Feedback on: Kaur B, Rowe BH, Arnold E. Vitamin C supplementation for asthma. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD000993.

24 March 2009

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This document: https://doi.org/10.5281/zenodo.6405776

This is Feedback on the following Cochrane review:

Kaur B, Rowe BH, Arnold E. Vitamin C supplementation for asthma.
Cochrane Database Syst Rev. 2009 Jan 21;(1):CD000993.
https://www.ncbi.nlm.nih.gov/pubmed/19160185
https://doi.org/10.1002/14651858.CD000993.pub3

This Feedback was published within the Cochrane review, see:
https://helda.helsinki.fi/handle/10138/296440

The **first version** of the Cochrane review was published in **2001**:
Kaur B, Rowe BH, Ram FS. Vitamin C supplementation for asthma.
Cochrane Database Syst Rev. 2001;(4):CD000993.
https://www.ncbi.nlm.nih.gov/pubmed/11687089

The **second version** of the Cochrane review was published in **2004**:
Ram FS, Rowe BH, Kaur B. Vitamin C supplementation for asthma.
Cochrane Database Syst Rev. 2004;(3):CD000993.
https://www.ncbi.nlm.nih.gov/pubmed/15266435

This Feedback below points out errors in Analyses 1.1, 1.2, 1.3 and 1.5 of the Cochrane review (2009 version). However, all these analyses were identical already in the first version (2001) of the Cochrane review. Thus, because of the errors described in this feedback, the Cochrane review "Vitamin C supplementation for asthma" had been misleading readers for a decade.

In addition to the problems described in this Feedback (2009) below, there are a number of additional problems in the Cochrane review "vitamin C supplementation for asthma", which are described in:
https://helda.helsinki.fi/handle/10138/40816
https://doi.org/10.5281/zenodo.6405804

The solution of the editors of the Cochrane Library to the flaws in the Analyses figures 1.1, 1.2, 1.3 and 1.5 of the Cochrane review "vitamin C supplementation for asthma" was to remove the published Analysis figures from the original published version. Such a removal of parts of a published paper is inconsistent with COPE objectives regarding the integrity of the academic record:
https://publicationethics.org/

Editor of the Cochrane Library, David Tovey, was unwilling to make available the original published review with the above described Analysis figures. However, COPE required that the original publication need to be made available. See a summary of that process at:
https://doi.org/10.1111/eci.13216
https://hdl.handle.net/10138/326823

Because of the above actions, one single PubMed record:
https://pubmed.ncbi.nlm.nih.gov/19160185
currently links to two different versions of the same Cochrane review:

1) The PubMedCentral (2009) version includes all the original Analysis figures (1.1 to 1.6), but not this feedback below.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6176494

2) The Cochrane Library (2012) version includes this feedback below, but does not include the Analysis figures to which my feedback was focused on. Thereby the Cochrane Library made my feedback appear irrelevant:
https://doi.org/10.1002/14651858.cd000993.pub3

Finally,
3) The University of Helsinki Digital Archive has available a third version (2010), which has both the original figures and my feedback below:
https://helda.helsinki.fi/handle/10138/296440

Feedback on: Kaur B, Rowe BH, Arnold E. Vitamin C supplementation for asthma. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD000993.

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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 (crossover). 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 **Cochrane 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 (crossover). 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 **Cochrane 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 = 0.00012. Thus, although the **Cochrane 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 = 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.

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