy 2002.

Asthma exacerbation as defined by hospital admission or treatment with a course of oral corticosteroids

We found no asthma exacerbation data in Murphy 2002.

Measures of lung function: FEV_1, PEF

In Murphy 2002,,a very small study with only eight participants with exercise-induced asthma, no differences in pulmonary function between vitamins C and E and placebo were detected during exercise with supplementation. However, study authors report that vitamins C and E 'led to significant improvements (P < 0.05) in pulmonary function' of EIA participants at the following times post exercise.

- Five minutes [FVC (4.7 ± 1.0%); FEV_1 (9.0 ± 1.9%); PEF (10.5 ± 2.0%); $FEF_{25–75}$ (17.5 ± 3.5%)].
- 15 minutes [FVC (3.5 ± 2.8%); FEV_1 (10.9 ± 2.6%); PEF (22.0 ± 4.2%); FEF_{25-75} (25.9 ± 4.9%)].
- 30 minutes [FVC (2.1 ± 0.5%); FEV_1 (7.0 ± 1.5%); PEF (4.6 ± 3.1%); FEF_{25-75} (14.6 ± 2.3%)].

It is unclear whether these differences refer to an improvement between before and after supplementation or, alternatively,

between supplementation and placebo. The quality of evidence on this outcome as based on GRADE criteria was evaluated as low (Summary of findings 2).

Asthma symptoms

We found no symptom data in Murphy 2002.

Cost

We found no economic data related to this outcome in the included study.

Adverse events

Murphy 2002 did not report adverse event data.

Withdrawals

No withdrawals were reported in Murphy 2002.

DISCUSSION

Summary of main results

Only five studies met our inclusion criteria (Hernandez 2009; Kiss 2000; Murphy 2002; Romieu 2004; Trenga 2001). Four of these studies were performed in adults (Hernandez 2009; Kiss 2000; Murphy 2002; Trenga 2001); all were small, with the largest trial including 17 participants. The heterogeneous design and structure, dosing regimen and selection of end points in these studies meant that collating results was not possible, and only individual descriptions of the studies were possible. ..

Hernandez 2009 reported no differences in FEV_1 among those receiving vitamin C and E supplementation versus placebo

Only one study (Murphy 2002) looked at the response to vitamin C and E supplements in EIA and showed no effect on lung function, but outcomes important to participants such as quality of life, adverse events and exacerbations were not reported.

Although one study recorded symptom scores, showing no difference between those receiving vitamin supplements and those given placebo (Hernandez 2009), it is disappointing to note that no study looked at HRQL scores as a primary outcome measure. In addition, the important clinical outcome of exacerbation rate has not been studied in any of these trials.

The only trial involving paediatric participants was the largest, with 160 participants (Romieu 2004). End points included responses of inflammatory markers such as interleukin (IL)-6 and IL-8 and forced expiratory flow rates in response to ozone exposure, however these outcomes were not listed in our prespecified outcomes for this systematic review and are therefore not included here. Although it was reported that vitamin C and E supplementation was associated with changes in these indices compared with placebo, no other clinical outcomes such as effects on symptoms, quality of life or exacerbations were reported.

Overall completeness and applicability of evidence

The primary outcomes prespecified in our protocol for this review (exacerbation rates and HRQL) are important in evaluating the impact of treatment in relation to ongoing asthma management. They are outcomes of direct relevance to people with asthma. The absence of any information relevant to these clinically significant end points hampers any interpretation of how useful vitamins C and E, given in combination, may be for asthma and exercise-induced bronchoconstriction. Only one study provided evidence in relation to asthma symptoms (Hernandez 2009), and these investigators described no advantage between vitamin C and E supplementation and placebo in this respect; however, this is a very small study, and evidence provided is inadequate to support any robust conclusions on this particular issue.

Measures of lung function were used in all five of the included studies but were reported in only four; Kiss 2000 mentioned measuring lung function, but these results are not included in the trial report (a short conference abstract). We are mindful that with the exception of Romieu 2004, the studies were small, and as a group they were disparate in design. It is not possible to draw conclusions about overall clinical effectiveness on the basis of the results.

No randomised controlled studies have compared vitamins C and E versus vitamin C alone, or versus vitamin E alone.

Quality of the evidence

Most of the trials were very small, and one (Trenga 2001) was only partially relevant to the review, as the main focus was on ozone-induced bronchial hyperresponsiveness, and we were limited to reporting only one aspect of the study, in which participants were tested whilst exposed only to air. One study, reported as a conference abstract only, reported none of our prespecified outcomes (Kiss 2000). The one study that was relevant to EIA included only eight participants (Murphy 2002), and clearly no firm conclusions can be drawn in this area.

In relation to vitamins C and E for asthma, the trials provided data for only two outcomes prespecified in our protocol: symptoms (Hernandez 2009) and lung function (Hernandez 2009; Romieu 2004; Trenga 2001). In terms of vitamins C and E for exercise-induced asthma, Murphy 2002 provided data for only one outcome prespecified in our protocol.

We are mindful of the limitations of the five studies in relation to our risk of bias assessment and the overall quality of evidence. The limitations of these studies with respect to our assessment of the quality of the evidence Summary of findings for the main comparison; Summary of findings 2 is most noticeable in terms of randomisation (all included studies were assessed as unclear in this respect) and imprecision (were data were provided by a single small trial). On balance we decided to not make additional deductions to reflect indirectness as it was felt that with respect to these particular studies such a judgment was too subjective, and the lack of opportunity for statistical aggregation led us to conclude that judgments relating to inconsistency were not relevant.

Potential biases in the review process

We acknowledge the potential for publication bias in this review. It is possible that failure to identify unpublished negative trials may exaggerate the effects of vitamin C and E supplementation; conversely, failure to identify unpublished positive trials in this area may have led to underestimation of treatment benefits. We are mindful that as this stands, in this review, firm conclusions in either direction cannot be made owing to the paucity of data.

To the best of our knowledge, a very significant proportion of the trials meeting our inclusion criteria in addressing this clinical question have been identified through comprehensive systematic database searches of the Cochrane Airways Review Group Specialised Register. Study selection bias is possible; we tried to address this issue by having two review authors independently evaluate all identified studies. We were careful to ensure that assessment of trials in relation to our inclusion criteria was conducted on a consistent basis.

Agreements and disagreements with other studies or reviews

This review follows from Milan 2013, which considered vitamin C supplementation alone compared with placebo. Whilst the opportunity to draw from conclusions in Milan 2013 was limited owing to paucity of data, opportunities to do so in the current review are even more minimal. Together, the two reviews highlight the need for further research in this area.

AUTHORS' CONCLUSIONS

Implications for practice

The currently available studies contained in this review provide no convincing evidence to support any recommendation for vitamin C and E supplementation in the management of asthma or exercise-induced bronchoconstriction in adults or in children. Trials to date are small and heterogeneous in design (the largest study with the main focus on reducing the impact of atmospheric pollution) and have variable dosage regimens. None of the clinical trials to date include clinically informative end points such as exacerbation rates and HRQL scores to inform the clinician about the role of these supplements in asthma.

Implications for research

Large, adequately powered, randomised, placebo-controlled trials are required to clarify potential uses for antioxidants such as vitamins C and E in the management and control of asthma. These trials should include clinically important end points such as robust symptom recording, HRQL and exacerbation rates. Evidence from these trials should also inform appropriate dosage regimens and adverse effects of these supplements. Lung function parameters including markers of dyspnoea and changes in spirometry should be recorded.

Similar robust trials are required to clarify the use of supplements in the important subgroup of exercise-induced bronchoconstriction/asthma, including clinically relevant data such as effects on bronchoconstriction, exercise tolerance and quality of life and impact on work and school.

No randomised controlled studies have compared vitamins C and E versus vitamin C alone, or versus vitamin E alone.

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Chris Cates was the Editor for this review and commented critically on the review.

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CHARACTERISTICS OF STUDIES

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

Hernandez 2009

Methods	Randomised, double-blind, parallel-group trial
Participants	People with moderate to severe asthma 18-50 years of age Participants: 6 in intervention arm and 9 in control arm. Completed: 6 (100%) in intervention arm and 8 (89%) in control arm Baseline lung function: mean %predicted FEV_1 (SD not provided in trial report); mean 97.7% in intervention arm; mean 106% in control arm Inclusion criteria: • Confirmed allergy to at least 1 of the following allergen preparations: house dust mite f; house dust mite P; cockroach; tree mix; grass mix; weed mix; mold mix 1; mold mix 2; rat; mouse; guinea pig; rabbit; cat; or dog • Oxygen saturation > 94% at baseline • Systolic blood pressure between 150 and 90 mmHg, diastolic blood pressure between 90 and 60 mmHg • Physician-diagnosed asthma or history of episodic wheezing, chest tightness or shortness of breath consistent with asthma • Airway reactivity as determined by a provocative concentration of methacholine, producing a 20% fall in FEV_1 (PC20 methacholine) of less than 10 mg/mL by the method used, or 12% reversibility of baseline lung function with albuterol therapy for 2 of the 3 measures: FVC, FEV_1, and FEF_{25-75} • Consent to discontinue use of vitamin supplements for the duration of the study • Receiving a stable regimen of maintenance asthma therapy that has not changed within the month before participation Exclusion criteria: • Chronic medical condition that may make vitamin E and vitamin C treatment medically inadvisable (e.g. significant cardiovascular disease, diabetes requiring medication, chronic kidney disease, chronic thyroid disease, coagulation defects) • History of kidney stones • Use of anticoagulants (e.g. warfarin, heparin, clopidogrel) • Pregnant or breastfeeding • Use of inhaled steroids, cromolyn or leukotriene inhibitors (montelukast or zafirkulast) for at least 1 month is not a criterion for exclusion
Interventions	500 mg alpha-tocopherol combined with 2000 mg ascorbate (vitamin E combined with vitamin C), each orally administered daily for 12 weeks versus placebo
Outcomes	Primary outcome measures: sputum cell ascorbate and alpha-tocopherol levels, measured bi-weekly and at week 12 Secondary outcome measures: methacholine reactivity, measured at weeks 6 and 12 Lung function and symptom scores: measured weekly and at week 12 Adverse events Serum and sputum supernatant vitamin C levels Serum and sputum supernatant alpha-tocopherol levels Serum and sputum supernatant and sputum cells, gamma-tocopherol levels

Hernandez 2009 *(Continued)*

	Cumulative total cell count from induced sputum (also by different types)
Notes	Treatments administered daily for 12 weeks Funding: the 2 supplements were provided as a gift from Yasoo Health, Inc (Johnson City, TN)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details included in trial report
Allocation concealment (selection bias)	Unclear risk	No details included in trial report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Protocol states that participants, caregivers and investigator were all blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Protocol states that outcomes assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/15 is a low attrition rate
Selective reporting (reporting bias)	Low risk	All outcomes seem to be reported
Other bias	Low risk	

Kiss 2000

Methods	Randomised, double-blind, cross-over trial
Participants	14 mild steroid-naive asthma participants
Interventions	Viatmin C (1000 mg) plus vitamin E (400 mg) supplementation
Outcomes	Exhaled nitric oxide (NO), carbon monoxide (CO), hydrogen peroxide (H_2O_2), sputum eosinophils, cellular composition of induced sputum, bronchial responsiveness to methacholine and lung function
Notes	Supplementation given for 2 weeks Andras Kiss confirmed that this study was randomised; this information is not clear in the conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear: conference abstract report; no details given. However, our correspondence with trialists confirmed that this was a randomised study

Kiss 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unclear: conference abstract report; no details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported as double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear: conference abstract report; no details given
Selective reporting (reporting bias)	Unclear risk	Unclear: conference abstract report. Lung function was recorded but was not reported in the abstract
Other bias	Unclear risk	No details of washout period

Murphy 2002

Methods	Single-blind, randomised, cross-over trial
Participants	8 clinically diagnosed participants with EIA and 5 healthy controls. Other details unclear (conference abstract with limited information)
Interventions	AsA 500 mg and [alpha]-tocopherol 300 IU (200 mg)[1] (vitamin C and vitamin E) versus placebo daily
Outcomes	Ten-minute exercise bouts at 90% VO_2max were performed every 7 days, with pulmonary function testing (FVC, FEV_1, FEF_{25-75}, PEF) measured before exercise and during recovery at minutes 1, 5, 15 and 30
Notes	Treatments administered daily for 3 weeks (followed by 3 weeks of alternative treatment) Funding: support from American Heart Association and Parker B. Francis Foundation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Conference abstract: limited information
Allocation concealment (selection bias)	Unclear risk	Conference abstract: limited information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind

Murphy 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Conference abstract: limited information
Selective reporting (reporting bias)	Unclear risk	Conference abstract: limited information
Other bias	Unclear risk	No mention of washout period

Romieu 2004

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Participants: 160 total (as described in some reports), but data are provided for only 80 in the intervention group and 78 in the control group Mean age: 8.9 years in intervention and 9.2 years in control Asthma severity: mild 47.5%, moderate and severe 52.5% in intervention arm; mild 58.6%, moderate and severe 41.4% in control arm Particpants' asthma was diagnosed according to National Heart, Lung and Blood Institute criteria Information on environmental tobacco smoke exposure (ETS) was obtained from the baseline questionnaire, which included questions on smokers in the home (mother, father, others) and number of cigarettes smoked per day in the home and in the presence of the child Intervention: • Mother 22.8% • Father 48.2% • Others 19.0% Control: • Mother 15.5% • Father 43.6% • Others 21.0% Research conducted in large public hospital in Mexico City between 1998 and 2000
Interventions	Daily supplement of vitamins (50 mg/d vitamin E and 250 mg/d vitamin C) versus placebo
Outcomes	glutathione (GSx), uric acid, IL-6, IL-8, plasma alpha-tocopherol levels, FEF_{25-75}, FEV_1, FVC data collected at weeks 6 and 12. Subgroup analysis on GSTM1 null genotype versus GSTM1 positivity
Notes	12-Week period with 2 spirometric tests per week Supported by the Mexican Sciences and Technology Council (No. 26206-M), Mexico; the National Center for Environmental Health at the Centers for Disease Control and Prevention, USA; and the Division of Intramural Research of the National Institute of Environmental Health Sciences (ZO1 ES 49019) at the National Institutes of Health, Department of Health and Human Services, USA

Risk of bias

Bias	Authors' judgement	Support for judgement

Romieu 2004 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details included in trial report
Allocation concealment (selection bias)	Unclear risk	Reported as, 'Children were assigned randomly to receive either supplement (vitamin C 250 mg/day and vitamin E 50 mg/day) or placebo in a doubled-blinded manner, informing neither the health personnel at the clinic [n]or the patients of the assignment code.' However no explicit details of allocation concealment were provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo and supplement were presented in similar pills (provided by Roche Laboratory)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo and supplement were presented in similar pills (provided by Roche Laboratory)
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants did not complete follow-up
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias
Other bias	Unclear risk	No apparent indication of other bias

Trenga 2001

Methods	Randomised, double-blind, cross-over study (treatment randomly assigned each day)
Participants	Participants: 17 (cross-over study) (100% completed) Mean age: 27 (SD 6) years Men: 5 (29%) Asthma was documented by participant's medical history and by physician diagnosis Baseline lung function: mean % predicted FEV_1 (SD): 92 (13) Only non-smokers were accepted Used a provocative SO_2 challenge test to select participants sensitive to SO_2. The challenge required the participant to inhale 0.5 ppm SO_2 during 10 minutes of moderate exercise on a treadmill. Spirometry was measured immediately before and after the challenge. The criterion for acceptance was an 8% or greater decrease in $FVC_{l.0}$ from baseline
Interventions	1-Week placebo run-in (blinded) 400 IU (267 mg) vitamin E and 500 mg vitamin C at breakfast versus placebo Bronchodilator, anti-inflammatory treatment permitted Participants were exposed to 0.12 ppm of ozone or to air for 45 minutes during intermittent moderate exercise

Trenga 2001 *(Continued)*

	Following the 45-minute exposures, participants were challenged with two 10-minute inhalations of SO_2 during exercise to assess ozone-induced bronchial hyperresponsiveness (BHR): the first at 0.10 ppm and the second at 0.25 ppm
Outcomes	Percentage change in pulmonary function (FEV_1, FVC, FEF_{25-75} and PEF), each after exposure to air or ozone Plasma vitamin levels Time periods for pulmonary function measures • Before and after 45-minute exposures to air or ozone • Preexposure to post 100-ppb SO_2 challenge • Preexposure to post 250-ppb SO_2 challenge • Difference between 100-ppb and 250-ppb SO_2 challenges In subgroup analyses, asthma severity was defined by clusters derived from screening FEV_1 responses to SO_2
Notes	Once a day, vitamins or placebo for 5 weeks Vitamins and placebo were provided by Roche Vitamins (Parsippany, NJ)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details included in trial report
Allocation concealment (selection bias)	Unclear risk	No details included in trial report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (matched placebo)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind (matched placebo)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all N = 17
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias; however we are unable to assess the completeness of reported outcomes
Other bias	Unclear risk	No washout period: 24 hours deemed to be adequate

[1]"The new recommendations for vitamin E are expressed as milligrams of RRR—tocopherol equivalents. Dietary supplements of vitamin E are labelled in terms of international units (IU). One mg of synthetic vitamin E (all-rac—tocopheryl acetate is equivalent to 1 IU vitamin E, but only 0.45 mg RRR—tocopherol). One mg of natural vitamin E (RRR—tocopherol) provides 1.5 IU" (Hathcock 2005).
Abbreviations:
BHR: bronchial hyperresponsiveness.
CO: carbon monoxide.
EIA: exercise-induced asthma.

ETS: environmental tobacco smoke exposure.
FEF_{25-75}: forced expiratory flow from 25% to 75% of vital capacity.
FEV_1: forced expiratory volume in one second.
FVC: forced vital capacity.
H_2O_2: hydrogen peroxide.
IL: interleukin.
IU: international unit.
NO: nitric oxide.
PC20: 20%.
PEF: peak expiratory flow.
ppb: parts per billion.
SD: standard deviation.
SO_2 challenge: sulfur dioxide challenge.
VO_2max: maximal oxygen uptake.

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

Study	Reason for exclusion
Al-Biltagi 2009	This study did not include a condition for which vitamins C and E were used in combination. The trial was later retracted
Aliyali 2010	This study did not include a condition for which vitamins C and E were used in combination
Anah 1980	This study did not include a condition for which vitamins C and E were used in combination
Anderson 1983	This study did not include a condition for which vitamins C and E were used in combination
Bagnato 1999	This study did not include a condition for which vitamins C and E were used in combination
Baumann 2005	This study did not include a condition for which vitamins C and E were used in combination
Bede 2008	This study did not include a condition for which vitamins C and E were used in combination
Belousova 2006	This study did not include a condition for which vitamins C and E were used in combination
Bensenor 2001	This study did not include a condition for which vitamins C and E were used in combination
Bernorio 1996	This study did not include a condition for which vitamins C and E were used in combination
Cakmak 2004A	This study did not include a condition for which vitamins C and E were used in combination
Carlsten 2011	Includes healthy controls, diesel exhaust–induced symptoms AND not treated with vitamin C+E (treated with *N*-acetylcysteine)
Carlsten 2011a	Includes healthy controls, diesel exhaust–induced symptoms AND not treated with vitamin C+E (treated with *N*-acetylcysteine)
Carlsten 2011b	This study did not include a condition for which vitamins C and E were used in combination
Chazan 1981	This study did not include a condition for which vitamins C and E were used in combination
Clark 2012	This study did not include a condition for which vitamins C and E were used in combination
Cohen 1997	This study did not include a condition for which vitamins C and E were used in combination
Covar 2010	This study did not include a condition for which vitamins C and E were used in combination

Study	Reason for exclusion
Cristofalo 1999	This study did not include a condition for which vitamins C and E were used in combination
Cuomo 2004	Intervention included not just vitamin C+E: The aim was to determine the effects of daily supplementation of vitamins C and E and other antioxidants (Difensil Junior/Humana)
Daniliak 1995	This study did not include a condition for which vitamins C and E were used in combination
Darabi 2013	This study did not include a condition for which vitamins C and E were used in combination
Dauletbaev 2001	This study did not include a condition for which vitamins C and E were used in combination
De Lucia 1991	This study did not include a condition for which vitamins C and E were used in combination
Dunstan 2007	The antioxidant supplement used in the trial included beta-carotene (9 mg/d), vitamin C (1500 mg/d), vitamin E (130 mg/d), zinc (45 mg/d), selenium (76 microg/d) and garlic (150 mg/d) and was not restricted to just vitamins C and E
Echazarreta 2000	This study did not include a condition for which vitamins C and E were used in combination
Echazarreta 2005	This study did not include a condition for which vitamins C and E were used in combination
Ensom 2003a	This study did not include a condition for which vitamins C and E were used in combination
Falk 2005	This study did not include a condition for which vitamins C and E were used in combination
Fogarty 2003	This study did not include a condition for which vitamins C and E were used in combination
Fogarty 2003a	This study did not include a condition for which vitamins C and E were used in combination
Greenough 2010	Intervention is provided for mothers antenatally, and focus of the study is on respiratory outcomes in infants at 2 years of age. Participants do not have diagnosed asthma
Gvozdjakova 2005	Co-enzyme Q10 combined with vitamins C and E in intervention (rather than vitamins C and E in combination alone)
Hosseini 2001a	This study did not include a condition for which vitamins C and E were used in combination
Houdard 1969	This study did not include a condition for which vitamins C and E were used in combination
Jabbari 2005	This study did not include a condition for which vitamins C and E were used in combination
Jahnova 2002	This study did not include a condition for which vitamins C and E were used in combination
Kligler 2011	This study did not include a condition for which vitamins C and E were used in combination
Kolpakova 2007	This study did not include a condition for which vitamins C and E were used in combination
Kordansky 1979	This study did not include a condition for which vitamins C and E were used in combination
Kriukov 2003	This study did not include a condition for which vitamins C and E were used in combination
Kurth 2008	This study did not include a condition for which vitamins C and E were used in combination
Labhe 2001	This study did not include a condition for which vitamins C and E were used in combination

Study	Reason for exclusion
Lau 2004	This study did not include a condition for which vitamins C and E were used in combination
Lipman 1964	This study did not include a condition for which vitamins C and E were used in combination
Lisitsa 2007	This study did not include a condition for which vitamins C and E were used in combination
Ma 2013	The intervention used in this study is the DASH diet (which is broader alone than vitamins C and E in combination)
Malo 1986	This study did not include a condition for which vitamins C and E were used in combination
Mastronarde 2009	This study did not include a condition for which vitamins C and E were used in combination
McEvoy 2013	This study did not include a condition for which vitamins C and E were used in combination
Medvedeva 2002	This study did not include a condition for which vitamins C and E were used in combination
Moreira 2005	This study did not include a condition for which vitamins C and E were used in combination
Moreira 2007	This study did not include a condition for which vitamins C and E were used in combination
Nadi 2012	This study did not include a condition for which vitamins C and E were used in combination
NCT00386178	Non-randomised study, not a study of vitamins C and E
NCT00466596	Non-randomised study, not a study of vitamins C and E
NCT00581048	Non-randomised study, not a study of vitamins C and E
NCT00672529	The formulation proposed in this study comprises vitamins C, E, B6 and B12, magnesium, selenium, quercetin and fish oil in relatively large doses (rather than vitamin C+E alone) versus placebo
NCT00836368	Study of in vitro basophil activation by the allergen *D. farinae* and did not use vitamin C&E together
NCT01317563	The formulation proposed in this study comprises vitamins A, E and C and selenium (rather than vitamins C+E alone) versus placebo
NCT01661530	Study of a dietary soup intervention during pregnancy, did not use vitamin C&E together
Neuman 1999	This study did not include a condition for which vitamins C and E were used in combination
Neuman 2000	This study did not include a condition for which vitamins C and E were used in combination
Nikitin 1993	This study did not include a condition for which vitamins C and E were used in combination
O'Sullivan 2000	This study did not include a condition for which vitamins C and E were used in combination
Olekhnovich 1982	Vitamin E was used alone, not in combination with vitamin C in the intervention arm
Onur 2011	This study did not include a condition for which vitamins C and E were used in combination
Panahi 2012	Intervention contained a range of vitamins and was not limited to vitamins C and E
Panina 2002	Comparison of formoterol versus fenoterol, not vitamin C+E

Study	Reason for exclusion
Pearson 2003	This study did not include a condition for which vitamins C and E were used in combination
Pearson 2004	This study did not include a condition for which vitamins C and E were used in combination
Pearson 2004a	This study did not include a condition for which vitamins C and E were used in combination
Pearson 2005	This study did not include a condition for which vitamins C and E were used in combination
Pennings 1999	This study did not include a condition for which vitamins C and E were used in combination
Peters 2001	This study did not include a condition for which vitamins C and E were used in combination
Prieto 1988	This study did not include a condition for which vitamins C and E were used in combination
Pui 2010	This study did not include a condition for which vitamins C and E were used in combination
Ratanamaneechat 2010	This study did not include a condition for which vitamins C and E were used in combination
Romieu 1998	The formulation used in this study comprised 75 mg vitamin E, 650 mg vitamin C and 15 mg beta-carotene (rather than vitamin C+E alone) versus placebo
Safa 2012	This study did not include a condition for which vitamins C and E were used in combination
Schachter 1982	This study did not include a condition for which vitamins C and E were used in combination
Schertling 1990	This study did not include a condition for which vitamins C and E were used in combination
Shaheen 2007	This study did not include a condition for which vitamins C and E were used in combination
Shimizu 1996	This study did not include a condition for which vitamins C and E were used in combination
Smith 2004b	This study did not include a condition for which vitamins C and E were used in combination
Song 2010	This study did not include a condition for which vitamins C and E were used in combination
Szlagatys 2005	Study of the effect of treatment with inhaled corticosteroids and long-acting beta$_2$-agonists on antioxidative-pro-oxidative balance in children with asthma
Tecklenburg 2007	This study did not include a condition for which vitamins C and E were used in combination
Tug 2007	This study did not include a condition for which vitamins C and E were used in combination
Tunnicliffe 2003	This study did not include a condition for which vitamins C and E were used in combination
Varshavskii 2003	This study did not include a condition for which vitamins C and E were used in combination
Vazquez-Armenta 2012	This study did not include a condition for which vitamins C and E were used in combination
Voitsekhovskaia 2007	This study did not include a condition for which vitamins C and E were used in combination
Wiser 2008	This study did not include a condition for which vitamins C and E were used in combination
Wood 2007	This study did not include a condition for which vitamins C and E were used in combination
Wood 2008	This study did not include a condition for which vitamins C and E were used in combination

Study	Reason for exclusion
Wood 2012	This study did not include a condition for which vitamins C and E were used in combination
Wood 2012a	This study did not include a condition for which vitamins C and E were used in combination
Yamamoto 2013	This study did not include a condition for which vitamins C and E were used in combination

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kurti 2016

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Liu 2003

Methods	No details available on this trial. Information in searches was very limited
Participants	
Interventions	
Outcomes	
Notes	Study report unavailable in 2013

ADDITIONAL TABLES

Table 1. Daily dosage of vitamins C and E

	Baseline asthma severity	Daily dose of vitamin C	Daily dose of vitamin E	Duration	Age
Asthma					
Hernandez 2009	Moderate to severe	2000 mg	500 mg	12 weeks	Adults
Kiss 2000	Mild	1000 mg	400 mg	2 weeks	Adults
Trenga 2001	Unclear	500 mg	400 IU (267 mg)[1]	5 weeks	Adults

Table 1. Daily dosage of vitamins C and E *(Continued)*

Romieu 2004	Approximately half mild and half moderate to severe	250 mg	50 mg	12 weeks	Children
EIA					
Murphy 2002	Participants with clinically diagnosed exercise-induced EIA	500 mg	300 IU (200 mg)[1]	3 weeks	Adults

[1]We used the following conversions to derive milligrams vitamin E from international units (IU): "The new recommendations for vitamin E are expressed as milligrams of RRR—tocopherol equivalents. Dietary supplements of vitamin E are labelled in terms of international units (IU). One mg of synthetic vitamin E (all-rac—tocopheryl acetate is equivalent to 1 IU vitamin E, but only 0.45 mg RRR—tocopherol. One mg of natural vitamin E (RRR—tocopherol) provides 1.5 IU" (Hathcock 2005).

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Review Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PSYCINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards

(Continued)

European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy for Cochrane Airways Review Group Specialised Register

#1 AST:MISC1

#2 MeSH DESCRIPTOR Asthma Explode All

#3 asthma*:ti,ab

#4 #1 or #2 or #3

#5 MeSH DESCRIPTOR Ascorbic Acid

#6 ascorbic* near acid*

#7 vitamin* NEAR C

#8 MeSH DESCRIPTOR Vitamin E

#9 MeSH DESCRIPTOR Tocopherols Explode All

#10 vitamin* NEAR E

#11 *tocopherol*

#12 antioxidant*

#13 anti-oxidant*

#14 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 #4 and #14

[In search line #1, MISC1 denotes the field where the reference has been coded for condition, in this case, asthma]

WHAT'S NEW

Date	Event	Description
12 June 2018	Amended	A search update was run on 9 May 2018 in the Cochrane Airways Trial Register by Elizabeth Stovold (Information specialist, Cochrane Airways). Elizabeth Stovold and Rebecca Normansell (CoEd Cochrane Airways) screened the update search. The search returned 88 records. 37 records were excluded on the basis of title and abstract. One was retrieved in full text. We found one small studies (Kurti 2016) added to Characteristics of ongoing studies. We have decided not to update the review at this point in time.

HISTORY

Protocol first published: Issue 9, 2013
Review first published: Issue 6, 2014

Date	Event	Description
23 March 2015	Amended	Changed plain language summary headings from italics to bold.

CONTRIBUTIONS OF AUTHORS

SJM, AH, KS and MW drafted the protocol. MW and KS independently selected studies for inclusion, with support from SJM; SJM and AH independently extracted the data, and SJM and AH independently evaluated each included study for risk of bias. SJM and AH completed the analyses and results sections. MW, KS, SJM and AH completed the discussion and conclusions sections. SJM and AH assessed the quality of evidence for the summary of findings tables with input from Chris Cates.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

INDEX TERMS

Medical Subject Headings (MeSH)

*Exercise; Antioxidants [*therapeutic use]; Ascorbic Acid [*therapeutic use]; Asthma [*drug therapy] [etiology]; Asthma, Exercise-Induced [drug therapy]; Bronchoconstriction [*drug effects]; Chronic Disease; Randomized Controlled Trials as Topic; Vitamins [*therapeutic use]

MeSH check words

Adult; Child; Humans