**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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin C group</th>
<th>Placebo group</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schachter 1982</td>
<td>12 0.21 (0.19)</td>
<td>12 0.08 (0.26)</td>
<td>0.13 [-0.05, 0.31]</td>
<td></td>
</tr>
</tbody>
</table>

Favours Placebo, Favours Vitamin C

**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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin C group</th>
<th>Placebo group</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schachter 1982</td>
<td>12 0.1 (0.23)</td>
<td>12 -0.03 (0.17)</td>
<td>0.13 [-0.03, 0.29]</td>
<td></td>
</tr>
</tbody>
</table>

Favours Placebo, Favours Vitamin C
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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin C group</th>
<th>Placebo group</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schachter 1982</td>
<td>12</td>
<td>0.59 (0.53)</td>
<td>12</td>
<td>0.1 (0.83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.49 [-0.07, 1.05]</td>
<td></td>
</tr>
</tbody>
</table>

Favours Placebo
Favours Vitamin C

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference (SE)</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
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<tbody>
<tr>
<td>Tecklenburg 2007</td>
<td>0</td>
<td>0</td>
<td>6.5 (3.29)</td>
<td></td>
<td>6.50 [0.05, 12.95]</td>
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</tbody>
</table>

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

Comparison: Oral vitamin C vs placebo (long-term studies)
Outcome: Geometric mean decrease in inhaled corticosteroid use (µg)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin C</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Fogarty 2003</td>
<td>29 49 (156.6)</td>
<td>32 11 (37.5)</td>
<td>38.00 [-20.46, 96.46]</td>
<td></td>
</tr>
</tbody>
</table>

<p>|</p>
<table>
<thead>
<tr>
<th>-100</th>
<th>-50</th>
<th>0</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favours placebo</td>
<td>Favours vitamin C</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

ADDITIONAL TABLES

Table 1. Search history

<table>
<thead>
<tr>
<th>Search dates</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2001</td>
<td>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</td>
</tr>
<tr>
<td>January 2001 - April 2004</td>
<td>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</td>
</tr>
</tbody>
</table>

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 \( P[1\text{-tail}] = 0.028 \).
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 1997 and 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 Hemila 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.

Contributors
Harri Hemilä, Department of Public Health, University of Helsinki, Helsinki, Finland

WHAT'S NEW
Last assessed as up-to-date: 29 October 2008.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 June 2012</td>
<td>Amended</td>
<td>Feedback incorporated, We are aware of a new relevant study, this has been added to studies awaiting classification</td>
</tr>
<tr>
<td>13 June 2012</td>
<td>Feedback has been incorporated</td>
<td>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</td>
</tr>
<tr>
<td>13 June 2012</td>
<td>Review declared as stable</td>
<td>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</td>
</tr>
</tbody>
</table>

HISTORY
Review first published: Issue 1, 1999
Vitamin C supplementation for asthma

Balvinder Kaur¹, Brian H Rowe², Elizabeth Stovold³

¹Department of Primary Care and Public Health, Faculty of Medicine, Imperial College London, London, UK. ²Department of Emergency Medicine, University of Alberta, Edmonton, Canada. ³Population Health Sciences and Education, St George’s, University of London, London, UK.

Contact address: Emma J Welsh, Population Health Sciences and Education, St George’s, University of London, Cranmer Terrace, Tooting, London, SW17 0RE, UK. ewelsh@sgul.ac.uk.

Editorial group: Cochrane Airways Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), comment added to review, published in Issue 8, 2012.
Review content assessed as up-to-date: 29 October 2008.

Citation: Kaur B, Rowe BH, Stovold E. Vitamin C supplementation for asthma. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD000993. DOI: 10.1002/14651858.CD000993.pub3.

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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.