Vitamin C supplementation for asthma (Review)

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TABLE OF CONTENTS

[Intervention Review]

Vitamin C supplementation for asthma

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ABSTRACT

Background

Vitamin C is one of the key antioxidant vitamins which is abundant in the extracellular fluid lining the lung and low vitamin C intake has been associated with pulmonary dysfunction.

Objectives

To evaluate the evidence for the efficacy of vitamin C in the treatment of asthma.

Search methods

The Cochrane Airways Review Group asthma register was searched and bibliographies of studies identified were also checked for further trials. This review has been updated by searches to August 2008.

Selection criteria

Only randomised controlled trials were eligible for inclusion. Studies were considered for inclusion if they dealt with the treatment of asthma using vitamin C supplementation. Two independent reviewers identified potentially relevant studies using pre-defined criteria and selected studies for inclusion.

Data collection and analysis

Data were abstracted independently by two reviewers. Information on patients, methods, interventions, outcomes and results was extracted using standard forms.

Main results

Nine studies met the review entry criteria, randomising a total of 330 participants. Study design varied and the reporting was generally poor. Five trials contributed numerical data to the review. They provided outcome data on lung function, symptom scores, IgE levels and inhaled steroid use. One small study showed a significant difference in % drop in FEV1 post-exercise.

Authors' conclusions

At present, evidence from randomised-controlled trials is insufficient to recommend a specific role for vitamin C in the treatment of asthma. 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.

PLAIN LANGUAGE SUMMARY

Vitamin C supplementation for asthma

Asthma is a chronic inflammatory disease of the airways characterised by wheeze and breathlessness. One theory for the observed increase in the number of people with asthma is the 'western' diet with it's lack of nutrients from fresh food. We reviewed evidence from nine trials of the antioxidant vitamin C as a treatment for asthma. In general the trials were small, varied greatly in their design and the reporting was poor. From the available evidence it is not possible to recommend either the use or avoidance of vitamin C supplements in asthma.

BACKGROUND

Asthma is now recognised as a chronic inflammatory disease resulting in reversible airways bronchoconstriction (Holgate 1990). The incidence and prevalence of asthma has increased in many countries over the past few decades. The most marked increase has been observed in children (Strachan 1999; Lewis 1996). This may be due to changing environmental exposures or the increased susceptibility of populations with reduced host resistance (Seaton 1994).

One hypothesised cause for this increase is that changes in "western" diet have produced a reduction in host resistance over time. In particular recent interest has focused on the association between anti-oxidants in diets and health outcomes. Cross-sectional studies show that infrequent fruit consumption is associated with reduced lung function, both in children (Cook 1997) and adults (Butland 1999). In addition, the National Food Survey has documented a drop in the consumption of antioxidant food sources such as fresh fruit and vegetables in countries such as Great Britain since the 1950's (Seaton 1994).

Vitamin C is one of the key antioxidant vitamins which is abundant in the extracellular fluid lining the lung. Low vitamin C intake is associated with pulmonary dysfunction (Schwartz 1994). Both adults (Olusi 1979) and children (Aderele 1985) with asthma have been found to have lower concentrations of vitamin C when compared to normal subjects. Patients with asthma may have low supplies of vitamin C or an increased demand for vitamin C in the face of an oxidant load resulting in depletion. There is a need to clarify whether supplementation with vitamin C may bring benefits in reducing morbidity, improving pulmonary function or quality of life in patients with asthma.

There have been three recent reviews of the literature on the role of vitamin C in asthma (Bielory 1994; Hatch 1995; Monteleone 1997). However, the review by Bielory et al (Bielory 1994) only searched the English language literature using MEDLINE and gave no further details as to how the studies had been located. The other two reviews did not specify their methodology. These reviews reached different conclusions. Bielory et al (Bielory 1994) concluded that the role of vitamin C in asthma was unclear and that current literature did not support its use. The review by Hatch et al (Hatch 1995) found 7 out of 11 studies indicated that vitamin C supplementation might reverse or improve asthma symptoms. The review by Monteleone et al (Monteleone 1997) offers the opinion that vitamin C provides a short term protective effect on airway responsiveness, but less clear impact on other objective lung function measurements. All three reviews recommend further studies into the role of vitamin C in asthma. As a first step, a review using the Cochrane methodology is needed to systematically weigh the quality of the existing evidence before recommending any future studies.

OBJECTIVES

To determine the overall efficacy of vitamin C supplementation in patients with stable chronic asthma.

METHODS

Criteria for considering studies for this review

Types of studies

To be eligible, all studies needed to be randomised-controlled trials (RCTs). Double-blinded trials were preferred, but single blind and open studies were also reviewed for possible inclusion.

Types of participants

Studies were considered for inclusion if they recruited adults and/or children with chronic stable asthma, seasonal asthma or those with exercise-induced bronchospasm. Studies of other allergic conditions such as hay fever, allergic rhinitis and eczema were only considered if the results for subjects with asthma were presented separately. Vitamin C studies, which reported outcomes on patients with asthma separately as a sub-group, were also considered for inclusion.

Types of interventions

Vitamin C supplementation compared to placebo or "standard care". We considered studies that administered vitamin C via any route, dosage or dose interval. Both single dose and longer -term studies were considered for inclusion.

Types of outcome measures

Primary outcome measures

1) Lung function (e.g. FEV1, PEFR)
2) Symptoms (e.g. symptom scores)

Secondary outcome measures

3) Functional outcomes (e.g. quality of life, sickness absence, exercise capacity)
4) Non-specific bronchial hyper-reactivity (BHR) to histamine or methacholine
5) Immunological markers (IgE levels)
6) Asthma medication requirements (e.g. additional steroid or bronchodilator usage)
7) Health service utilisation (e.g. GP attendance, hospital admissions)
8) Asthma exacerbations

Search methods for identification of studies

Electronic Searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from 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 the Airways Group Module for further details). All records in the Specialised Register coded as 'asthma' were searched using the following terms:
ascorbic* or "vitamin c" or antioxid*
The most recent search was conducted in August 2008.

Other sources

Reference lists of all primary studies and review articles were reviewed for additional references. Authors of identified trials were contacted.

Data collection and analysis

Retrieval of studies

All trials that appeared potentially relevant were assessed by two independent reviewers for relevance using abstract and title from the electronic search. Using texts from all potentially relevant articles, final inclusion was also determined independently by two reviewers. Disagreements about study inclusion were resolved with discussion.

Assessment of methodological quality

The quality of included studies was assessed using the Cochrane approach. A risk of bias table was completed for each study assessing the reporting of method of randomisation, allocation concealment and blinding. Each item was judged as being adequate, unclear or inadequate. Any disagreements between reviewers were resolved by discussion.

Data abstraction

Data were extracted independently by two reviewers and entered in the Cochrane Collaboration Software, Review Manager (RevMan). For studies where the original data were not presented, when possible, they were extracted from graphically representations. Study outcomes that were reported post-bronchial challenge (e.g. exercise or histamine) were analysed separately from outcomes

that did not involve bronchial challenge or when results were reported before such challenges (but post-dose vitamin C administration).

Statistical considerations

Outcomes from included trials were combined using RevMan. For continuous outcomes the weighted mean difference (WMD) with fixed effect was used to estimate the individual effect sizes and 95% confidence intervals (95% CI). If there were any dichotomous outcomes the Peto fixed or random effect model was to be used to estimate the pooled odds ratio (OR) and 95% CI.

The main planned comparison for statistical consideration was any form or dose of vitamin C supplementation versus placebo or "standard care". If there were adequate included studies, the following pre-defined sub-group analysis were planned:

1. Single dose versus chronic administration of vitamin C
2. Dietary advice to increase vitamin C consumption versus no intervention
3. Oral vitamin C versus intravenous vitamin C supplementation
4. Adults versus children
5. Males versus females

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Details of the search history and results can be found in Table 1. For the 2008 update, 39 new references were identified and the full text of 15 of these were retrieved. One additional included study (Tecklenburg 2007), an extension to a previously included study (Fogarty 2003), and 5 further excluded studies were identified. The review now contains a total of nine studies which meet the inclusion criteria. Further details can be found in the table, "Characteristics of included studies". A total of twelve studies were excluded after examining the full-text paper. Please see "Characteristics of excluded studies" for further details.

The included studies were conducted in the USA (Kordansky 1979; Schachter 1982,Tecklenburg 2007), Nigeria (Anah 1980), South Africa (Anderson 1983), Canada (Malo 1986), Israel (Cohen 1997) and the UK (Fogarty 2003; O'Sullivan 2000).

Three studies examined the impact of vitamin C supplementation on exercise challenge tests in subjects with a confirmed diagnosis of exercise-induced asthma (Cohen 1997; Schachter 1982, Tecklenburg 2007). Two studies examined the impact of vitamin C administration on bronchial hyper responsiveness to histamine challenge tests in participants with asthma (Malo 1986; O'Sullivan 2000). Four studies examined the impact of vitamin C on bronchial hyper responsiveness to allergen challenge in subjects sensitive to ragweed allergen (Kordansky 1979), frequency of asthma exacerbations due to infection (Anah 1980), lung function and immunological markers in patients with asthma (Anderson 1983) and clinical control of asthma in primary care (Fogarty 2003).

Three of the studies (Anah 1980; Anderson 1983; Fogarty 2003) followed a parallel study design and the remaining 6 used crossover designs. Data from the two types of study designs were presented separately in RevMan. No usable data could be extracted from the reports of four studies (Anah 1980;Kordansky 1979; Malo 1986; O'Sullivan 2000), despite attempts at author contact.

Seven studies (Anah 1980; Fogarty 2003; Kordansky 1979; Malo 1986; O'Sullivan 2000; Schachter 1982, Tecklenburg 2007) involved adult patients, one study (Anderson 1983) involved only children and one (Cohen 1997) had both adults and children. The smallest study had six participants (Kordansky 1979). Others ranged from 8 to 41. The largest was Fogarty 2003 with 210 participants. This review contains a total of 330 randomised participants.

All treatments were administered orally, either as tablets or as an oral solution. Three studies (Anah 1980; Anderson 1983; Fogarty 2003) featured long-term supplementation with 1 g vitamin C daily for 14 weeks, 6 months and 16 weeks, respectively. Another long-term study (Kordansky 1979) used 500 mg vitamin C supplementation daily for seven days. One study looked at supplementation with 1500mg over a short -term period of two weeks (Tecklenburg 2007) and the remaining four studies (Cohen 1997; Malo 1986; O'Sullivan 2000; Schachter 1982) used single doses of vitamin C 2g, 2g, 2g and 500 mg, respectively.

Two of the crossover studies (Cohen 1997, Tecklenburg 2007) mentioned a washout period. None of the other crossover studies (Kordansky 1979; Malo 1986; O'Sullivan 2000; Schachter 1982) reported a washout period. It has been suggested that after a single oral dose of vitamin C, at least 1-2 days is required for excretion depending on pre-existing body levels (Bates 2001).

Included studies reported disparate outcome measures, which made aggregation for the purpose of a meta-analysis difficult. Most of the studies did not report the actual data in the published papers or did not provide sufficient data for a meta-analysis, although attempts were made to contact the authors for data. Outcome measures included a variety of lung function tests, symptoms and symptom scores, immune markers and reduction in the use of inhaled steroids.

Risk of bias in included studies

In general, the reporting quality of the studies was poor. All the included studies were reported as being randomised, however, only one study (Fogarty 2003) reported the method of randomisation and just three of the nine studies reported the method of allocation concealment (Anah 1980, Fogarty 2003, Malo 1986). Four

studies reported the method of blinding (Anah 1980, Malo 1986, Schachter 1982, Tecklenburg 2007), while one study was inadequately blinded (Anderson 1983) and the remaining four were unclear.

None of the studies adequately reported all three methods of randomisation, allocation concealment or blinding. Anah 1980, Fogarty 2003 and Malo 1986 gave the most detailed account. An overview of our judgments of are presented in Figure 1 and Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

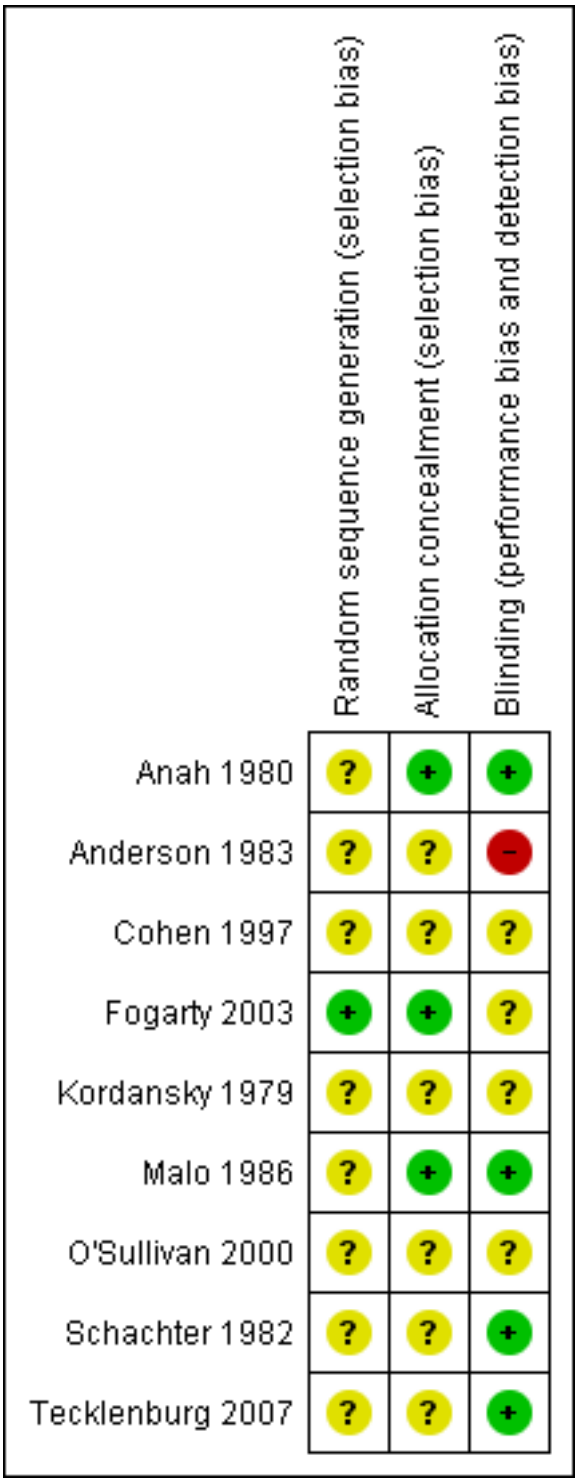
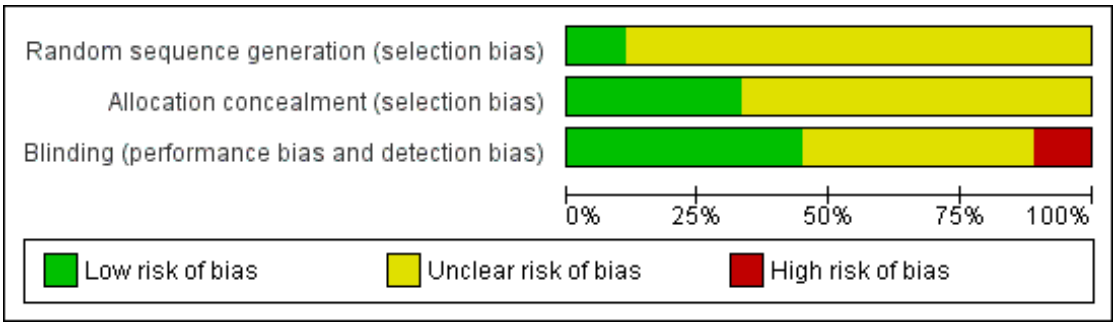


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Effects of interventions

Of the nine included studies, five have contributed numerical data to the review: Anderson 1983, Cohen 1997, Fogarty 2003, Schachter 1982 and Tecklenburg 2007. Four studies (Anah 1980; Kordansky 1979; Malo 1986; O'Sullivan 2000) did not report data in an manner that permitted further analysis and author contact has been unsuccessful. However, none of these studies found a significant difference for the effect of vitamin C on lung function or symptoms.

Studies could not be combined statistically, because those which addressed similar comparisons used different interventions or outcome variables. For example, there were three studies where the protective effects of vitamin C were investigated using exercise challenge. All three reported pulmonary function outcomes, but Cohen 1997 only reported results from 11 of the 20 randomised participants (who were found to have a fall in FEV1 of less than 15% following vitamin C), Schachter 1982 reported absolute change post-exercise and Tecklenburg 2007 was a two week intervention study rather a single dose study, and reported maximum percentage fall from baseline.

Primary outcomes

Lung function

Single dose studies

Change in FEV1 (L) - post-exercise challenge: (MD 0.13; 95% CI -0.05 to 0.31) (, Schachter 1982). Cohen reported that 11 of the 20 participants had a change of FEV1 after exercise of less than 15% following vitamin C but all 20 participants had a change of 15% or more following placebo. Mean changes were only presented for the 11 participants who had better results with vitamin C, and these are not included as this is a biased estimate of the true expected treatment effect.

Change in FVC (L) - post-exercise challenge: (MD 0.13; 95% CI -0.03 to 0.29) (Schachter 1982)

Change in PEFR (L/min) - post-exercise challenge: (MD 0.49; 95% CI -0.07 to 1.05) (Schachter 1982)

Short term studies

FEV1 (%) drop post-exercise: a significant difference was shown in favour of vitamin C: (MD 6.50%; 95% CI 0.05 to 12.95) (Tecklenburg 2007)

Long term studies

FEV1 mL at four months:(MD -11.00; 95% CI -91.36 to 69.36) (Fogarty 2003)

Peak flow L/min (morning and evening) at 4 months: (Mean difference am 0.90; 95% CI -11.74 to 13.54) and (Mean difference pm 2.20; 95% CI -9.95 to 14.35) (Fogarty 2003)

Symptom Scores

One study (Tecklenburg 2007) reported data on symptom scores (Asthma Quality of Life Questionnaire). There was no significant difference (MD 0.50; 95% CI -0.24 to 1.24).

Secondary outcomes

IgE (IU/ml serum) - absolute values at one month: (MD 4.00; 95% CI -140.42 to 148.42) (Anderson 1983)

IgE (IU/ml serum) - absolute values at three months: (MD -312.00; 95% CI -628.21 to 4.21) (Anderson 1983)

IgE (IU/ml serum) - absolute values at six months: (MD -143.00; 95% CI -425.38 to 139.38)(Anderson 1983)

Decrease in inhaled corticosteroid use (µg): no significant difference (Fogarty 2003)

There were no data from any of the included studies for health service utilisation.

Data on acute exacerbations was provided by one study (Anah 1980). There were nine exacerbations in the intervention group

which had 22 patients and 35 exacerbations in the placebo group which had 19 patients. Thus some patients had more than one exacerbation. Data concerning the number of patients who had one or more exacerbations would be more meaningful since it would not be subjected to bias from a few patients with recurrent exacerbations.

Adverse effects

Only one study (Anah 1980) reported on adverse effects. None of the participants in either group experienced any side effects.

DISCUSSION

We found nine randomised controlled trials assessing vitamin C supplementation as a treatment for asthma. These covered single-dose, short-term and long-term administration. Because the studies were very diverse and reported outcomes in different ways, it was not possible to pool the results. Four of the studies did not contribute any numerical data to the review, although none of these reported a significant difference for either of our primary outcomes of lung function and symptom scores. The only outcome reported by more than one study was pre-exercise FEV1, but the results from the different studies were not suitable for pooling in a meta-analysis.

One study (Tecklenburg 2007) found a significant difference in favour of vitamin C on the percentage drop in FEV1 post-exercise in mild-to-moderate persistent asthmatics with exercise-induced asthma. This was a small study of eight participants who were assigned to vitamin C or placebo for two weeks, then crossed over after a one week washout period. The size and duration of the trial means that the positive outcome should be interpreted with caution.

The reporting of the trial methods was generally poor. The method of randomisation, allocation concealment and blinding was not always clear, leaving the results open to bias. Only one study reported on adverse effects. No side effects were experienced by any participant in the vitamin C or placebo group, and Vitamin C is generally considered to be safe in recommended amounts, however, mega-doses can cause adverse effects (MedlinePlus 2008) so it is still important for adverse effects to be documented in trial reports.

Previous reviews of vitamin C in asthma (Bielory 1994, Hatch 1995, Monteleone 1997) all recommended more research before any solid conclusions can be drawn. Although all but one of the studies included in this review appear to show no effect of vitamin C on asthma, the diversity of the study designs meant that it was not possible to combine them to gain an overall picture. The role of vitamin C in asthma is still unclear.

AUTHORS' CONCLUSIONS

Implications for practice

At present, evidence from the limited number of randomised-controlled trials is insufficient to recommend a specific role for vitamin C in the treatment or management of asthma.

Implications for research

Further randomised, double blind, placebo controlled trials of vitamin C supplementation in asthma are needed, particularly in children. When designing such a trial, attention must be paid to well defined interventions excluding known confounders (e.g., smoking, caffeine, drugs), statistical power (to show clinically relevant differences) and the relevance of outcomes (e.g., lung function, symptoms, medication usage, quality of life, exacerbations). It is also important to consider the pharmacokinetics / pharmacodynamics of vitamin C for adequate dosing and washout period especially when using a crossover design.

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REFERENCES

References to studies included in this review

Anah 1980 *{published data only}*
Anah CO, Jarike LN, Baig HA. High dose ascorbic acid in Nigerian asthmatics. *Tropical and Geographical Medicine* 1980;**32**(2):132–7. [: PMID: 7423602]

Anderson 1983 *{published data only}*
Anderson R, Hay I, van Wyk HA, Theron A. Ascorbic acid in bronchial asthma. *South African Medical Journal* 1983; **63**(17):649–52.

Cohen 1997 *{published data only}*
Cohen HA, Neuman I, Nahum H. Blocking effect of vitamin C in exercise-induced asthma. *Archives of Pediatrics and Adolescent Medicine* 1997;**151**(4):367–70.

Fogarty 2003 *{published data only}*
Fogarty A, Lewis SA, Scrivener SL, Antoniak M, Pacey S, Pringle M. Corticosteroid sparing effects of vitamin C and magnesium in asthma: a randomised trial. *Respiratory Medicine* 2006;**100**(1):174–9. [PUBMED: 16338599]
* Fogarty A, Lewis SA, Scrivener SL, Antoniak M, Pacey S, Pringle M, et al.Oral magnesium and vitamin C supplements in asthma: a parallel group randomized placebo-controlled trial. *Clinical and Experimental Allergy* 2003;**33**(10):1355–9. [PUBMED: 14519140]

Kordansky 1979 *{published data only}*
Kordansky DW, Rosenthal RR, Norman PS. The effect of vitamin C on antigen-induced bronchospasm. *Journal of Allergy and Clinical Immunology* 1979;**63**(1):61–64.

Malo 1986 *{published data only}*
Malo JL, Cartier A, Pineau L, L'Archeveque J, Ghezzo H, Martin RR. Lack of acute effects of ascorbic acid on spirometry and airway responsiveness to histamine in subjects with asthma. *Journal of Allergy and Clinical Immunology* 1986;**78**(6):1153–8.

O'Sullivan 2000 *{published data only}*
O'Sullivan S, Doyle S, Cormican L, Gunaratnam C, Poulter LW, Burke CM. Attenuation of bronchial hyperresponsiveness to histamine by vitamin C in asthmatic subjects. *American Journal of Respiratory and Critical Care Medicine* 2000;**161**(3 Suppl):A106.

Schachter 1982 *{published data only}*
Schachter EN, Schlesinger A. The attenuation of exercise-induced bronchospasm by ascorbic acid. *Annals of Allergy* 1982;**49**(3):146–151.

Tecklenburg 2007 *{published data only}*
Tecklenburg SL, Mickleborough TD, Fly AD, Bai Y, Stager JM. Ascorbic acid supplementation attenuates exercise-induced bronchoconstriction in patients with asthma. *Respiratory Medicine* 2007;**101**(8):1770–8. [PUBMED: 17412579]

References to studies excluded from this review

Cuomo 2004 *{published data only}*
Cuomo B, Fasoli L, Guerrea T, Cosettini M, Don M, Saretta F, et al.Efficacy of antioxidant supplementation diet in asthmatic children [Abstract]. *European Respiratory Journal* 2004;**24**(Suppl 48):167s.

Forastiere 2000 *{published data only}*
Forastiere F, Pistelli R, Sestini P, Fortes C, Renzoni E, Rusconi F, et al.Consumption of fresh fruit rich in vitamin C and wheezing symptoms in children. SIDRIA Collaborative Group, Italy (Italian Studies on Respiratory Disorders in Children and the Environment). *Thorax* 2000; **55**(4):283–8. [: PMID: 10722767]

Gvozdjakova 2005 *{published data only}*
Gazdik F, Gazdikova K, Jahnova E, Pijak MR. Sparing effect of coenzyme Q10, a-tocopherol and ascorbic acid on the consumption of corticosteroids in allergic asthmatics [Abstract]. *Allergy & Clinical Immunology International* 2003;**1 Suppl**:Abstract No: P-2-38.
Gazdik F, Gvozdjakova A, Kucharska J, Kucharikova Z, Jahnova E, Gazdikova. Coenzyme Q10 supplementation therapy decreased corticosteroid consumption in patients with asthma. Advances in Immunopathology & Respiratory Allergy. 2005:29–33.
* Gvozdjakova A, Kucharska J, Bartkovjakova M, Gazdikova K, Gazdik FE. Coenzyme Q10 supplementation reduces corticosteroids dosage in patients with bronchial asthma. *Biofactors* 2005;**25**:235–40. [PUBMED: 16873952]

Kongerud 2003 *{published data only}*
Kongerud J, Crissman K, Hatch G, Alexis N. Ascorbic acid is decreased in induced sputum of mild asthmatics. *Inhalation Toxicology* 2003;**15**:101–109.

Miric 1991 *{published data only}*
Miric M, Haxhiu MA. Effect of vitamin C on exercise-induced bronchoconstriction [Article in Serbo–Croatian (Roman)]. *Plucne Bolesti* 1991;**43**(1-2):94–97. [MEDLINE: PMID: 1766998; : UI: 92115812]

Mohsenin 1983 *{published data only}*
Mohsenin V, Dubois AB, Douglas JS. Effect of ascorbic acid on response to methacholine challenge in asthmatic subjects. *American Review of Respiratory Diseases* 1983; **127**(3):143–147. [MEDLINE: PMID: 6830027; : UI: 83150876]

Mohsenin 1987 *{published data only}*
Mohsenin V. Effect of vitamin C on NO2-induced airway hyperresponsiveness in normal subjects. *American Review of Respiratory Diseases* 1987;**136**:1408–1411.

Murphy 2002 *{published data only}*
Murphy JD, Ferguson CS, Brown KR, Harms CA. The effect of dietry antioxidants on lung function in exercise induced asthmatics. *Medicine & Science in Sports & Exercise* 2002;**34**(5 Suppl 1):S155.

Omenaas 2003 *{published data only}*
Omenaas E, Fluge O, Buist AS, Vollmer WM, Gulsvik. Dietary vitamin C intake is inversely related to cough and

wheeze in young smokers. *Respiratory Medicine* 2003;**97**(2): 134–42.

Panina 2002 ***{published data only}***

Panina NT, Yakovleva NG, Kotenko TV, Danilov LN. Role of antioxidant and trace element complex in outpatient care of bronchial asthma [Abstract]. *European Respiratory Journal* 2002;**20**(Suppl 38):52s.

Romieu 2002 ***{published data only}***

Ramirez M, Morena H, Sienra JJ, Reyes N, DelRio BE, Hatch G, et al.Modulation of air pollution impact on peak expiratory flow by serum levels of a-tocopherol and ascorbic acid among asthmatic children in Mexico City. American Thoracic Society 99th International Conference. 2003: B091 Poster 917.

Romieu I, Sienra JJ, Ramirez M, Moreno H, Del Rio BE, Hatch G, et al.Antioxidant supplementation and inflammatory responses among young asthmatics exposed to high levels of air pollutants [Abstract]. *European Respiratory Journal* 2004;**24**(Suppl 48):623s.

Romieu I, Sienra J J, Ramirez M, Moreno H, Reyes N I, Del Rio BE, et al.Antioxidant supplementation and generic susceptibility to ozone: a randomized controlled trial of children with asthma [abstract]. American Thoracic Society 99th International Conference. 2003:C014.

Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, Moreno-Macias H, Reyes-Ruiz NI, Del Rio-Navarro BE. Incidence of wheezing and genetic polymorphism of GSTM1 among asthmatic children supplemented with antioxidants in Mexico City [Abstract]. American Thoracic Society 100th International Conference, May 21-26, 2004, Orlando. 2004:C24 Poster 701.

Romieu I, Sienra-Monge J J, Ramirez-Aguilar M, Moreno-Macias H, Reyes-Ruiz N I, Estela del Rio-Navarro B, et al.Genetic polymorphism of GSTM1 and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in Mexico City. *Thorax* 2004;**59**(1):8–10.

* Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, Tellez-Rojo MM, Moreno-Macias H, Reyes-Ruiz NI, et al.Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants. *American Journal of Respiratory & Critical Care Medicine* 2002;**166**(5):703–9. [PUBMED: 12204869]

Sienra-Monge JJ, Ramirez-Aguilar M, Moreno-Macias H, Reyes-Ruiz NI, Del Rio-Navarro BE, Ruiz-Navarro MX, et al.Antioxidant supplementation and nasal inflammatory responses among young asthmatics exposed to high levels of ozone. *Clinical & Experimental Immunology* 2004;**138**(2): 317–22. [PUBMED: 15498043]

Ting 1983 ***{published data only}***

Ting S, Mansfield LE, Yarbrough J. Effects of ascorbic acid on pulmonary functions in mild asthma. *Journal of Asthma* 1983;**20**(1):39–42. [MEDLINE: PMID: 6853425; : UI: 83213036]

References to studies awaiting assessment

Al-Biltagi ***{published data only}***

Al-Biltagi MA, Baset AA, Bassiouny M, Kasrawi MA, Attia M. Omega-3 fatty acids, vitamin C and Zn supplementation in asthmatic children: a randomized self-controlled study. *Acta Paediatrica* 2009;**4**:737–42.

Additional references

Aderele 1985

Aderele WI, Ette SI, Oduwole O, Ikpeme SJ. Plasma vitamin C (ascorbic acid) levels in asthmatic children. *African Journal of Medical Science* 1985;**14**(3-4):115–120. [MEDLINE: PMID: 3004170; : UI: 86126797]

Bates 2001

Bates C (Human Nutrition Unit, University of Cambridge). Personal communication 2001.

Bielory 1994

Bielory L, Gandhi R. Asthma and vitamin C. *Annals of Allergy* 1994;**73**:89–99.

Butland 1999

Butland BK, Strachan DP, Anderson HR. Fresh fruit intake and asthma symptoms in young British adults: confounding or effect modification by smoking?. *European Respiratory Journal* 1999;**13**(4):744–50. [MEDLINE: PMID:10362034; : UI:99288880]

Cook 1997

Cook DG, Carey IM, Whincup PH, Papagosta O, Chirico S, Bruckdorfer KR, Walker M. Effect of fresh fruit consumption on lung function and wheeze in children. *Thorax* 1997;**52**:628–33.

Fisher 1948

Fisher RA. Combining independent tests of significance. *Am Stat* 1948;**2**:30.

Hatch 1995

Hatch GE. Asthma, inhaled oxidants and dietary antioxidants. *American Journal of Clinical Nutrition* 1995; **61**(Suppl 3):625S–630S.

Holgate 1990

Holgate ST. Interfaces in medicine: asthma. Report of a conference. *Journal of the Royal College of Physicians of London* 1990;**24**(4):313–7. [MEDLINE: PMID: 2258849; : UI: 91080048]

Lewis 1996

Lewis S, Butland B, Strachan D, Bynner J, Richards D, Butler N, et al.Study of the aetiology of wheezing illness at age 16 in two national British birth cohorts. *Thorax* 1996;**51**(7):670–6. [MEDLINE: PMID: 8882071; : UI: 97036423]

MedlinePlus 2008

MedlinePlus. Vitamin C (ascorbic acid). http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-vitaminc.html (accessed 29 August 2008).

Monteleone 1997

Monteleone CA, Sherman AR. Nutrition and asthma. *Archives of Internal Medicine* 1997;**157**:23–34.

Olusi 1979
Olusi SO, Ojutiku OO, Jessop WJ, Iboko MI. Plasma and white blood cell ascorbic acid concentrations in patients with bronchial asthma. *Clinica Chimica Acta* 1979;**92**(2): 161–6. [MEDLINE: PMID: 487570; : UI: 80023020]

Rundell 2009
Rundell KW, Slee JB. Exercise and other indirect challenges to demonstrate asthma or exercise-induced bronchoconstriction in athletes. *J Allergy Clin Immunol* 2009;**122**:238–46.

Schwartz 1994
Schwartz J, Weiss ST. Relationship between dietary vitamin C intake and pulmonary function in the First National Health and Nutrition Examination Survey (NHANES I). *American Journal of Clinical Nutrition* 1994;**59**(1):110–4. [MEDLINE: PMID: 8279390; : UI: 94106429]

Seaton 1994
Seaton A, Godden DJ, Brown K. Increase in asthma: a more toxic environment or a more susceptible population?. *Thorax* 1994;**49**(2):171–4. [MEDLINE: PMID: 8128408; : UI: 94174476]

Strachan 1999
Strachan D. The epidemiology of childhood asthma. *Allergy* 1999;**54**(Suppl 49):7–11.

References to other published versions of this review

Ram 2001
Ram FSF, Rowe BH, Kaur B. Vitamin C supplementation for asthma. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD000993]

Ram 2004
Ram FSF, Rowe BH, Kaur B. Vitamin C supplementation for asthma. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD000993.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Anah 1980

Methods	Randomised double-blind, placebo controlled, parallel trial.
Participants	41 Nigerian adults (22 males, 19 females), aged 15-46, attending a hospital clinic. Non-smokers, asthmatic for at least 4 years, with exacerbations in the rainy season due to respiratory infections. All continued with regular medication (mostly bronchodilators but N not specified, 1 on oral steroids)
Interventions	For 14 weeks over the rainy season 1g vitamin C orally, once daily (n=22) compared to placebo dummy pill (n=19)
Outcomes	Asthma attacks during the rainy season - mild (self-reported increase in wheeze/breathlessness), moderate (required increase in inhaler use, addition of medication on regular basis) severe (emergency admission)
Notes	Data not presented in an abstractable format, no reply from author to date

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Low risk	Allocation of treatment was coded and the code revealed after the completion of the study
Blinding (performance bias and detection bias) All outcomes	Low risk	Tablets described as identical

Anderson 1983

Methods	Randomised, parallel trial.
Participants	16 white South African children (12 males, 4 females) aged 6-13 on beta agonists, cromoglycates & aminophylline for asthma but no steroids. No intestinal parasites
Interventions	1g vitamin C plus standard therapy daily for 6 months (n=7) vs standard therapy (n=9). Study also included i.v. arm but has no placebo arm for this i.v. group and the i.v. patients were not randomised
Outcomes	IgE titres

Anderson 1983 (*Continued*)

Notes	Reported insignificant decreases in serum IgG, IgA, secretory IgA and IgM in both groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding (performance bias and detection bias) All outcomes	High risk	There was no placebo, control patients received standard therapy only. Trial is not described as blinded

Cohen 1997

Methods	Randomised double blind placebo controlled crossover study.
Participants	20 patients (adults & children) with diagnosed exercise-induced asthma with a fall in FEV1 >15% after exercise test on a motorised treadmill (13M;7F). Age ranging from 7-28 yrs with mean 13.8 yrs
Interventions	2g of oral ascorbic acid or placebo 1 hour before a 7-minute exercise session on a treadmill. Pulmonary function tests were performed after an 8-minute rest. Procedure repeated 1 week later, with each subject receiving the alternative medication. 5 patients continued on a 2 week treatment but not able to use data as there was no control or placebo arm for this group of patients were selected as they showed protective effect with vitamin C in the 1 hour study (not randomised)
Outcomes	FEV1
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study described as double blind but method of blinding (e.g. identical placebo pill) not described

Fogarty 2003

Methods	Randomised placebo-controlled double-blind parallel group trial. Study was powered to detect a 310ml change in FEV1, a 20l/min increase in PEFR or a 1.5 fold in airway reactivity relative to placebo
Participants	Patients were identified from computer records of 24 general practices in Nottingham, UK. At the start of the study there were 95 participants in the vitamin C group and 106 in the placebo group (and 99 in a third group randomised to magnesium). Vitamin C group: 37 males, mean age 42, mean daily inhaled steroids 715ug, number of long acting beta 2 agonists 20, current smokers 5, mean pack years 1.2, mean dietary vitamin C 90mg Placebo group: 42 males, mean age 40, mean daily inhaled steroids 618ug, number of long acting beta 2 agonists 14, current smokers 4, mean pack years 1.1, mean dietary vitamin C 82mg
Interventions	Parallel comparison of daily supplementation with vitamin C 1g/day and placebo
Outcomes	FEV1, FVC, PD20, morning and evening PEFR, beta 2 use, symptoms
Notes	Randomisation was stratified according to dose of regular corticosteroids usage An extension to the trial provided data on the reduction in use of inhaled steroids. Ninety two of the original participants agreed to continue taking their allocated supplement for a further 10 weeks and enter a corticosteroid reduction protocol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned using a random number generator
Allocation concealment (selection bias)	Low risk	Particpants were allocated by an individual code number. The code was broken only after the last participant left the trial. All randomisation table preparation and dispensing were carried out independently from the recruitment and assessment of participants
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study is described as double-blind but the appearance of the tablets is not specifically mentioned

Kordansky 1979

Methods	Randomised double-blind placebo controlled trial with crossover design
Participants	6 adults (2 female, 4 male) in Baltimore, USA, with ragweed sensitive asthma, defined by skin-prick positivity. Tested out of the ragweed season. Asymptomatic and not on treatment
Interventions	500mg once daily vitamin C for 7 days compared to lactose placebo
Outcomes	PD20 FEV1, PD35 SGaw, tested on day 7, 3hrs after dose of placebo/vitamin C
Notes	Data not presented in an abstractable format, no reply from author to date

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study described as double blind but method of blinding (e.g. identical placebo pill) not described

Malo 1986

Methods	Randomised double blind placebo controlled crossover study.
Participants	16 adults (3M; 13F) with asthma that met the ATS criteria. Age range 19-59, mean 43. 1 (SD 7.7) yrs, mean duration of asthma 10.5 yrs (SD 14.6)
Interventions	The subjects were studied on 4 different days. Subjects received treatment or placebo which consisted of 250ml of a transparent and odourless sweet liquid in which was dissolved either 2g ascorbic acid or placebo. One hour later spirometry measured and histamine challenge done until PC20 reached
Outcomes	FEV1, FVC, PC20
Notes	Data not presented in an abstractable format. Values reported for different days rather than different groups. No reply from author to date

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described

Malo 1986 (*Continued*)

Allocation concealment (selection bias)	Low risk	Concealment of treatments were done using codes. The oral solutions were prepared by hospital pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Oral solutions were described as being of similar taste

O'Sullivan 2000

Methods	Randomised double-blind, cross-over placebo controlled study
Participants	Ten mild (ATS criteria) asthmatic participants.
Interventions	Each participant completed two treatment periods with ingestion of either 2g of ascorbic acid or placebo 45 minutes prior histamine bronchoprovocation
Outcomes	Spirometry was measured before, during and after the histamine challenges
Notes	Abstract only published, data not presented in an abstractable format, no reply from author to date

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study described as double blind but method of blinding (e.g. identical placebo pill) not described

Schachter 1982

Methods	Randomised double-blind controlled trial, crossover design.
Participants	12 adults (5 male, 7 female) with exercise-induced asthma, never on corticosteroids or admitted to hospital
Interventions	Single dose of 500 mg vitamin C orally or sucrose placebo. Study done on 2 subsequent days. 90 minutes post does subjects underwent exercise challenge. No washout indicated. Exercise challenge in incremental workload and until subjects heart rate reach 170bpm or the subject fatigued. Pulmonary function was measured before & after oral dose and after exercise

Schachter 1982 (*Continued*)

Outcomes	FVC, FEV1, PEFR before and after exercise challenge on cyclegometer to 170bpm or exhaustion	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo capsule

Tecklenburg 2007

Methods	Randomised, double-blind, crossover trial over 5 consecutive weeks	
Participants	Eight participants (2 male, 6 female) with physician diagnosed mild-to-moderate asthma and documented exercise-induced bronchoconstriction. Particpants were recruited from University population and the local community and were active	
Interventions	Ascorbic acid supplement 1500mg/day (3x500mg capsules) or placebo (sucrose) (3 capsules). Manufactured by NOW Foods. Particpants were randomised to active treatment or placebo for two weeks. There was a wash-out period of one week and then the participants crossed over Particpants were advised to avoid foods that were high in vitamin C during the study	
Outcomes	Pulmonary function (FEV1) pre-and post-exercise; Exhaled nitric oxide (F_ENO) pre- and post-exercise; symptom questionnaire	
Notes	Study conducted in the USA	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described.

Blinding (performance bias and detection bias) All outcomes	Low risk	Matching placebo manufactured by the same company as the active treatment

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

Study	Reason for exclusion
Cuomo 2004	Study used a combined supplement of vitamin C, vitamin E and other antioxidants
Forastiere 2000	Not a randomised controlled trial (before and after questionnaire survey)
Gvozdjakova 2005	Study used a combined supplement of vitamin C, Coenzyme Q_{10} and α-tocopherol.
Kongerud 2003	Not a randomised controlled trial and intervention not testing efficacy of vitamin C. Study examined the levels of ascorbic acid in induced sputum of asthmatic patients compared to healthy volunteers
Miric 1991	Not a randomised controlled trial. All subjects given placebo first than followed later with all patients receiving vitamin C
Mohsenin 1983	Study did not have a placebo arm (only had before and after effects of vitamin C administration)
Mohsenin 1987	Study used healthy subjects and excluded subjects who had asthma
Murphy 2002	Study used a combination of vitamin C and α-tocopherol
Omenaas 2003	Postal questionnaire not a randomised controlled trial.
Panina 2002	Study used a complex of oral antioxidants. It is not clear that the study was randomised
Romieu 2002	Study used both vitamin C and E in the intervention group.
Ting 1983	Study did not have a placebo arm and was not randomised (only had before and after effects of vitamin C)

DATA AND ANALYSES

Comparison 1. Oral vitamin C vs placebo (single-dose studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1 (L) - post-exercise challenge	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 FVC (L) - post-exercise challenge	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 PEFR (L/min) - post-exercise challenge	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 2. Oral vitamin C vs placebo (short term studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (% drop) post-exercise	1		Mean Difference (Fixed, 95% CI)	Totals not selected
2 Symptom scores (Asthma Quality of Life Questionnnaire)	1		Mean Difference (Fixed, 95% CI)	Totals not selected

Comparison 3. Oral vitamin C vs placebo (long-term studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IgE (IU/ml serum) - absolute values	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 1 month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 3 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 FEV1 mL 4 months	1		Mean Difference (Fixed, 95% CI)	Totals not selected
3 Peak Flow (L/min) 4 months	1		Mean difference (Fixed, 95% CI)	Totals not selected
3.1 Morning	1		Mean difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Evening	1		Mean difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Geometric mean decrease in inhaled corticosteroid use (μg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Oral vitamin C vs placebo (single-dose studies), Outcome 1 Change in FEV1 (L) - post-exercise challenge.

Review: Vitamin C supplementation for asthma

Comparison: 1 Oral vitamin C vs placebo (single-dose studies)

Outcome: 1 Change in FEV1 (L) - post-exercise challenge

Study or subgroup	Vitamin C group N	Mean(SD)	Placebo group N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Schachter 1982	12	0.21 (0.19)	12	0.08 (0.26)		0.13 [-0.05, 0.31]

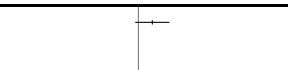
Analysis 1.2. Comparison 1 Oral vitamin C vs placebo (single-dose studies), Outcome 2 FVC (L) - post-exercise challenge.

Review: Vitamin C supplementation for asthma

Comparison: 1 Oral vitamin C vs placebo (single-dose studies)

Outcome: 2 FVC (L) - post-exercise challenge

Study or subgroup	Vitamin C group N	Mean(SD)	Placebo group N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Schachter 1982	12	0.1 (0.23)	12	-0.03 (0.17)		0.13 [-0.03, 0.29]



Analysis 1.3. Comparison 1 Oral vitamin C vs placebo (single-dose studies), Outcome 3 PEFR (L/min) - post-exercise challenge.

Review: Vitamin C supplementation for asthma

Comparison: 1 Oral vitamin C vs placebo (single-dose studies)

Outcome: 3 PEFR (L/min) - post-exercise challenge

Study or subgroup	Vitamin C group N	Mean(SD)	Placebo group N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Schachter 1982	12	0.59 (0.53)	12	0.1 (0.83)		0.49 [-0.07, 1.05]

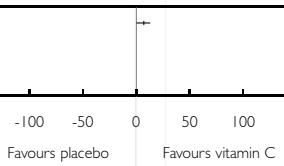
Analysis 2.1. Comparison 2 Oral vitamin C vs placebo (short term studies), Outcome 1 FEV1 (% drop) post-exercise.

Review: Vitamin C supplementation for asthma

Comparison: 2 Oral vitamin C vs placebo (short term studies)

Outcome: 1 FEV1 (% drop) post-exercise

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Tecklenburg 2007	0	0	6.5 (3.29)		6.50 [0.05, 12.95]



Analysis 2.2. Comparison 2 Oral vitamin C vs placebo (short term studies), Outcome 2 Symptom scores (Asthma Quality of Life Questionnnaire).

Review: Vitamin C supplementation for asthma

Comparison: 2 Oral vitamin C vs placebo (short term studies)

Outcome: 2 Symptom scores (Asthma Quality of Life Questionnnaire)

Study or subgroup	Vitamin C N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Tecklenburg 2007	0	0	0.5 (0.38)		0.50 [-0.24, 1.24]

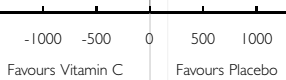
Analysis 3.1. Comparison 3 Oral vitamin C vs placebo (long-term studies), Outcome 1 IgE (IU/ml serum) - absolute values.

Review: Vitamin C supplementation for asthma

Comparison: 3 Oral vitamin C vs placebo (long-term studies)

Outcome: 1 IgE (IU/ml serum) - absolute values

Study or subgroup	Vitamin C group N	Mean(SD)	Placebo group N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 1 month						
Anderson 1983	7	246 (124.92)	9	242 (169.71)		4.00 [-140.42, 148.42]
2 3 months						
Anderson 1983	7	211 (93.08)	9	523 (472.35)		-312.00 [-628.21, 4.21]
3 6 months						
Anderson 1983	7	253 (146.97)	9	396 (398.81)		-143.00 [-425.38, 139.38]



Analysis 3.2. Comparison 3 Oral vitamin C vs placebo (long-term studies), Outcome 2 FEV1 mL 4 months.

Review: Vitamin C supplementation for asthma

Comparison: 3 Oral vitamin C vs placebo (long-term studies)

Outcome: 2 FEV1 mL 4 months

Study or subgroup	Vitamin C N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Fogarty 2003	95	106	-11 (41)		-11.00 [-91.36, 69.36]

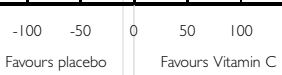
Analysis 3.3. Comparison 3 Oral vitamin C vs placebo (long-term studies), Outcome 3 Peak Flow (L/min) 4 months.

Review: Vitamin C supplementation for asthma

Comparison: 3 Oral vitamin C vs placebo (long-term studies)

Outcome: 3 Peak Flow (L/min) 4 months

Study or subgroup	Vitamin C N	Placebo N	Mean difference (SE)	Mean difference IV,Fixed,95% CI	Mean difference IV,Fixed,95% CI
1 Morning					
Fogarty 2003	95	106	0.9 (6.45)		0.90 [-11.74, 13.54]
2 Evening					
Fogarty 2003	95	106	2.2 (6.2)		2.20 [-9.95, 14.35]



Analysis 3.4. Comparison 3 Oral vitamin C vs placebo (long-term studies), Outcome 4 Geometric mean decrease in inhaled corticosteroid use (μg).

Review: Vitamin C supplementation for asthma

Comparison: 3 Oral vitamin C vs placebo (long-term studies)

Outcome: 4 Geometric mean decrease in inhaled corticosteroid use (??g)

Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Fogarty 2003	29	49 (156.6)	32	11 (37.5)		38.00 [-20.46, 96.46]

ADDITIONAL TABLES

Table 1. Search history

Search dates	Results
January 2001	Thirty-five abstracts were identified from the search of the Cochrane Airways Group register, of which 6 met the inclusion criteria (Anah 1980, Anderson 1983, Cohen 1997, Kordanksy 1979, Malo 1986, Schachter 1987) and 5 were added as excluded studies
January 2001 - April 2004	Twenty-four abstracts were identified by the updated search. Two additional included studies (Fogarty 2003, O'Sullivan 2000) and 4 excluded studies were added to the review

FEEDBACK

Feedback submitted by Harri Hemila, 24 March 2009

Summary

"The Cochrane review vitamin C for asthma (2009 version) has errors in the extraction of data and in the analysis.

Schachter 1982 carried out a trial with participants who had exercise-induced bronchoconstriction (EIB) so that each of the 12 participants was administered placebo and vitamin C at different times. Thus, each participant served as his or her own control (cross-over). In Table III Schachter reported pre-post-exercise change of FEV1, so that the later FEV1 was measured 5 minutes after the exercise. Because two observations are measured from the same participant, the placebo period and vitamin C period difference in FEV1 change should be analysed using the paired t-test. The FEV1 data in Schachter's Table III gives the mean difference between the vitamin C and placebo periods as 0.20 (SD 0.33) litres/s. Schachter 1982 calculated t = 2.13 in their paper, corresponding to P[1-tail] = 0.028.

The review presents Schachter's FEV1 changes in Analysis 1.2. However, data in Analysis 1.2 were extracted from Schachter's Table II, which presents post-exercise FEV1 value measured immediately after the exercise. In EIB the fall in FEV1 occurs 5 to 20 minutes after the end of exercise (Rundell 2009), and even Schachter reported that, on the screening day, there was no fall in FEV1 immediately

after exercise, but a significant fall 5 minutes after the exercise (Schachter 1982 Fig. 2). Therefore, extracting the FEV1 changes from Schachter's Table II (FEV1 immediately after the exercise) is not reasonable if the purpose is to examine the effect of vitamin C on EIB.
Cohen 1997 carried out an EIB trial with 20 participants who were administered placebo and vitamin C at different times (cross-over). Post-exercise FEV1 was measured 8 minutes after the end of the exercise. The observations are paired also in this case and the results should be analysed using a paired test. 9 participants had FEV1 decrease >15% on both vitamin C and placebo treatments. 11 participants had >15% FEV1 decrease on placebo but <15% FEV1 decrease on vitamin C (Cohen 1997 Fig. 2). None of the participants had the opposite effect: <15% FEV1 decrease on placebo and >15% FEV1 decrease on vitamin C. In the paired 2x2 table analysis, the question is whether the difference between the corners (here 11 and 0) is statistically significant. This difference gives z = (11-0)/sqrt(11+0) = 3.31, corresponding to P[1-tail] = 0.0005.
A basic principle in controlled trial analysis requires that all randomised participants should be included in the analysis (the ITT principle). However, the review does not give the results for all of Cohen's 20 participants (Cohen 1997 Fig. 2); Analysis 1.2 gives the results for only the 11 participants who had benefit of vitamin C (Cohen 1997 Table 2).
Furthermore, the review presents the average of post-exercise FEV1 values and not the pre-post-exercise difference in FEV1 in analysis 1.2. The post-exercise averages for Cohen's Table 2 are 1.66 (SD 0.80) litres/s in the placebo period and 1.93 (SD 0.78) litres/s in the vitamin C period (P = 0.42). However, given that the EIB is defined by the pre-post change in FEV1, the measurement of the effect on EIB should be based on the pre-post-exercise difference in FEV1 (Rundell 2009). Furthermore, the relative effect calculated by Cohen (Table 2; in %units) is a better measure than the absolute value (in litres/s) because the relative effect adjusts for the great variation in baseline FEV1; the relative decrease in FEV1 is also used in guidelines (Rundell 2009). Cohen reports that the average relative fall in FEV1 is 25% in the placebo period and 5% in the vitamin C period (Cohen 1997 table 2). Because the observations are paired, the paired t-test should be used. The average of the differences is 20% (SD 12%, SE 3.7%), which gives t = 5.57, corresponding to P[1-tail] = 0.00012. Thus, although the review presented only the 11 participants in which vitamin C was beneficial, the calculation suggests that even in this subgroup vitamin C was without effect (P = 0.42), whereas a correct calculation gives a much smaller P-value.
In their EIB trial, Tecklenburg 2007 studied 8 participants who were administered vitamin C and placebo at different times. They measured post-exercise FEV1 at 1, 5, 10, 15, 20, and 30 min after the exercise. Tecklenburg 2007 reported that the decrease in FEV1 in the vitamin C period was 6.4% (SE 2.4%) and decrease in the placebo period was 12.9% (SE 2.4%). Tecklenburg did not publish the paired comparison, nor original data so that the paired t-test could be calculated. Nevertheless, these averages give unpaired t = 1.91, corresponding to P[1-tail] = 0.038, which is conservative, the paired test P-value would be smaller.
Thus, three trials included in the review found benefit of vitamin C supplementation against EIB at 5 and 8 minutes after the exercise (Cohen 1997; Schachter 1982), or at the time of maximum fall in FEV1 (Tecklenburg 2007). The three P-values calculated above (0.028, 0.0005, 0.038) can be combined by using the Fisher method (Fisher 1948). The combined P[1-tail] = 0.00007 provides evidence that the effects of vitamin C on EIB in these three trials are not explained by random fluctuations.
Analyses 1.1, 1.3 and 1.5 present baseline data of two EIB trials discussed above (Cohen 1997; Schachter 1982). However, when a trial specifically examines the effect of vitamin C on EIB, the relevant outcome is the difference between the baseline and the 5-10 minutes post-exercise FEV1 values (the pre-post change), and not the baseline FEV1 value alone.
Finally, diagnosis of EIB by the change in FEV1 is well established (Rundell 2009) and the authors should have considered whether there is any benefit for readers from making additional analyses of the FVC and PEFR values of the oldest trial by Schachter 1982. The more recent trials by Cohen 1997and Tecklenburg 2007 did not report changes in FVC and PEFR."

Reply

This comment on the trials relating to exercise induced bronchoconstriction (EIB) was submitted in March 2009 and published alongside the review in November 2010.
We thank Dr Hemilä for the feedback, but do not think that the technical issues raised over the analysis of data from the three small cross-over trials (including a total of 40 participants), substantively alter the strength or direction of the results, the quality of the evidence, or the conclusions of the review.
We agree that crossover trials are best analysed using paired t-tests, but do not agree with the presentation of one-tail P values above. A two-tailed paired t-test did not show a statistically significant difference in change in FEV1 either immediately after exercise (shown in analysis 1.2) or five minutes later in Schachter 1982 (P = 0.18 and 0.057 from Table II and Table III respectively). Therefore the author's choice not to include the latter observation does not mislead the reader in our opinion.
We agree that the mean differences in FEV1 reported from only 11 of the 20 participants in Cohen 1997 should not be included in the review, and this has been removed from the analyses.

The authors entered data for the fall in FEV1 from Tecklenburg 2007, using a standard error derived from a conservative estimate of the P value based on the paired t-test (reported in the paper as $P < 0.05$). We see no compelling reason to overturn this approach since the average effect is unaltered and the data come from a study of only eight participants.
We agree that the baseline lung function is not a useful outcome for this review and have removed the pre-exercise outcomes.
We do not agree with the suggested approach of combining P values from Cohen 1997, Schachter 1982 and Tecklenburg 2007 in view of the clinical heterogeneity between the studies and outcomes under consideration. Such an approach focuses attention on whether any effect observed is attributable to chance. This is itself potentially misleading since it does not take account of the magnitude of effect across the studies. The analyses presented in the review have now been amended so that only mean differences and confidence intervals for the studies are presented, and not associated P values.
We are content for readers to consider the comment from Dr Hemilä alongside our response, and to make up their own minds regarding the authors' approach to the analysis of data and the conclusions of the review.
Posted by Emma Welsh, Mangaging Editor of the Cochrane Airways Group, on behalf of the author and editorial teams.

Contributors

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WHAT'S NEW

Last assessed as up-to-date: 29 October 2008.

Date	Event	Description
13 June 2012	Amended	Feedback incorporated, We are aware of a new relevant study, this has been added to studies awaiting classification
13 June 2012	Feedback has been incorporated	In light of the feedback, we have removed three instances of reporting of baseline lung function values and deleted statistical data from a trial who only reported data on participants who benefited from treatment. These changes have not altered the conclusions of the review and we do not believe the review will mislead the reader
13 June 2012	Review declared as stable	The methods used in the review are somewhat outdated and therefore a new review is required in this topic. Applications to register this title will be subject to our prioritisation procedure

HISTORY

Protocol first published: Issue 3, 1996

Review first published: Issue 1, 1999

Date	Event	Description
5 November 2010	Amended	Feedback has been published alongside the original text of the review
1 December 2008	Amended	Contact details of B Kaur altered
29 October 2008	New citation required but conclusions have not changed	One new included study, one extension to a previously included study (Fogarty 2003) and five excluded studies were identified. Conclusions remain unchanged. Change in authorship
29 August 2008	New search has been performed	New search.
14 August 2008	Amended	Converted to new review format.
1 April 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Felix Ram and BK conducted the original version of this review in 2001. BR was the assigned editor contributing to the protocol and review editing. FR updated the review in April 2004. ES updated the review in August 2008.

DECLARATIONS OF INTEREST

There are no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- St George's, University of London, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Antioxidants [*therapeutic use]; Ascorbic Acid [*therapeutic use]; Asthma [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans