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Vitamin C for asthma and exercise-induced bronchoconstriction (Review)

Milan SJ, Hart A, Wilkinson M

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[Intervention Review]

Vitamin C for asthma and exercise-induced bronchoconstriction

Stephen J Milan[1], Anna Hart[2], Mark Wilkinson[3]

[1]Medical School, Lancaster University, Lancaster, UK. [2]Lancaster Medical School, Clinical Research Hub, Lancaster University, Lancaster, UK. [3]University Hospitals of Morecambe Bay NHS Foundation Trust, Lancaster, UK

Contact: Stephen J Milan, Medical School, Lancaster University, Lancaster, UK. s.milan@lancaster.ac.uk.

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ABSTRACT

Background

Dietary antioxidants, such as vitamin C, in the epithelial lining and lining fluids of the lung may be beneficial in the reduction of oxidative damage (Arab 2002). They may therefore be of benefit in reducing symptoms of inflammatory airway conditions such as asthma, and may also be beneficial in reducing exercise-induced bronchoconstriction, which is a well-recognised feature of asthma and is considered a marker of airways inflammation. However, the association between dietary antioxidants and asthma severity or exercise-induced bronchoconstriction is not fully understood.

Objectives

To examine the effects of vitamin C supplementation on exacerbations and health-related quality of life (HRQL) in adults and children with asthma or exercise-induced bronchoconstriction compared to placebo or no vitamin C.

Search methods

We identified trials from the Cochrane Airways Group's Specialised Register (CAGR). The Register contains trial reports identified through systematic searches of a number of bibliographic databases, and handsearching of journals and meeting abstracts. We also searched trial registry websites. The searches were conducted in December 2012.

Selection criteria

We included randomised controlled trials (RCTs). We included both adults and children with a diagnosis of asthma. In separate analyses we considered trials with a diagnosis of exercise-induced bronchoconstriction (or exercise-induced asthma). We included trials comparing vitamin C supplementation with placebo, or vitamin C supplementation with no supplementation. We included trials where the asthma management of both treatment and control groups provided similar background therapy. The primary focus of the review is on daily vitamin C supplementation to prevent exacerbations and improve HRQL. The short-term use of vitamin C at the time of exacerbations or for cold symptoms in people with asthma are 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 expected by The Cochrane Collaboration.

Main results

A total of 11 trials with 419 participants met our inclusion criteria. In 10 studies the participants were adults and only one was in children. Reporting of study design was inadequate to determine risk of bias for most of the studies and poor availability of data for our key outcomes may indicate some selective outcome reporting. Four studies were parallel-group and the remainder were cross-over studies. Eight studies included people with asthma and three studies included 40 participants with exercise-induced asthma. Five studies reported results using

single-dose regimes prior to bronchial challenges or exercise tests. There was marked heterogeneity in vitamin C dosage regimes used in the selected studies, compounding the difficulties in carrying out meaningful analyses.

One study on 201 adults with asthma reported no significant difference in our primary outcome, health-related quality of life (HRQL), and overall the quality of this evidence was low. There were no data available to evaluate the effects of vitamin C supplementation on our other primary outcome, exacerbations in adults. One small study reported data on asthma exacerbations in children and there were no exacerbations in either the vitamin C or placebo groups (very low quality evidence). In another study conducted in 41 adults, exacerbations were not defined according to our criteria and the data were not available in a format suitable for evaluation by our methods. Lung function and symptoms data were contributed by single studies. We rated the quality of this evidence as moderate, but further research is required to assess any clinical implications that may be related to the changes in these parameters. In each of these outcomes there was no significant difference between vitamin C and placebo. No adverse events at all were reported; again this is very low quality evidence.

Studies in exercise-induced bronchoconstriction suggested some improvement in lung function measures with vitamin C supplementation, but theses studies were few and very small, with limited data and we judged the quality of the evidence to be low.

Authors' conclusions

Currently, evidence is not available to provide a robust assessment on the use of vitamin C in the management of asthma or exercise-induced bronchoconstriction. Further research is very likely to have an important impact on our confidence in the estimates of effect and is likely to change the estimates. There is no indication currently that vitamin C can be recommended as a therapeutic agent in asthma. There was some indication that vitamin C was helpful in exercise-induced breathlessness in terms of lung function and symptoms; however, as these findings were provided only by small studies they are inconclusive. Most published studies to date are too small and inconsistent to provide guidance. Well-designed trials with good quality clinical endpoints, such as exacerbation rates and health-related quality of life scores, are required.

PLAIN LANGUAGE SUMMARY

Vitamin C for asthma and exercise-induced breathlessness

Review question

This review considered the question of whether vitamin C may be helpful for people with asthma or exercise-induced breathlessness.

Background

Asthma is an inflammatory lung condition characterised by the narrowing of airways and is associated with wheezing, breathlessness, cough and chest tightness. Vitamin C has been suggested as a possible treatment for asthma.

Study characteristics

Eleven studies on 419 people with asthma or exercise-induced breathlessness were included in this review comparing vitamin C compared to placebo (no vitamin C). Most studies were in adults and one small study was in children. The small number of studies available for review and their different designs meant that we were only able to describe individual studies, rather than pooling the results together to get an average from the trials. The study design was not well described in most study reports and therefore it was impossible to determine risk of bias for most of the studies. There was very little data available in the trials for our key outcomes and this may indicate some selective outcome reporting.

Key results

There was no indication of benefit from the studies that considered vitamin C in relation to asthma. However, it is not possible to form any clear conclusions on the basis of those studies at this stage. The review concludes that there is insufficient evidence currently available to evaluate the use of vitamin C as a treatment in asthma. Larger, well-designed research is needed to provide clearer guidance. There was some indication that vitamin C was helpful in exercise-induced breathlessness in terms of how easily people breathe and their symptoms; however, as these findings were provided by only very small studies they do not provide complete answers to guide treatment.

Quality of the evidence

Details of the way patients were allocated to receive vitamin C or not were not clearly described in 10 of the 11 studies and we considered this carefully in the review in relation to our level of uncertainty in interpreting the results. Taking this into account, together with the imprecision of the results, we judged the estimates of the usefulness of vitamin C as a treatment to be of either low or moderate quality in relation to asthma.

Additionally, for exercise-induced breathlessness the three studies providing data to the review were small and we are mindful of the need to draw very cautious conclusions about the results.

This plain language summary is current as of December 2012.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings: Vitamin C supplementation compared with placebo for asthma

Vitamin C supplementation compared with placebo for asthma

Patient or population: adults and children with asthma

Settings: community

Intervention: vitamin C supplementation

Comparison: placebo

Outcomes	Analyses in study report	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Health-related quality of life (HRQL)	There was no evidence of a difference in HRQL between the groups after 16 weeks treatment as measured by the available SF-36 data	201 adults (1 study)	⊕⊕⊖⊖ **low** [1, 2]	Authors' note: "SF-36 data on physical functioning were incomplete and this section was excluded from analysis"
Asthma exacerbations	No exacerbations in either group	16 children (1 study)	⊕⊖⊖⊖ **very low**[1,3]	
Lung function: FEV1 (ml) (change from 0 to 16 weeks)	MD -11 (95% CI -92 to 70)	201 adults (1 study)	⊕⊕⊕⊖ **moderate**[1]	The 95% CI excludes a clinically important mean difference in FEV1, so the outcome was not downgraded for imprecision
Asthma symptoms (change from 0 to 16 weeks)	MD 0 (95% CI -0.2 to 0.1)	201 adults (1 study)	⊕⊕⊕⊖ **moderate**[1]	
Adverse events	No adverse events in either group	41 adults (1 study)	⊕⊖⊖⊖ **very low**[1,3]	

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.

FEV1: forced expiratory volume in one second; MD: mean difference

[1]One point deducted to reflect selective reporting as data reported by only one trial.
[2]One point deducted because results were not available from all components of the quality of life instrument which reduces our confidence in this result.
[3]We deducted two points for imprecision and unclear randomisation.

Summary of findings 2. Summary of findings: Vitamin C supplementation compared with placebo for exercise - induced bronchoconstriction/asthma

Vitamin C supplementation compared with placebo for exercise-induced bronchoconstriction/asthma

Patient or population: adults and children with exercise-induced bronchoconstriction/asthma

Settings: community

Intervention: vitamin C supplementation

Comparison: placebo

Outcomes	Analyses in study report	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Health-related quality of life (HRQL)	See comment	See comment	See comment	No between-group data reported
Asthma exacerbations	See comment	See comment	See comment	Not reported
Lung function: FEV1 % drop Postexercise	Reported that the maximum percentage drop in FEV1 postexercise on the vitamin C diet was -6.4% (95% CI -12.0% to -0.8%; the effect size using omega-squared (ES) was 0.40) which is indicative of an attenuated EIB response. This was significantly different (P < 0.05) from the maximum drop of -12.9% (95% CI -18.6% to -12.3%) on placebo	8 adults (1 study)	⊕⊕⊖⊖ **low**[1,2]	Cross-over study
Asthma symptoms	Reported that a significant improvement (P < 0.05) in mean asthma symptom scores was observed (6.3; 95% CI 5.8 to 6.8) on the vitamin C diet compared to the placebo diet (5.8; 95% CI 5.1 to 6.2)	8 adults (1 study)	⊕⊕⊖⊖ **low**[1,2]	Cross-over study
Adverse events	See comment	See comment	See comment	Not reported

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.

CI: confidence interval; EIB: exercise-induced bronchoconstriction; FEV1: forced expiratory volume in one second

[1]One point deducted for selective reporting as data provided by only one small trial.
[2]One point deducted to reflect the 'Risk of bias' assessment for this trial (unclear randomisation).

BACKGROUND

Description of the condition

Asthma is a chronic inflammatory airways disease that is associated with episodic symptoms of breathlessness, wheeze and chest tightness. The spectrum of severity of this condition is wide, ranging from no or minimal symptoms to it being disabling or life-threatening. It can affect all age groups although it often starts in children. It is estimated that 300 million people suffer from asthma worldwide and it is predicted that this number will increase to 400 million by 2025 (WHO 2007). Between 2001 and 2009 the number of people in the US with asthma increased by five million, from 20 to 25 million (CDC 2012; CDCP 2011); during 2008 to 2010 there were higher asthma prevalence rates among Alaska Native (9.4%), American Indian (also 9.4%), black (11.2%) and multiple-race (14.1%) people than 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 US (CDCP 2011).

There are quality of life (Clayton 2005) and financial (Wu 2007) implications for many people with asthma. Over 65,000 hospital admissions for asthma were recorded In the period between 2005 and 2006 in the UK (NHS 2011) and in the US approximately 10 million people experience asthma exacerbations each year (Krishnan 2006).

National (e.g. BTS/SIGN 2011; NIH 2007) and international (e.g. GINA 2011) guidelines have been produced for the management of asthma.

Exercise-induced bronchoconstriction describes narrowing of airways during or following exercise and is associated with exercise-induced symptoms of breathlessness, wheeze and cough. It is a common symptom in asthma and is a marker of the presence of airways inflammation. However, up to 20% of individuals with exercise-induced bronchoconstriction do not have a diagnosis of asthma (Parsons 2013) and therefore may represent a discreet clinical entity.

Description of the intervention

There is some evidence that a lower level of fruit consumption is associated with paediatric wheezing (Chatzi 2007; Okoko 2007). Benefits of fruit intake to adults with asthma have also been reported, suggesting that this aspect of diet may be a modifiable risk factor for asthma symptoms (Patel 2006).

In the UK consumption of fresh fruit and vegetables declined between the 1950s and early 1990s (Seaton 1994). In the US fruit and vegetable consumption remained at the same level between 1994 and 2005 (Blanck 2008), and there are numerous recent examples of national initiatives to promote consumption of fresh fruit and vegetables both in Europe (EUFIC 2012) and worldwide (WHO 2012). It has been hypothesised that this reduction in fruit intake in a 'western diet' is associated with the increase in prevalence of asthma and its severity in the developed countries (Misso 2005; Patel 2006). This association may be related to a reduction in intake of the dietary antioxidants, including vitamin C, and hence vitamin C supplementation may ameliorate some of the symptoms of asthma.

How the intervention might work

Vitamin C is a recognised dietary antioxidant and it has been suggested that dietary antioxidants in the epithelial lining and lining fluids of the lung may be beneficial in the reduction of oxidative damage (Arab 2002). A reduction in the intake of naturally occurring antioxidants, such as vitamin C, may result in greater exposure to reactive oxygen species and hence result in inflammation. This may be implicated in the aetiology of asthma or in its severity. Misso 2005 reported particularly low vitamin C intake in males with severe asthma, and noted the need for more research to assess the benefits of vitamin C supplementation in patients with severe asthma. However, the association of dietary antioxidants with asthma severity is not fully understood. Misso 2005 noted, for example, that whilst there was some indication of an association between vitamin C intake and asthma severity in men, data from women, who had a significantly higher vitamin C intake than men in the sample, did not indicate a similar pattern. Alternative mechanisms for the potential action of vitamin C in asthma are its effects on the arachidonic acid pathway (Cohen 1997) or its antiviral properties (Anah 1980).

Why it is important to do this review

This review aims to establish whether vitamin C supplementation may have a positive role in the management of asthma in children and adults.

OBJECTIVES

To examine the effects of vitamin C supplementation on exacerbations and health-related quality of life (HRQL) in adults and children with asthma or exercise-induced bronchoconstriction compared to placebo or no vitamin C.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs). We planned to include studies reported in full text, those published as an abstract only and also unpublished data.

Types of participants

We included both adults and children with a diagnosis of asthma. In separate analyses we considered trials with a diagnosis of exercise-induced bronchoconstriction (or exercise-induced asthma).

Types of interventions

We included trials comparing vitamin C supplementation with placebo, or vitamin C supplementation with no supplementation. The primary focus of the review is on daily vitamin C supplementation to prevent exacerbations and improve HRQL. The short-term use of vitamin C at the time of exacerbations or for cold symptoms in people with asthma are outside the scope of this review and we planned to exclude clinical trials addressing these issues if they were identified in our searches.

Types of outcome measures

Primary outcomes

1. Health-related quality of life.

2. Asthma exacerbation as defined by hospital admissions or treatment with a course of oral corticosteroids.

Secondary outcomes

1. Measures of lung function: forced expiratory flow in one second (FEV1), peak expiratory flow rate (PEFR) including changes related to exercise.
2. Asthma symptoms.
3. Adverse events reported to be related to vitamin C supplementation.

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

In the separate analysis of patients with a diagnosis of exercise-induced bronchoconstriction (or exercise-induced asthma) we focused on measures of lung function: FEV1, PEFR.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group's Specialised Register (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), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We searched all records in the CAGR using the search strategy in Appendix 2.

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO trials portal (www.who.int/ictrp/en/) using search terms based on those in Appendix 2. We searched all databases from their inception up to December 2012, with no restriction on language of publication.

Searching other resources

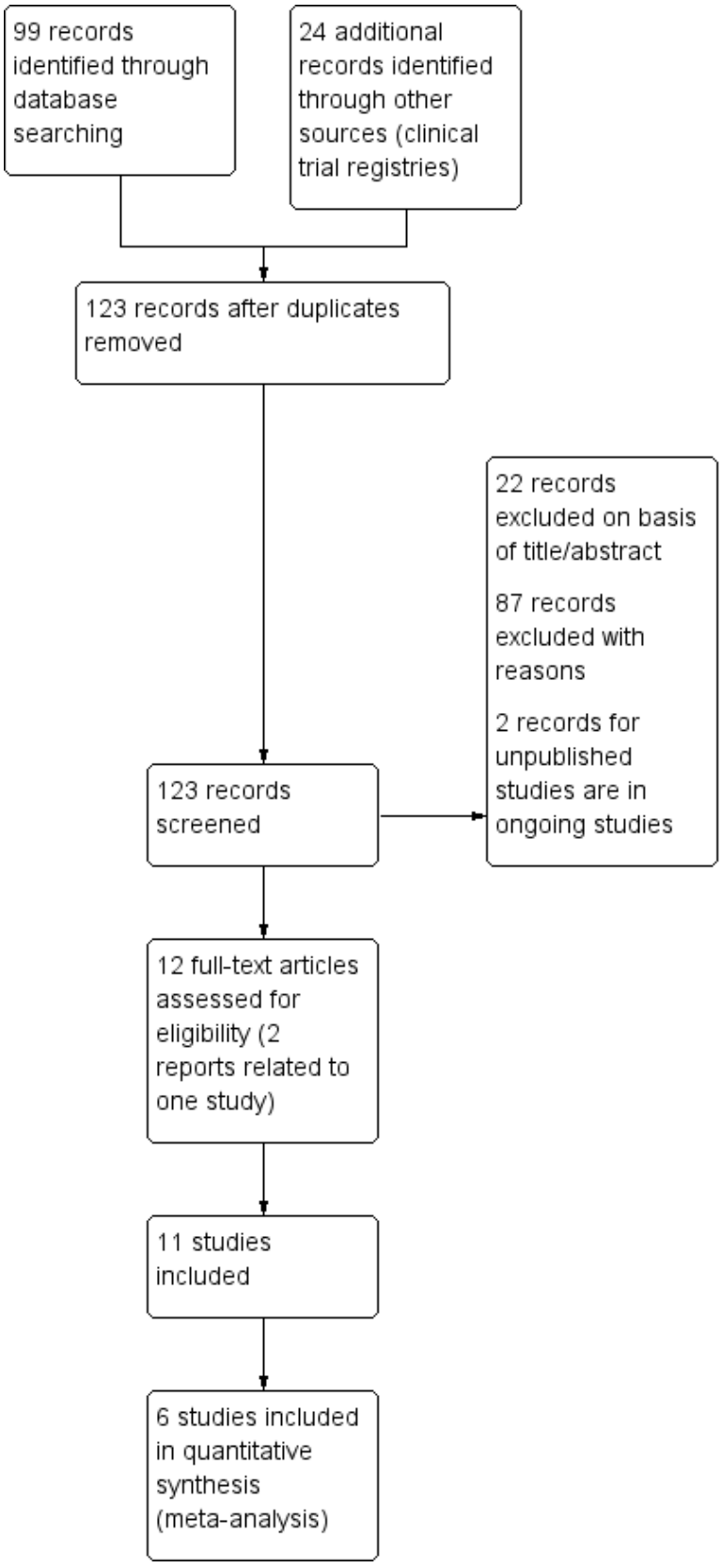
We checked reference lists of all primary studies and review articles for additional references, and we searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed). We reported the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (SJM and AH) independently screened the titles and abstracts of all the potential studies we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We included trials where the asthma management of both treatment and control groups provided similar background therapy. We retrieved the full-text study reports/publication and two review authors (SJM and AH) independently screened the full text, identified studies for inclusion and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreement through discussion and consulted a third member of the author team (MW). We identified and excluded duplicates and collated multiple reports of the same study so that each included study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and 'Characteristics of excluded studies' table.

Figure 1. Study flow diagram.



Data extraction and management

We used a data collection form for study characteristics and outcome data which we piloted on one study in the review. Two review authors (SJM and AH) extracted study characteristics from the included studies. We extracted the following study characteristics.

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

Two review authors (SJM and AH) independently extracted outcome data from the included studies. We have noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third author (MW). One review author (SJM) transferred data into the Review Manager (RevMan) file. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (AH) spot-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 risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another author (MW). We assessed the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

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

Measures of treatment effect

We analysed dichotomous data as odds ratio and continuous data as mean difference or standardised mean difference. We entered data presented as a scale with a consistent direction of effect.

We undertook meta-analyses only where this was meaningful, i.e. if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense.

We planned to describe skewed data reported as medians and interquartile ranges narratively. The issue did not arise in the included trials.

Where multiple trial arms were reported in a single trial, we included only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) had been combined in the same meta-analysis, we planned to halve the control group to avoid double-counting. The issue did not arise in our evaluation of the included trials.

Unit of analysis issues

In all studies the unit of analysis was the patient. In repeated measures studies (cross-over trials) we have reported within-patient differences. As no statistical aggregation of studies was possible in this review we have reported results as presented in the trial reports.

Dealing with missing data

We planned to contact investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only). Where this was not possible, and the 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 a sensitivity analysis; however this issue did not arise.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we had identified substantial heterogeneity we planned to report it and explore possible causes by prespecified subgroup analysis. This was, however, not an issue as there were no opportunities to aggregate studies statistically.

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 possible small study biases. However, this was not an issue in this review.

Data synthesis

We planned to use a fixed-effect model and perform a sensitivity analysis with a random-effects model. However, these concerns did not arise with the included studies. We planned to analyse dichotomous outcomes using odds ratio and continuous data as mean difference; however, there was no opportunity for statistical

aggregation of studies and the results reported in the review were obtained directly from the trial reports.

'Summary of findings' table

We created two 'Summary of findings' tables using the following outcomes:

1. health-related quality of life;
2. asthma exacerbation as defined by hospital admissions or treatment with a course of oral corticosteroids;
3. measures of lung function: FEV1, PEFR;
4. asthma symptoms;
5. adverse events.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies which contributed data to the review for the prespecified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the GRADEpro software. We have justified all decisions to downgrade or upgrade the quality of studies using footnotes and we have included comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses:

1. age (children under 12 years of age versus adults and adolescents);
2. severity (requirement for regular preventative treatment or not).

We planned to use the following outcomes in subgroup analyses:

1. health-related quality of life;
2. asthma exacerbation as defined by hospital admissions or treatment with a course of oral corticosteroids;
3. measures of lung function: FEV1, PEFR;
4. asthma symptoms;
5. adverse events.

There was, however, no opportunity to pursue these planned analyses as studies could not be aggregated.

We planned to use the formal test for subgroup interactions in Review Manager (Review Manager (RevMan)) if the requirement to do so had arisen.

Sensitivity analysis

We planned to carry out the following sensitivity analyses:

1. study quality as defined by standard Cochrane 'Risk of bias' criteria;
2. use of random-effects meta-analysis instead of fixed-effect.

However, the need to do this did not arise as it was not possible to combine data from different trials in any single analysis.

Reaching conclusions

We based our conclusions only on findings from the quantitative or narrative synthesis of the included studies in this review. We avoided making recommendations for practice and our implications for research suggests priorities for future research and outlines uncertainties in the area.

RESULTS

Description of studies

Results of the search

We identified 99 records through Cochrane Airways Group database searches and a further 24 from other sources. Further details are provided in Figure 1.

Included studies

Eleven studies met our inclusion criteria (Anah 1980; Anderson 1983; Cohen 1997; Fogarty 2003; Kordansky 1979; Malo 1986; O'Sullivan 2000; Nadi 2012; Schachter 1982; Schertling 1990; Tecklenburg 2007). Eight of these (Anah 1980; Anderson 1983; Fogarty 2003; Kordansky 1979; Malo 1986; O'Sullivan 2000; Nadi 2012; Schertling 1990) focused on asthma and three (Cohen 1997; Schachter 1982; Tecklenburg 2007) on exercise-induced bronchoconstriction. In total there were 419 participants (379 for asthma and 40 for exercise-induced bronchoconstriction).

In 10 studies the participants were adults and only one (Anderson 1983) focused on a paediatric group (16 children). Four of the 11 studies were parallel-group in design (Anah 1980; Anderson 1983; Fogarty 2003; Nadi 2012) (318 participants in total), and the remainder (Kordansky 1979; Malo 1986; O'Sullivan 2000; Schachter 1982; Schertling 1990; Tecklenburg 2007) were cross-over design studies (101 participants in total).

However, only six of the 11 studies on 338 participants provided data that could be included in our analyses (Anah 1980; Anderson 1983; Fogarty 2003; Nadi 2012; Schachter 1982; Tecklenburg 2007). The majority were parallel-group in design (Anah 1980; Anderson 1983; Fogarty 2003; Nadi 2012 (318 participants in total)) and the remaining two cross-over studies (Schachter 1982; Tecklenburg 2007) contributed eight and 12 participants respectively. These two cross-over trials (Schachter 1982; Tecklenburg 2007) contributed to the exercise-induced asthma/bronchoconstriction analyses reported in Table 1. The four parallel-group studies contributed to the analysis of asthma outcomes reported in Table 2.

There was marked heterogeneity in vitamin C dosage regimes used in the selected studies.

Six studies used regular regimes with differing dosages varying from 1 g (Anah 1980; Anderson 1983; Fogarty 2003; Nadi 2012) and 1.5 g (Tecklenburg 2007) to 5 g once daily (Schertling 1990). Duration of treatment was also very variable, ranging from two weeks to six months.

Five studies (Cohen 1997; Kordansky 1979; Malo 1986; O'Sullivan 2000; Schachter 1982) reported results using single-dose regimes prior to bronchial challenges or exercise tests. The dosages varied from 500 mg (Kordansky 1979; Schachter 1982) to 2 g (Cohen 1997; Malo 1986; O'Sullivan 2000).

Anah 1980 was funded by the Research Grant Committee of the College of Medical Sciences, University of Benin. Fogarty 2003 was funded by the NHS National Research and Development Programme on Asthma Management administered by the National Asthma Campaign. Kordansky 1979 was funded by the National Institute of Allergy and Infectious Diseases and Tecklenburg 2007 was funded, in part, by the Gatorade Sports Science Institute (Gatorade is a sports drinks). The source of funding was unspecified in the trial reports for Anderson 1983; Cohen 1997; Malo 1986; Nadi 2012; O'Sullivan 2000; Schachter 1982 and Schertling 1990

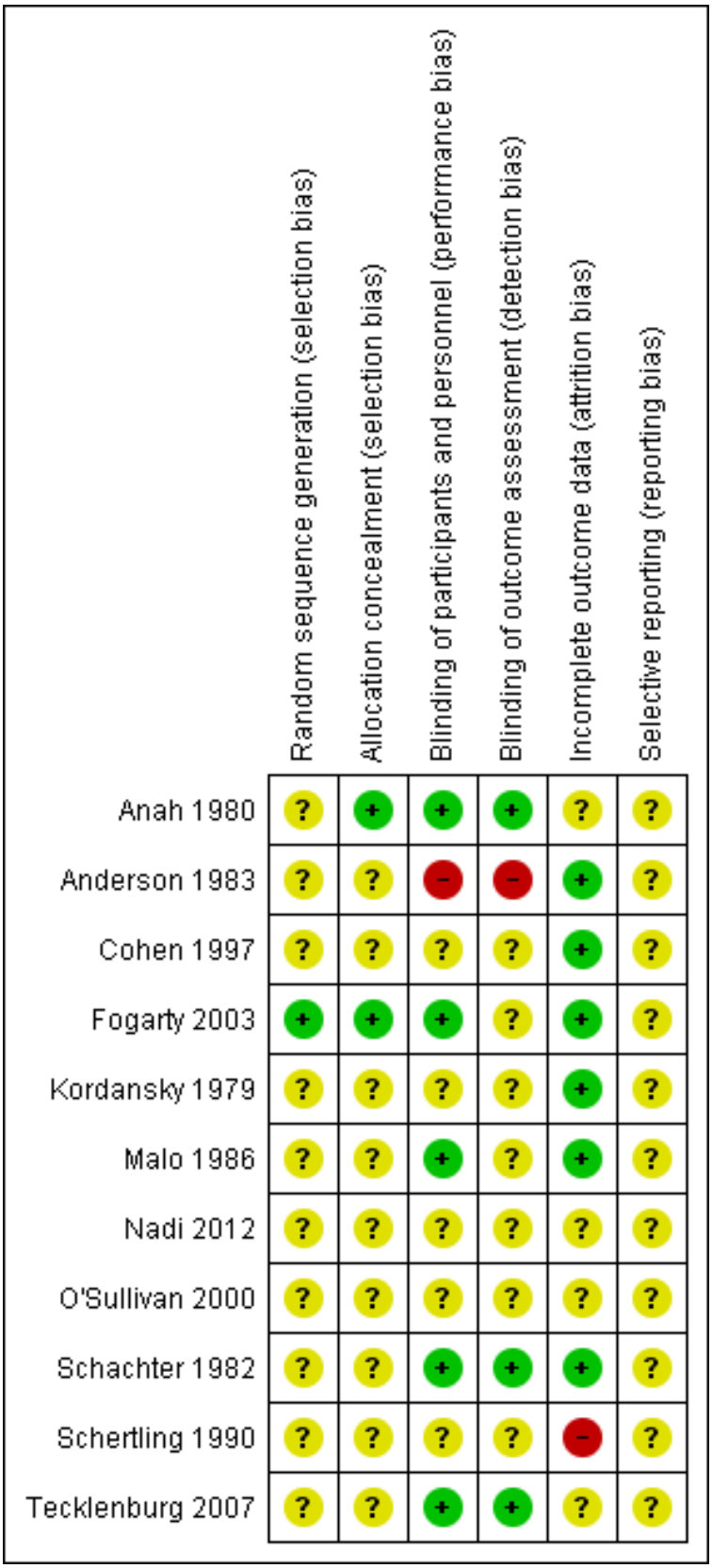
Excluded studies

We excluded 83 references for the following reasons: 77 (93%) did not compare vitamin C with placebo or no treatment; three (4%) were non-randomised, one (1%) was not focused on participants with asthma, one (1%) was a summary of an excluded study and the remaining study (1%) was retracted by the authors following publication. Full details can be found in Characteristics of excluded studies.

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.

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



Allocation

We judged only one trial as low risk with regard to random sequence generation (Fogarty 2003) and assessed the remainder as unclear in this respect. We evaluated two trials as low risk in terms of allocation concealment (Anah 1980; Fogarty 2003) with the remaining nine in the unclear category.

Blinding

We assessed five studies as low risk with regard to performance bias (Anah 1980; Fogarty 2003; Malo 1986; Schachter 1982; Tecklenburg 2007). We judged five to be in the unclear category (Cohen 1997; Kordansky 1979; Nadi 2012; O'Sullivan 2000; Schertling 1990) and one (the only paediatric study in the review) was in the high risk of bias category (Anderson 1983). Our assessment of detection bias led to similar judgements as in the performance bias although two studies (Fogarty 2003; Malo 1986) were placed in the unclear rather than the low category and there were, therefore, only three studies in the low risk of bias category, seven in unclear and one which we assessed as high risk of bias.

Incomplete outcome data

We judged six studies to be at low risk of bias (Anderson 1983; Cohen 1997; Fogarty 2003; Kordansky 1979; Malo 1986; Schachter 1982). One study (Schertling 1990) was in the high risk of bias category, and we rated the remaining four as unclear in terms of attrition bias.

Selective reporting

We rated all studies as unclear in terms of reporting bias, but we had concerns about the SF-36 data from Fogarty 2003, as SF-36 data on physical functioning were noted by the authors to be incomplete and this section was excluded from the analysis.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: Vitamin C supplementation compared with placebo for asthma; **Summary of findings 2** Summary of findings: Vitamin C supplementation compared with placebo for exercise -induced bronchoconstriction/asthma

Asthma

Health-related quality of life

We found no health-related quality of life (HRQL) data in the included studies that could be included in our analyses. However, Fogarty 2003 narratively reported no evidence of a difference in HRQL between the vitamin C and placebo groups after 16 weeks of treatment in terms of the available SF-36 data; we rated the quality of this evidence as low (Summary of findings for the main comparison). Details of data reported in the included trials relevant to our prespecified outcomes are included in Table 1. No mean difference or confidence interval is reported in the paper.

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

Only one small study, involving 16 children, reported data for asthma exacerbations (as defined by hospital admissions or treatment with a course of oral corticosteroids) and there were no events in either the vitamin C or control group (Anderson 1983); we rated the quality of this evidence as very low (Summary of findings for the main comparison). Although data on exacerbations were provided for 22 adults on vitamin C and 19 adults on placebo in Anah 1980, the data were not reported in a format consistent with our prespecified criteria (defined by hospital admissions or treatment with a course of oral corticosteroids). Anah 1980 reported nine asthma attacks in the vitamin C group and 35 asthma attacks in the placebo group; these data include mild, moderate and severe asthma attacks as defined by the authors. There were two severe asthma attacks in the vitamin C group and eight in the placebo group, one moderate asthma attack in the vitamin C group and 16 in the placebo group, and six mild attacks in the vitamin C group and 11 in the placebo group. It is unclear how many asthma attacks were experienced by each participant.

Measures of lung function: FEV1, PEFR

In five studies there was no significant difference between vitamin C and placebo in FEV1 outcomes (Fogarty 2003; Kordansky 1979; Malo 1986; Nadi 2012; O'Sullivan 2000).

- FEV1 (L) at one month was reported in one study with 60 participants (Nadi 2012) and based on within-group analyses (paired t-tests). A slight but significant advantage was reported for change in FEV1 in the placebo group (before 1.63 ± 0.68, after 1.82 ± 0.78, P = 0.044) but not in the vitamin C group (before 1.40 ± 0.56, after 1.44 ± 0.59, P = 0.65). Data were not reported in a form that enabled us to do an appropriate between-group analysis, given pretreatment imbalances for this outcome.
- Change in FEV1 (ml) from zero to 16 weeks was reported in one study with 201 participants(Fogarty 2003). There was no significant difference between placebo and vitamin C (MD 11 ml; 95% CI -70 to 92); we rated the quality of this evidence as moderate, as the confidence interval excluded a clinically important change in FEV1 on vitamin C (Santanello 1999; Summary of findings for the main comparison).
- FEV1 outcomes were recorded in Kordansky 1979. However, they could not be included in our analysis as the data were not reported; there is an indication in the trial report that no significant difference was detected for this outcome between vitamin C and placebo.
- FEV1 data were also collected in Malo 1986. The data were not reported in a format that we could transfer to a meta-analysis, however it is indicated in the trial report that there was no significant difference between vitamin C and placebo for this outcome.
- FEV1 % predicted was reported in O'Sullivan 2000 (a conference abstract) but insufficient details were reported to transfer to a meta-analysis. The authors reported that "There was no significant change in FEV1 after vitamin C administration (95 ± 2.7% versus 94.2 ± 3.2%)".

In Fogarty 2003 and Schertling 1990, the only two studies reporting PEFR outcomes, there was no significant difference between vitamin C and placebo.

- PEFR data collected at both AM and PM were reported by one study with 201 participants (Fogarty 2003). There was no significant difference between vitamin C and placebo with respect to AM (MD 0.90 L/min; 95% CI -11.8 to 13.5) or PM scores (MD 2.20 L/min; 95% CI -10.0 to 14.3). This study has a narrow confidence interval and therefore implies no clinically important change in PEFR with vitamin C.

- In relation to PEFR, Schertling 1990 reported that there were no statistically significant differences, or clinically relevant differences, between vitamin C and placebo. Insufficient details were reported to transfer to a meta-analysis.

Asthma symptoms

Data were provided by one study with 201 participants (Fogarty 2003) regarding the change in symptom scores between zero and 16 weeks. There was no significant difference between vitamin C and placebo (MD 0.0; 95% CI -0.2 to 0.1); we rated the quality of this evidence as moderate (Summary of findings for the main comparison).

With regard to asthma symptoms, Schertling 1990 reported that there were no statistically significant differences, or clinically relevant differences, between vitamin C and placebo

Adverse events

Only one parallel-group study (Anah 1980) with 41 participants explicitly reported adverse event data. There were no adverse events in either in the vitamin C or the placebo groups; we rated the quality of this evidence as very low (Summary of findings for the main comparison).

In Schertling 1990, a cross-over trial with 29 participants, one patient reported nausea during the ascorbic acid period, and a few patients noted other mild symptoms during the study, but the authors report "no relevant differences for occurrences between two groups / testing periods".

Withdrawals

Only one study specifically reported withdrawals. Fogarty 2003 documented a withdrawal rate of 24%, mostly for non-medical reasons with a small number withdrawing due to asthma deterioration or "other medical reasons" which were not specified.

Exercise-induced asthma/bronchoconstriction

Health-related quality of life

None of the three included studies reported between-group differences in HRQL in relation to exercise-induced asthma/ bronchoconstriction. Tecklenburg 2007 provided data from the symptoms component of the Asthma Quality of Life Questionnaire (AQLQ), reporting a significant improvement on the vitamin C diet (mean score 6.3; 95% CI 5.8 to 6.8) versus placebo (mean score 5.8; 95% CI 5.1 to 6.2) (P < 0.05). However, we are mindful that this measure may be more relevant to asthma studies considering the effects of vitamin C supplementation over longer periods and arguably of less relevance in short-term studies investigating more immediate outcomes. Data reported in the included trials relevant to our prespecified outcomes are included in Table 2.

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

This outcome, in relation to exercise-induced asthma/ bronchoconstriction, was not reported in the included studies. Again this outcome is of particular importance in asthma trials measuring the effects of vitamin C supplementation over longer periods and less relevant in contexts where more immediate outcomes are informative.

Measures of lung function: FEV1, PEFR

The change in FEV1 (L) following exercise, compared with FEV1 (L) before exercise, was reported in a small cross-over study with 12 participants (Schachter 1982). The comparison of vitamin C versus placebo change scores was recorded immediately following exercise (MD 0.13; vitamin C 0.21 (standard error (SE) 0.06) versus placebo 0.08 (SE 0.08), P = 0.18), at five minutes after exercise (MD 0.20; vitamin C -0.24 (SE 0.06) versus placebo -0.44 (SE 0.14), P = 0.057) and following postexercise bronchodilator (MD 0.21; vitamin C 0.43 (SE 0.12) versus placebo 0.22 (SE 0.10), P < 0.01). The authors report significantly greater increases in post-bronchodilator pulmonary function in patients on vitamin C compared with placebo).

The maximum % drop in FEV1 scores following exercise was reported in a very small cross-over study with eight participants (Tecklenburg 2007). The authors reported that the maximum percentage drop in FEV1 postexercise on the vitamin C diet was 6.4% (95% CI 12.0% to 0.8%; effect size using omega-squared (ES) 0.40), which is indicative of an attenuated exercise-induced bronchoconstriction response. We rated the quality of this evidence as low (Summary of findings for the main comparison). This was significantly different (P < 0.05) from the maximum drop of 12.9% (95% CI 18.6% to 12.3%) on the placebo diet. There are uncertainties regarding the reported CI for the placebo diet and the data were not reported in a form that enabled us to do a between-group analysis

Categorical outcomes relating to FEV1 were reported in Cohen 1997, a cross-over trial. In the vitamin C group 11 of the 20 participants demonstrated less deterioration in their postexercise change scores (with a % fall in FEV1 no greater than 15%), however in the placebo group all participants had a % fall greater than 15%. These data suggest a protective effect of vitamin C in exercise-induced asthma.

Postexercise change in PEFR was also reported by Schachter 1982. In a comparison of vitamin C versus placebo change scores recorded immediately following exercise there was a significant difference favouring vitamin C (MD 0.49 L/second; vitamin C 0.59 (SE0.16) versus placebo 0.10 (SE 0.25), P < 0.05). However, at five minutes after exercise this difference was not significant (MD 0.22; vitamin C -0.73 (SE 0.28) versus placebo -0.95 (SE 0.40), non-significant). Following postexercise bronchodilator there was a significant difference favouring vitamin C (MD 0.44 L/second; vitamin C 0.83 (SE 0.26) versus placebo 0.39 (SE 0.29), P < 0.05).

Asthma symptoms

One very small cross-over study with eight participants (Tecklenburg 2007) reported asthma symptom data using the AQLQ and showed a significant improvement in patients on the vitamin C diet (MD .6.3; 95% CI 5.8 to 6.80) versus the placebo diet (MD 5.8; 95% CI 5.1 to 6.2, P < 0.05); we rated the quality of this evidence as low (Summary of findings for the main comparison). The minimally important difference on this scale is regarded as 0.5 units.

Adverse events

None of the included studies explicitly reported adverse event data.

Withdrawals

No study specifically reported withdrawals.

DISCUSSION

Summary of main results

Eleven studies were identified as meeting the inclusion criteria for this review: vitamin C versus no vitamin C supplementation. All but one of the studies were in adults, and the studies varied considerably with respect to severity (Characteristics of included studies). The small number of studies available for review and their disparate designs meant that only descriptions of the individual studies were possible with no prospect of aggregating the current studies available. We are also mindful that only three of the 11 included studies were published in the last 10 years (Fogarty 2003; Nadi 2012; Tecklenburg 2007) and the management context for the most of the studies may not be comparable to the treatment patients receive today

Given the significant impact exacerbations of asthma may have on lung function and quality of life, this is an important endpoint for studies in this condition. None of the studies provided robust evidence of vitamin C supplementation influencing asthma exacerbations or health-related quality of life. Only one study (Anah 1980) used exacerbation rate as a primary outcome, but the data could not be included in our review as the definition of exacerbation did not meet our inclusion criteria and there was a lack of statistical analysis. This study reported a reduction in the numbers of severe exacerbations, defined as asthma attacks requiring hospital admission. However, no statistical analysis was presented to allow comparison of the number of participants with one or more exacerbations in each group, or the exacerbation rates between groups.

Fogarty 2003 was the largest included trial with 201 participants and looked at changes in symptom scores in patients with a clinical diagnosis of asthma taking supplements of vitamin C, magnesium or placebo. No significant difference in symptom scores was demonstrated during the period of this study, either as an individual outcome or in combination with others.

The fundamental importance of considering the impact of exacerbations (Fitzgerald 2006) and health-related quality of life (Wilson 2012) in relation to asthma has been well appreciated for several years, and these outcomes are commonly assessed in clinical trials of asthma. It is therefore particularly disappointing that there is very little information in the trials relating to these outcomes.

Nine studies used lung function (including FEV1, PEFR or measures of bronchial hyperreactivity) as their primary outcome measures. There was some evidence from very small studies of improved lung function but it would be necessary to replicate these findings in larger trials for any robust conclusions to be drawn. The largest study (Fogarty 2003), which was at lowest risk of bias, reported narrow confidence intervals for FEV1 and PEFR; this implies no clinically important effect of vitamin C on these measures of lung function.

Table 1 clarifies the data available from the trials including our prespecified primary and secondary outcomes for asthma. There was a paucity of data for our primary outcomes (health-related quality of life and asthma exacerbations) and the available data for measures of lung function and symptoms scores reported in the table do not indicate a significant benefit of vitamin C supplementation. The strength of the evidence is generally low (Summary of findings for the main comparison) and most of the studies contributing data are very small, with disparate approaches. It is therefore not feasible to draw firm conclusions either for or against the use of supplementary vitamin C in the management of asthma. In summary, we would suggest that currently there is insufficient robust evidence from the available trials to evaluate the benefits of vitamin C supplementation and that such judgements should be reserved until data are available from further adequately powered studies.

Our concerns about the available data for the impact of vitamin C supplementation on exercise-induced bronchoconstriction/asthma are similar. The data are tabulated in Table 2. There is some evidence of a significant benefit in post-bronchodilator FEV1 and PEFR; however, in each case these data are contributed only by a single small study. There is also suggestive evidence of a benefit in symptoms scores, but these data are drawn from only one small study. As with the primary and secondary outcomes for asthma, the strength of evidence is of a low order (Summary of findings 2). In summary, there is a need for additional adequately powered studies, with appropriate outcome measures, to bring more clarity to the assessment of the role of vitamin C supplementation in exercise-induced bronchoconstriction/asthma.

Overall completeness and applicability of evidence

The primary outcomes chosen, exacerbation rates and health-related quality of life, are important in assessing asthma control and the impact of treatment. Data for these clinically significant endpoints were lacking, with no studies reporting complete health-related quality of life data and only one using exacerbations as a primary endpoint.

Measures of lung function were used more frequently, including exercise-induced changes in lung function or bronchial challenge tests. However, the studies were small and disparate in design and it is not possible to draw conclusions about overall clinical effectiveness from the results.

One of the two studies identified in our searches, but for which data are currently not posted (IRCT138904224359N1a), may meet our inclusion criteria in the update of this review. However, we note that it will not contribute to our primary outcomes as it does not focus on health-related quality of life or asthma exacerbations. We also note that the other ongoing trial (NCT01057615a) may well not meet our inclusion criteria as the comparison appears to be essentially between vitamin C supplementation and fish oil, rather than vitamin C supplementation versus placebo, and the trial specifically focuses on exercise-induced bronchoconstriction. However, a more adequate assessment will be possible when the full details of the trial are reported

There is currently only a single small study in children (Anderson 1983 including 16 children), so we currently have very limited evidence to assess the impact of vitamin C on asthma in children.

Quality of the evidence

Only one of the 11 trials meeting our inclusion criteria included over 100 participants (Fogarty 2003) and on average the sample size per trial was just 38. In the remaining 10 included studies the sample sizes ranged from six to 60 and the average per trial was just 22. Only six of the 11 studies provided data that could be included

in our tables (Table 1; Table 2) and for each outcome we could include data from only one study in each case. There is, therefore, a worrying paucity of data available for this review and there is a substantial risk that there may have been reporting bias. With respect to the quality of the included research, in terms of our 'Risk of bias' assessment using Cochrane criteria, we categorised only one trial as low risk with regard to random sequence generation (Fogarty 2003) and we evaluated the remainder as unclear. In terms of allocation concealment we evaluated three trials as low risk of bias (Anah 1980; Fogarty 2003; Schertling 1990) with the remaining eight assessed as unclear. In terms of both the quantity and quality of available data, with respect to our 'Risk of bias' assessment relating to randomisation procedures, it is clear that any robust interpretation of these data would be inappropriate and this conclusion is supported by our assessment of performance bias where we judged only five studies (Anah 1980; Fogarty 2003; Schachter 1982; Schertling 1990; Tecklenburg 2007) to be low risk of bias. We judged five to be in the unclear category (Cohen 1997; Kordansky 1979; Malo 1986; O'Sullivan 2000; Nadi 2012) with the remaining trial in the high risk of bias category (Anderson 1983). The evaluation of detection bias was consistent with our assessment of performance bias, apart from Schertling 1990 which we judged in this context as unclear rather than low risk of bias.

We primarily downgraded for risk of bias due to the inadequate description of study design across the included studies and the risk of selective reporting as noted above. For a number of outcomes we also downgraded for imprecision as the results came from small trials or were otherwise indeterminate. The notable exception to this was FEV1, where the estimated effect excludes a clinically meaningful difference of 120mL (Summary of findings for the main comparison).

Potential biases in the review process

A possibility of publication bias in this review is acknowledged, whereby a potential failure to identify unpublished negative trials could conceivably lead to the positive effects of vitamin C supplementation being overestimated and, similarly, any failure to identify unpublished positive trials may have led to a conservative assessment of the treatment benefits. These issues are present in most systematic reviews and we believe that a very significant proportion of the research addressing this clinical question has been identified through the Cochrane Airways Group's comprehensive systematic database searches, in the identification of both published and unpublished trials meeting our inclusion criteria.

We also acknowledge the possibility of study selection bias. We endeavoured to minimise this risk by two review authors independently evaluating all identified studies, and we are confident that trials judged as failing to meet our inclusion criteria were assessed on a consistent basis.

Agreements and disagreements with other studies or reviews

Our conclusions are very similar to a previous Cochrane review on vitamin C for asthma (Kaur 2009). However, in Kaur 2009 the primary outcomes were lung function and symptom scores as opposed to exacerbations and health-related quality of life in this review. Two additional studies meeting the inclusion criteria were identified in this review (Nadi 2012; Schertling 1990). However, our conclusions are consistent with those drawn in the 2009 review where the authors argue that "further methodologically strong and large-scale randomised controlled trials are needed in order to address the question of the effectiveness of vitamin C in asthma". We hope that such research will be conducted and that particular emphasis will be given to the assessment of efficacy with respect to any impact on asthma exacerbations and health-related quality of life.

AUTHORS' CONCLUSIONS

Implications for practice

The studies of vitamin C supplementation in asthma included in this review provide only very limited evidence with which to evaluate the use of vitamin C in stable asthma or exercise-induced bronchoconstriction/asthma. There is currently no indication that vitamin C can be recommended as a therapeutic agent in asthma or in the prevention of exercise-induced bronchoconstriction. The studies are generally too small to provide clinical recommendations. In addition, clinically important endpoints such as exacerbation rates and health-related quality of life scores are lacking.

Implications for research

Our conclusions are in line with a previous Cochrane review considering the use of vitamin C in stable asthma (Kaur 2009). We agree that larger, more robust research is required to clarify the use of this supplement.

Well-designed and adequately powered double-blind, placebo-controlled trials are required in both adults and children. These trials should include clinically meaningful endpoints including exacerbation rates, health-related quality of life measures, robust symptom scores and the use of rescue medications. In addition changes to lung function parameters, including markers of bronchial hyperreactivity and spirometric changes, should be examined and their clinical implications reported.

We concur with Hemila 2013 that more research would be helpful with respect to exercise-induced asthma. More specific trials are required to examine the inconclusive evidence reported for the use of vitamin C in exercise-induced asthma and to clarify its influence on bronchial hyperreactivity.

Future studies should report adverse effects of vitamin C, which to date have not been adequately reported.

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CHARACTERISTICS OF STUDIES

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

Anah 1980

Methods	Randomised, double-blind controlled trial. Parallel-group design
Participants	41 participants: vitamin C: 22, placebo: 19 Age: vitamin C: mean 26.5 (range 15 to 42), placebo mean 27.8 (range 15 to 46) Sex: vitamin C: males 12 (55%), placebo 10 (53%) PEFR: vitamin C: mean 274.1 (range 200 to 340), placebo mean 279.2 (range 200 to 325) Stated as recruited from Asthma Clinic. Each patient had the following investigations done on admission to the trial: haemoglobin or packed cell volume (PCV), white blood cell count (WBC) with eosinophil count (%), stool microscopy, peak expiratory flow rate (PEFR), plasma ascorbic acid. All had asthma for at least 4 years, but in remission. Most on maintenance therapy with bronchodilators. One

Anah 1980 *(Continued)*

	on low-dose oral steroids. Maintenance therapy continued in trial. All had history of attacks in rainy season and trial ran in rainy season Inclusion criteria: one criterion for selection was the increase in exacerbation during the rainy season. These exacerbations were precipitated by respiratory infection. Selection of participants for the study was simple: any person who agreed to participate after a full explanation of the procedure was accepted, unless he/she lived outside the city. If he/she could attend at regular intervals, including reporting to the hospital emergency service in the event of a severe attack at any time of the day or night, he/she was accepted Exclusion criteria: those with complicating bronchitis and/or emphysema were not admitted into the study group The trial was conducted in Benin City, Nigeria
Interventions	1 g of ascorbic acid as 1 effervescent tablet once daily versus matching placebo. The tablets were dissolved in a small quantity of water. 2 identical effervescent tablets were provided for the trial by Roche (Nig.) Limited Most were on maintenance therapy with bronchodilators. One patient was on a small dose of oral steroids (5 mg of prednisolone daily) on entry into the study. All remained on whatever drugs sustained their remission
Outcomes	Asthma attacks (reporting precludes us from including these data in our definition of exacerbations as hospital admission or course of oral steroids). Stool microscopy. Eosinophil count. Data collected at 4, 8, 12, 14 weeks
Notes	14-week trial Funded by the Research Grant Committee of the College of Medical Sciences, University of Benin Effervescent tablets were provided by Roche (Nig.) Limited

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	Coded allocation to A (vitamin C group) or B (placebo group) which was decoded on completion of the trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. 2 identical effervescent tablets were provided for the trial by Roche (Nig.) Limited
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. 2 identical effervescent tablets were provided for the trial by Roche (Nig.) Limited
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No indication of withdrawals
Selective reporting (reporting bias)	Unclear risk	Some outcomes not reported (genotype, stool microscopy and eosinophil count data not reported as the authors judged the data to be unreliable)

Anderson 1983

Methods	Randomised controlled trial, parallel-group design
Participants	16 children: vitamin C: 7, control: 9 Age: vitamin C: 9.3 (2.4), control: 9.2 (1.9) Severity: vitamin C: 4 moderate and 3 severe, control: 6 moderate and 3 severe Sex: vitamin C: 7 males (100%), control: 5 males (56%) Children with difficulty in asthma management who were randomly selected. Diagnostic criteria: MME-FR (resting maximal mid-expiratory flow rate): average 66% for moderate and 36% for severe Inclusion criteria: history of recurrent respiratory infections and asthma confirmed by lung function studies Exclusion criteria: none specified in trial report Paediatric Respiratory Clinic H F Verwoerd Hospital, Pretoria
Interventions	1 g ascorbic acid (Redoxon) as a single dose in the morning (as adjunct to standard therapy) versus nothing (as an adjunct to standard therapy) for 6 months Co-medication: each child received 3 daily doses of sodium cromoglycate (Ludamol) and either fenoterol (Berotec) or salbutamol (Ventolin). None received glucocorticoids during the study and none was hospitalised during the trial
Outcomes	Exacerbations (requiring glucocorticoids or hospitalisation), IgE (serum), antibodies to streptolysin 0 (ASO), polymorphonuclear leucocyte (PMNL) migration, secretory immunoglobulin A (IgA), serum immunoglobulin and total haemolytic complement levels
Notes	Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study compared ascorbic acid to no intervention and therefore the trial was unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	No statement that assessors were unblinded or any attempt so to do, but measurements objective
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data
Selective reporting (reporting bias)	Unclear risk	No stated primary objective; some outcomes not reported

Cohen 1997

Methods	Randomised, double-blind trial, cross-over design
Participants	20 patients with asthma received both vitamin C and placebo in a randomised, cross-over design Mean age 13.8 (7 to 28) Sex: 13 males (65%) Reported as: all participants demonstrated exercise-induced asthma (EIA) by having a decline of at least 15% in their forced expiratory volume in 1 second after a standard exercise test on a motorised treadmill (model Q50, Quinton Instrument Co, Seattle, Wash). The patients were advised to refrain from taking their regular medication, which consisted of inhaled steroids, antihistamines and bronchodilators, 12 hours before the test Baseline FEV1 (L) (before exercise): 2.36 (0.85); baseline FEV1 (L) (after exercise): 1.74 (0.72) Baseline FEV1 (% predicted) (before exercise): 86 (12); baseline FEV1 (% predicted) (after exercise): 63 (13) The setting was a university hospital in Israel
Interventions	Reported as: 2 g of oral ascorbic acid versus placebo 1 hour before a 7-minute treadmill exercise session. 8 minutes after exercise pulmonary function tests were performed. 1 week later participants received the alternative intervention
Outcomes	Development of exercise-induced asthma (EIA), FEV1 (L) and FEV1 (% predicted)
Notes	Summary of FEV1; a single large dose of ascorbic acid before exercise prevented the development of EIA in 9 of 20 patients and reduced the airways' responsiveness to exercise in 2 other patients Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind but method of blinding (whether it was a matched placebo) is unclear in trial report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blind but method of blinding (whether it was a matched placebo) is unclear in trial report
Incomplete outcome data (attrition bias) All outcomes	Low risk	Information included in trial report from all 20 participants
Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

Fogarty 2003

Methods	Randomised, placebo-controlled, double-blind, parallel-group
Participants	201 adults randomised: vitamin C: 95 (72 completed (76%)), placebo: 106 (82 completed (77%)) Age: vitamin C: 42 years, placebo: 40 years Sex: vitamin C: 37 males (39%), placebo: 42 (40%) Baseline lung function: mean FEV_1 (L) vitamin C: 2.8 (SD not reported), placebo: 2.8 (SD not reported) Baseline lung function: mean % predicted FEV_1 (SD): vitamin C: 85.3 (15.7), placebo: 83.3 (17.5) Inclusion criteria: stated as: patients aged 18 to 60 years with a physician diagnosis of asthma and using at least one dose of an inhaled corticosteroid daily for the last 6 months were identified from computerised records Exclusion criteria: stated as: participants currently taking oral corticosteroids or diuretics, had used vitamin C, magnesium or calcium supplements within 3 months, had experienced exacerbation of asthma within 4 weeks, had a cumulative smoking history of 10 pack-years or more, or were pregnant or planning a pregnancy Patients recruited from 24 GP practices, Nottingham, UK
Interventions	Run-in period: consenting individuals entered a 3-week run-in period. Participants who complied with the measurement protocol and experienced no exacerbation of asthma during the run-in period then proceeded into the supplementation study Interventions: vitamin C 1 g/day (5.6 mmol) plus magnesium placebo versus vitamin C placebo and magnesium placebo. A third group (not included in this review) received 450 mg/day magnesium chelate. No patient included in the vitamin C versus placebo comparison was receiving magnesium
Outcomes	Stated as: FEV1, forced vital capacity (FVC), inhaled dose of methacholine causing a 20% fall in FEV1 (PD20) to a maximum dose of 12.25 mmol methacholine (and values above this were censored), and average morning and evening peak flow, average daily bronchodilator use and daily symptom score recorded in a diary for the preceding 2 weeks. Study included a composite measure as their primary outcome. Data collected at the beginning and after 4, 8, 12 and 16 weeks of supplementation (but only reported at 16 weeks in trial report) We did not include data in our analyses from Fogarty 2006 (an additional study report related to this trial) due to the loss of randomisation at that stage
Notes	16-week trial Funded by: NHS National Research and Development Programme on Asthma Management administered by the National Asthma Campaign

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned using a random number generator, in blocks also stratified by a regular corticosteroid dose, defined as low or high
Allocation concealment (selection bias)	Low risk	Allocation by an individual code number, decoded after the last participant completed the trial. Randomisation and dispensing performed independently from the recruitment of trial participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomised to vitamin C 1 g/day (5.6 mmol) plus magnesium placebo, magnesium amino chelate (Lamberts Health Care, Tunbridge Wells, UK) 450 mg/day (27.6 mmol) plus vitamin C placebo, or double-matched placebo

Fogarty 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear in trial report
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for withdrawal listed in study report. Loss to follow-up, but taken into account. ITT analysis and as treated analysis reported: precise details of ITT imputation not given: "assuming deterioration in all outcomes in participants who withdrew". 66/300 withdrew (some from magnesium group not included in this review)
Selective reporting (reporting bias)	Unclear risk	Primary outcome measure reported, but secondary outcomes not all reported and incomplete reporting of SF-36 data

Kordansky 1979

Methods	Randomised controlled trial, cross-over design
Participants	6 adults (2 women and 4 men) ranging in age from 20 to 34 selected at random Participants with ragweed-sensitive asthma, defined by skin prick positivity. Tested out of the ragweed season. Asymptomatic and not on treatment Inclusion criteria: ragweed-sensitive asthmatics Trial conducted in Baltimore, USA
Interventions	500 mg once daily (2 capsules) vitamin C for 7 days versus lactose placebo (2 capsules) for 7 days Co-medication: during the study period, these patients were not receiving bronchodilators nor were they on corticosteroid therapy
Outcomes	PD20 to ragweed extract challenge FEV1, PD35 SGaw, tested on day 7, 3 hours after dose of placebo/vitamin C The FEV1 data were not reported in a format that we could use in our analyses
Notes	7-day cross-over trial Funded by the National Institute of Allergy and Infectious Diseases

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as double-blind but details of blinding (whether an identical placebo pill was used) were not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study described as double-blind but details of blinding (whether an identical placebo pill was used) were not described

Kordansky 1979 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	6 participants completed both periods of the cross-over. No information on withdrawals included in trial report
Selective reporting (reporting bias)	Unclear risk	Not all outcomes summarised. Sample dose-response curves given. No tables of summary statistics

Malo 1986

Methods	Randomised controlled trial, cross-over design
Participants	16 adults with asthma meeting the American Thoracic Society criteria Age range 19 to 59, mean 43.1 (11.9) years Sex: 3 men (19%) Mean duration of asthma: 10.5 (14.6) years Baseline lung function: mean % predicted FEV_1 (SD): 86.6 (19.6) Department of Chest Medicine, Hopital du Sacre-Coeur, Montreal, Canada
Interventions	Run-in: medication was withheld as follows: inhaled beta2-adrenergic agents for 8 hours and sustained release theophylline derivatives for 12 hours Intervention: 250 ml of a transparent and odourless sweet liquid in which was dissolved either 2 g ascorbic acid or placebo. 1 hour later spirometry was measured and histamine challenge done until PC20 reached Co-medication: all participants received beta2-adrenergic bronchodilators and/or sustained-release theophylline derivatives and 6 were also receiving beclomethasone
Outcomes	FEV1, FVC, PC20 during histamine challenge The FEV1 data were not reported in a format that we could use in our analyses
Notes	Funding source not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised according to a 4.3.1 two-treatment cross-over design, but details of random sequence generation were not included in trial report
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blind and details of blinding are provided as "The active and placebo medications consisted of 250 mL of a transparent and odourless sweet liquid in which was dissolved or not, respectively, 2 gm of ascorbic acid. These solutions of similar taste were prepared and coded by the hospital pharmacy"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	16 participants completed both periods of the cross-over. No information on withdrawals included in trial report

Malo 1986 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Trial report does not include complete details of outcomes

Nadi 2012

Methods	Randomised, double-blind trial, parallel-group design
Participants	60 participants with severe asthma: vitamin C: 30, placebo: 30 described as "matched" Age: vitamin C: 48.38 (± 9.03), placebo: 40.53 (± 10.48) Baseline lung function: mean FEV_1 L (SD) vitamin C: 1.40 (0.56), placebo: 1.63 (0.68) Inclusion criteria: bronchial asthma, where the diagnosis was established through demonstrating reversible airway obstruction. Severe asthma (stable asthma step 4, according to 2004 Global strategy for asthma management and prevention guideline) Exclusion criteria: smokers and patients with other chronic diseases were excluded from the study Participants recruited from Ekbatan hospital in Hamadan (Iran)
Interventions	1000 mg vitamin C daily versus placebo Co-interventions: standard asthma treatment (according to stepwise therapy in 4th step of bronchial asthma) in both groups, in which patients were controlled appropriately
Outcomes	FEV1, FVC and FEV1/FVC leukocyte vitamin C level. Data recorded at baseline and 1 month
Notes	1-month trial Funding source not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described. Participants were randomly divided into 2 groups, A and B (including 30 patients in each group), and were matched according to their age, weight, height, gender, BMI and drug consumption
Allocation concealment (selection bias)	Unclear risk	Described as "Both patients and physician were unaware of details of patient's distributions", however no further details available in trial report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind – however details of the placebo (whether it was matched to the intervention) are not included in trial report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind – however details of the placebo (whether it was matched to the intervention) are not included in trial report
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details of withdrawals in trial report

Nadi 2012 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

O'Sullivan 2000

Methods	Randomised, double-blind, controlled trial, cross-over design
Participants	10 participants diagnosed with mild asthma according to America Thoracic Society criteria. Very limited details in trial report (conference abstract) Location of trial not included in abstract
Interventions	Each participant completed 2 treatment periods with ingestion of either 2 g of ascorbic acid or placebo 45 minutes prior histamine broncho-provocation
Outcomes	FEV1 and bronchial hyper-responsiveness to inhaled histamine
Notes	Funding source not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as double-blind but unclear whether an identical placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No indication of withdrawals
Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

Schachter 1982

Methods	Randomised, double-blind, controlled trial, cross-over design
Participants	12 adults with exercise-induced asthma, never on corticosteroids or admitted to hospital Mean age 26 (5) years Sex: 5 males (41.7%) Baseline lung function: mean % predicted FEV_1 (SD): 75 (18.1)

Schachter 1982 *(Continued)*

	Participants were diagnosed with asthma as defined by the American Thoracic Society's criteria Inclusion criteria: all 12 participants gave a characteristic description of exercise-induced bronchoconstriction (EIB). Those participants who demonstrated sufficient EIB (20% reduction in maximal expiratory flow at 40% of the vital capacity below total lung capacity on the partial expiratory flow-volume curve (MEF40%(P)) after exercise were invited to proceed to the remaining challenges Trial conducted in New Haven, Connecticut, USA
Interventions	All 12 participants were instructed to take no medications for at least 8 hours prior to each challenge experiment. They were similarly instructed to refrain from foods or beverages containing large amounts of methylxanthines or ascorbic acid (coffee, fruits, juices, etc.) Intervention: single-dose vitamin C (500 mg) orally 1 hour before exercise challenge versus placebo (sucrose). The vitamin C and placebo were given in identical capsules in a double-blind random order
Outcomes	FEV1, FVC, maximal expiratory flow (MEF) and PEFR. Measured at before exercise, immediately after exercise, 5 minutes after exercise and post-bronchodilator following exercise
Notes	Trial conducted on 2 subsequent days. Participants underwent exercise challenge 90 minutes post-dose. No details of washout period provided in report Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Vitamin C and placebo in identical capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Vitamin C and placebo in identical capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for 12 participants
Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

Schertling 1990

Methods	Randomised, double-blind, controlled trial, cross-over design
Participants	29 participants with infection-related bronchial asthma Age: aged 18 to 60 years Sex: 18 men (62%) and 11 women

Schertling 1990 *(Continued)*

	Inclusion criteria: 18 years of age or older with infection-associated asthma Exclusion criteria: inhaled and systemic corticosteroids, kidney diseases, acute and severe purulent infections Participants recruited from an ambulatory healthcare centre in Berlin, East Germany
Interventions	2-week run-in period Intervention: 5 g/day oral ascorbic acid in 3 sugar-coated pills versus oral placebo (identical capsules) 2 weeks on first intervention, 1 week washout period and 2 weeks on second intervention The order of the test periods was chosen randomly
Outcomes	Daily asthma symptom score; 4 measurements per day of expiratory peak flow throughout the entire study; 3 checks throughout study of bronchial hyperreactivity, using histamine provocation; broncho-alveolar lavage at the end of testing periods, with determination of alveolar differential cell count and measurement of metabolic activity of broncho-alveolar cells, using chemiluminescence; global assessment of effectiveness and tolerance by doctor and patient
Notes	2 weeks on daily oral ascorbic acid or placebo Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The sequence of testing periods was chosen randomly. Details of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient details in trial report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details in trial report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information included in trial report about masking for data collectors/analysers
Incomplete outcome data (attrition bias) All outcomes	High risk	Data provided on 23 or 24 participants
Selective reporting (reporting bias)	Unclear risk	None apparent

Tecklenburg 2007

Methods	Randomised, double-blind, trial, cross-over design
Participants	8 participants Mean age: 24.5 (4.8) Sex: 2 males (25%)

Tecklenburg 2007 *(Continued)*

	All participants were diagnosed with clinically treated mild-to-moderate persistent asthma with an FEV1 greater than 70% of predicted and documented EIB (usual diet) as indicated by a drop of greater than 10% in postexercise FEV1 compared with pre-exercise values. Physician-diagnosed asthma. All participants had a history of chest tightness, shortness of breath and intermittent wheezing following exercise Baseline lung function: mean FEV_1 L (SD) 3.82 (0.37) Baseline lung function: mean % predicted FEV_1 (SD): 97.0 (6.1) Inclusion criteria: exercise-induced bronchoconstriction Participants: university students and the local community Indiana, USA
Interventions	Run-in: participants were asked to discontinue taking leukotriene receptor antagonists (LTRAs; N = 3 montelukast (Singulairs)) 12 h prior to testing, 10, 13, 14 and 4 days prior to testing to abstain from taking combined inhaled corticosteroids (ICS) and long-acting b2-agonists (N = 2, fluticasone propionate (Flovents) and salmeterol (Advairs)) or combined long-acting b2-agonists and LTRAs (N = 3 salmeterol (Advairs) and montelukast (Singulairs)). In addition, all participants were asked to refrain from taking caffeine, and to avoid physical activity for 12 h and 24 h, respectively, before exercise testing. Participants were asked to abstain from taking antioxidant supplements other than those given during the course of the study. Participants were advised to avoid foods that were high in vitamin C during the study Intervention: pharmaceutical grade ascorbic acid supplement (1500 mg/day: 3 500 mg capsules)(NOW foods, Bloomingdale, IL) versus a matched (colour/size) placebo (3 capsules/day of sucrose)(NOW foods, Bloomingdale, Illinois)
Outcomes	Pulmonary function (FEV1) pre- and postexercise, symptoms, exhaled nitric oxide and urine analysis
Notes	Participants were randomised to active treatment or placebo for 2 weeks. 1-week wash-out period. Participants crossed over to the alternative condition for the following 2 weeks Study was funded, in part, by the Gatorade Sports Science Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo manufactured by the same company as the active treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Matching placebo manufactured by the same company as the active treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No indication of withdrawals

Tecklenburg 2007 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

Abbreviations
ASO: antibodies to streptolysin O
BMI: body mass index
EIA: exercise-induced asthma
EIB: exercise-induced bronchoconstriction
FEV1: forced expiratory volume in one second
FVC: forced vital capacity
IgA: immunoglobulin A
ITT: intention-to-treat
MEF: maximal expiratory flow
MEF40%(P): maximal expiratory flow at 40% of the vital capacity below total lung capacity on the partial expiratory flow-volume curve
MEFR: mid-expiratory flow rate
mmol: millimoles
MMEFR: resting maximal mid-expiratory flow rate
PC20: histamine provocative concentration causing a 20% drop in FEV1
PCV: packed cell volume
PEFR: peak expiratory flow rate
PD35 sGaw: a 35% reduction in specific airway conductance
PMNL: polymorphonuclear leucocyte
WBC: white blood cell count

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

Study	Reason for exclusion
Al-Biltagi	This study was retracted by the authors in 2012 due to data analysis issues. Dr Al-Biltagi has confirmed that there are no plans to re-analyse the data and that the research is due to be repeated Retraction. Omega-3 fatty acids, vitamin C and Zn supplementation in asthmatic children: a randomised self-controlled study. *Acta Paediatrica* 2012;101(8):891
Aliyali 2010	Study did not compare vitamin C to placebo/no treatment
Bagnato 1999	Study did not compare vitamin C to placebo/no treatment
Baumann 2005	Study did not compare vitamin C to placebo/no treatment
Bede 2008	Study did not compare vitamin C to placebo/no treatment
Belousova 2006	Study did not compare vitamin C to placebo/no treatment
Bernorio 1996	Study did not compare vitamin C to placebo/no treatment
Bime 2012	Not a trial of vitamin C
Cakmak 2004A	Study did not compare vitamin C to placebo/no treatment
Carlsten 2011	Study did not compare vitamin C to placebo/no treatment
Carlsten 2011a	Study did not compare vitamin C to placebo/no treatment
Chazan 1981	Study not randomised

Study	Reason for exclusion
Covar 2010	Study did not compare vitamin C to placebo/no treatment
Cristofalo 1999	Study did not compare vitamin C to placebo/no treatment: combination intervention as vitamin C given with N-acetylcysteine
Cuomo 2004	Study did not compare vitamin C to placebo/no treatment: intervention was a mixture of antioxidants
Daniliak 1995	Study did not compare vitamin C to placebo/no treatment
Dauletbaev 2001	Study did not compare vitamin C to placebo/no treatment; not randomised
De Lucia 1991	Study did not compare vitamin C to placebo/no treatment
Dunstan 2007	Study did not compare vitamin C to placebo/no treatment: combination intervention
Echazarreta 2000	Study did not compare vitamin C to placebo/no treatment
Echazarreta 2005	Study did not compare vitamin C to placebo/no treatment
Ensom 2003	Study did not compare vitamin C to placebo/no treatment
Falk 2005	Study did not compare vitamin C to placebo/no treatment
Greenough 2010	Participants not diagnosed with asthma; a prophylactic study
Gvozdjakova 2005	Study did not compare vitamin C to placebo/no treatment
Gvozdjakova 2005b	Study did not compare vitamin C to placebo/no treatment: combination intervention
Gvozdjakova 2006	Study did not compare vitamin C to placebo/no treatment: combination intervention
Hernandez 2009	Study did not compare vitamin C to placebo/no treatment: combination intervention
Hosseini 2001	Study did not compare vitamin C to placebo/no treatment
Houdard 1969	Study did not compare vitamin C to placebo/no treatment
Jabbari 2005	Study did not compare vitamin C to placebo/no treatment
Jahnova 2002	Study did not compare vitamin C to placebo/no treatment
Kiss 2000	Study did not compare vitamin C to placebo/no treatment: combination intervention
Kligler 2011	Study did not compare vitamin C to placebo/no treatment
Kolpakova 2007	Study did not compare vitamin C to placebo/no treatment
Kongerud 2003	Study did not compare vitamin C to placebo/no treatment
Kriukov 2003	Study not focused on participants with asthma: evaluation of antioxidants in the prophylaxis of respiratory diseases in young servicemen
Kurth 2008	Study did not compare vitamin C to placebo/no treatment

Study	Reason for exclusion
Labhe 2001	Study did not compare vitamin C to placebo/no treatment
Lau 2004	Study did not compare vitamin C to placebo/no treatment
Lipman, 1964	Study did not compare vitamin C to placebo/no treatment
Lisitsa 2007	Study did not compare vitamin C to placebo/no treatment
Liu 2003	Study did not compare vitamin C to placebo/no treatment: intervention was a combination of vitamins C and E
Ma 2013	Study did not compare vitamin C to placebo/no treatment: intervention was enhanced diet and antioxidants
Medvedeva 2002	Study did not compare vitamin C to placebo/no treatment
Mohsenin 1983	Not a randomised controlled trial
Murphy 2002	Study did not compare vitamin C to placebo/no treatment
Neuman 1999	Study did not compare vitamin C to placebo/no treatment
Neuman 2000	Study did not compare vitamin C to placebo/no treatment
Nikitin 1993	Study did not compare vitamin C to placebo/no treatment.
Olekhnovich 1982	Study did not compare vitamin C to placebo/no treatment: the comparison was between vitamin E (intramuscular or orally) and lecithin versus lecithin, and there is no indication of randomisation
Onur 2011	Study did not compare vitamin C to placebo/no treatment
Panahi 2012	Study did not compare vitamin C to placebo/no treatment
Panina 2002	Study did not compare vitamin C to placebo/no treatment
Pearson 2004	Study did not compare vitamin C to placebo/no treatment
Peden 2005	Study did not compare vitamin C to placebo/no treatment
Pennings 1999	Study did not compare vitamin C to placebo/no treatment
Peters 2001	Study did not compare vitamin C to placebo/no treatment
Prieto 1988	Study did not compare vitamin C to placebo/no treatment
Ratanamaneechat 2010	Study did not compare vitamin C to placebo/no treatment
Romieu 1998	Study did not compare vitamin C to placebo/no treatment: combination intervention
Romieu 2001	Study did not compare vitamin C to placebo/no treatment: combination intervention
Romieu 2002	Study did not compare vitamin C to placebo/no treatment: combination intervention
Romieu 2002a	Study did not compare vitamin C to placebo/no treatment: combination intervention

Study	Reason for exclusion
Romieu 2003	Study did not compare vitamin C to placebo/no treatment: combination intervention
Romieu 2003a	Study did not compare vitamin C to placebo/no treatment: combination intervention
Romieu 2004	Study did not compare vitamin C to placebo/no treatment: combination intervention
Romieu 2004a	Study did not compare vitamin C to placebo/no treatment: combination intervention
Romieu 2004b	Study did not compare vitamin C to placebo/no treatment: combination intervention
Romieu 2004c	Study did not compare vitamin C to placebo/no treatment: combination intervention
Shaheen 2007	Study did not compare vitamin C to placebo/no treatment
Shimizu 1996	Study did not compare vitamin C to placebo/no treatment
Smith 2004	Study did not compare vitamin C to placebo/no treatment
Szlagatys 2005	Study did not compare vitamin C to placebo/no treatment
Ting 1983	Not a randomised controlled trial
Trenca 2001	Study did not compare vitamin C to placebo/no treatment: combination intervention
Tug 2007	Study did not compare vitamin C to placebo/no treatment
Tunnicliffe 2003	Study did not compare vitamin C to placebo/no treatment
Varshavskii 2003	Study did not compare vitamin C to placebo/no treatment
Vazquez-Armenta 2012	Not a trial of vitamin C, but of alpha-lipoic acid
Voelker 1997	A summary report of a trial (almost certainly Trenca 2001) using a combination intervention
Voitsekhovskaia 2007	Study did not compare vitamin C to placebo/no treatment
Wood 2007	Study did not compare vitamin C to placebo/no treatment
Wood 2008	Study did not compare vitamin C to placebo/no treatment
Wood 2012	Study did not compare vitamin C to placebo/no treatment
Wood 2012a	Study did not compare vitamin C to placebo/no treatment
Yamamoto 2013	Not a trial of vitamin C, but of N-acetylcysteine supplementation to people exposed to diesel exhaust

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

IRCT138904224359N1

Trial name or title	Effect of Vitamin E and C supplements on improving asthma

IRCT138904224359N1 *(Continued)*

Methods	Randomised controlled trial
Participants	History of at least 1 year asthma, age 18 to 50 years Exclusion criteria: suffering from diseases other than asthma, smoking, consumption of contraceptive pills
Interventions	800 mg of vitamin C daily for 12 weeks versus placebo (study also includes a vitamin E condition and a vitamin E + vitamin C condition)
Outcomes	Asthma severity and serum levels
Starting date	November 2010
Contact information	Dr Hesamodin Nabavi Zadeh Yasuj University of Medical Sciences
Notes	Study description stated as: "The purpose of this double blind clinical trial is to determine the effect of vitamin E & C, alone and in combination, on the improvement of asthma. 80 asthmatic patients, referred to Mofateh Special Clinics and Yasuj Imam Sajjad Hospital, will be randomly assigned into one of following groups to receive 400 mg Vitamin E per day, 800 mg vitamin C, 400 mg Vitamin E as well as 800 mg vitamin C, or placebo for 12 weeks. Holms-Rahe questionnaire was used to investigate daily stress. Dietary intake is measured using 24-hour dietary recalls questionnaire and respiratory factors are measured by peak flow meter and Spiro meter. Severity of asthma and the serum levels of vitamin C and E are measured before and after the intervention." Study results not posted at time of completion of this review

NCT01057615

Trial name or title	Effect of Fish Oil and Vitamin C on Exercise-Induced Bronchoconstriction and Airway Inflammation in Asthma
Methods	Randomised controlled trial
Participants	Diagnosis of asthma, based on medication use as well as history and symptoms as outlined in the NHLBI Guidelines for the Diagnosis and Management of Asthma
Interventions	Fish oil versus vitamin C versus fish oil + vitamin C
Outcomes	Pulmonary function and exhaled nitric oxide to measure airway inflammation
Starting date	January 2010
Contact information	Timothy D Mickleborough, PhD Indiana University
Notes	Study description stated as: "The aim of this study is to extend previous findings that nutritional supplementation or dietary modification can ameliorate exercise-induced bronchoconstriction. It has been shown in separate studies that fish oil and ascorbic acid (vitamin C) individually protect against EIB by improving pulmonary function and reducing airway inflammation. The main aim of this study is to determine the comparative and additive effects of fish oil and ascorbic acid supplementation on EIB and airway inflammation in asthmatic individuals" Study results not posted at time of completion of this review

ADDITIONAL TABLES

Table 1. Outcomes: chronic asthma

Vitamin C supplementation versus control (asthma)					
Outcome	**Studies**	**N**	**Age**	**Study ID**	**Study reported result**
Health-related quality of life	1	201 participants randomised Vitamin C: 95 (72 completed (76%)) Placebo: 106 (82 completed (77%))	Vitamin C mean: 42 years Placebo mean: 40 years	Fogarty 2003	No significant difference in HRQL between the groups after 16 weeks treatment as measured by the available SF-36 data*
Asthma exacerbations	1	16 children Vitamin C: 7 No treatment: 9	Vitamin C mean: 9.3 years (± 2.4) Control mean: 9.2 years (± 1.9)	Anderson 1983	No exacerbations in either group
FEV1 (L) (at one month)	1	60 participants Vitamin C: 30 Placebo: 30	Vitamin C mean: 48.38 years (± 9.03) Placebo mean: 40.53 years (± 10.48)	Nadi 2012	No direct comparison between vitamin C and placebo reported. Before versus after treatment comparison in vitamin C (P = 0.65) and in placebo (P = 0.044)
FEV1 (ml) (change from 0 to 16 weeks)	1	201 participants randomised Vitamin C: 95 (72 completed (76%)) Placebo: 106 (82 completed (77%))	Vitamin C mean: 42 years Placebo mean: 40 years	Fogarty 2003	No significant difference between vitamin C and placebo: MD -11 (95% CI -92 to 70), P = 0.78
FEV1 (% predicted)	1	10 participants (cross-over design)	Very limited details in trial report (conference abstract)	O'Sullivan 2000	No significant change in FEV1 after vitamin C administration (95 ± 2.7% versus 94.2 ± 3.2%)
PEFR (L/min) (change from 0 to 16 weeks) AM	1	201 participants randomised Vitamin C: 95 (72 completed (76%)) Placebo: 106 (82 completed (77%))	Vitamin C mean: 42 years Placebo mean: 40 years	Fogarty 2003	No significant difference between vitamin C and placebo: MD 0.9 (95% CI -11.8 to 13.5), P = 0.89
PEFR (L/min) (change from 0 to 16 weeks) PM	1	201 participants randomised Vitamin C: 95 (72 completed (76%)) Placebo: 106 (82 completed (77%))	Vitamin C mean: 42 years Placebo mean: 40 years	Fogarty 2003	No significant difference between vitamin C and placebo: MD 2.2 (95% CI -10.0 to 14.3), P = 0.73
Asthma symptoms (change from 0 to 16 weeks)	1	201 participants randomised Vitamin C: 95 (72 completed (76%))	Vitamin C mean: 42 years Placebo mean: 40 years	Fogarty 2003	No significant difference between vitamin C and placebo: MD 0 (95% CI -0.2 to 0.1), P = 0.33

Table 1. Outcomes: chronic asthma *(Continued)*

		Placebo: 106 (82 completed (77%))			
Adverse events	1	41 participants Vitamin C: 22 Placebo: 19	Vitamin C mean: 26.5 years (range 15 to 42) Placebo mean: 27.8 years (range 15 to 46)	Anah 1980	No adverse events in either group

*Authors note: "SF-36 data on physical functioning were incomplete and this section was excluded from analysis".
FEV1: forced expiratory volume in one second
HRQL: health-related quality of life
PEFR: peak expiratory flow rate

Table 2. Outcomes: exercise-induced bronchoconstriction/asthma

Vitamin C supplementation versus placebo (exercise-induced bronchoconstriction/asthma)					
Outcome	**Studies**	**N**	**Age**	**Study ID**	**Study reported result**
Health-related quality of life	0	0	—	—	—
Asthma exacerbations	0	0	—	—	—
FEV1 (L) (change scores)					
Immediately after exercise	1	12 participants (cross-over design)	Mean age 26 years (± 5)	Schachter 1982	No significant difference between vitamin C and placebo Vitamin C: mean +0.21 (standard error (SE) ± 0.06) Placebo mean +0.08 (SE ± 0.08) t = 1.46 (P = 0.18)
5 minutes after exercise	1	12 participants (cross-over design)	Mean age 26 years (± 5)	Schachter 1982	No significant difference between vitamin C and placebo Vitamin C: mean - 0.24 (SE ± 0.06) Placebo mean: -0.44 (SE ± 0.14) t = 2.13 (P = 0.057)
Post-bronchodilator	1	12 participants (cross-over design)	Mean age 26 years (± 5)	Schachter 1982	Post-bronchodilator scores significantly better on vitamin C Vitamin C: mean + 0.43 (SE ± 0.12) Placebo mean + 0.22 (SE ± 0.10) t = 3.42 (P < 0.01)
FEV1 % drop postexercise	1	8 participants (cross-over design)	Mean age: 24.5 years (4.8)	Tecklenburg 2007	A significant advantage in favour of vitamin C

Table 2. Outcomes: exercise-induced bronchoconstriction/asthma *(Continued)*

					Reported maximum % drop in FEV1 post-exercise on vitamin C diet was -6.4% (95% CI -12.0 to -0.8%; effect size using omega-squared (ES) 0.40); indicative of an attenuated EIB response. This was significantly different (P < 0.05) from the maximum drop of -12.9% (95% CI -18.6 to -12.3%) on placebo
PEF (change scores)					
Immediately after exercise	1	12 participants (cross-over design)	Mean age 26 years (± 5)	Schachter 1982	A significant advantage in favour of vitamin C Vitamin C: mean +0.59 (SE ± 0.16) Placebo mean +0.10 (SE ± 0.25) t = 2.3 (P < 0.05)
5 minutes after exercise	1	12 participants (cross-over design)	Mean age 26 years (± 5)	Schachter 1982	No significant difference between vitamin C and placebo Vitamin C: mean -0.73 (SE ± 0.28) Placebo mean -0.95 (SE ± 0.40) t = 0.90 (NS)
Post-bronchodilator	1	12 participants (cross-over design)	Mean age 26 years (± 5)	Schachter 1982	A significant advantage in favour of vitamin C Vitamin C: mean +0.83 (SE ± 0.26) Placebo mean +0.39 (SE ± 0.29) t = 2.69 (P < 0.05)
Asthma symptoms	1	8 participants (cross-over design)	Mean age: 24.5 years (4.8)	Tecklenburg 2007	A significant advantage in favour of vitamin C Reported asa significant improvement (P < 0.05) in mean asthma symptom scores (mean score 6.3; 95% CI 5.8 to 6.8) on the vitamin C diet compared to the placebo diet (mean score 5.8; 95% CI 5.1 to 6.2)
Adverse events	0	0	—	—	—

*Tecklenburg 2007 used Asthma Quality of Life Questionnaire symptom score component. These data are reported in the table under symptoms.
CI: confidence interval
FEV1: forced expiratory volume in one second
NS: non-significant
SE: standard error

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways 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
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 Group 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 antioxidant*

#9 #5 or #6 or #7 or #8

#10 #4 and #9

[In search line #1, MISC1 denotes the field in the reference record where the record 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 28 records. Twenty six records were excluded on the basis of title and abstract. Two were retrieved in full text. We found two small studies (Akhtar 2016; Hemila 2011 (subsequently retracted)) added to Characteristics of studies awaiting classification. We have decided not to update the review at this point in time.

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- SJM, UK.

  NIHR and St George's University of London

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Antioxidants [*administration & dosage]; Ascorbic Acid [*administration & dosage]; Asthma [*drug therapy]; Asthma, Exercise-Induced [drug therapy]; Health Status; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans