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Vitamin C for preventing and treating the common cold (Review)

Hemilä H, Chalker E



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[Intervention Review]

Vitamin C for preventing and treating the common cold

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ABSTRACT

Background

Vitamin C (ascorbic acid) for preventing and treating the common cold has been a subject of controversy for 70 years.

Objectives

To find out whether vitamin C reduces the incidence, the duration or severity of the common cold when used either as a continuous regular supplementation every day or as a therapy at the onset of cold symptoms.

Search methods

We searched CENTRAL 2012, Issue 11, MEDLINE (1966 to November week 3, 2012), EMBASE (1990 to November 2012), CINAHL (January 2010 to November 2012), LILACS (January 2010 to November 2012) and Web of Science (January 2010 to November 2012). We also searched the U.S. National Institutes of Health trials register and WHO ICTRP on 29 November 2012.

Selection criteria

We excluded trials which used less than 0.2 g per day of vitamin C and trials without a placebo comparison. We restricted our review to placebo-controlled trials.

Data collection and analysis

Two review authors independently extracted data. We assessed 'incidence' of colds during regular supplementation as the proportion of participants experiencing one or more colds during the study period. 'Duration' was the mean number of days of illness of cold episodes.

Main results

Twenty-nine trial comparisons involving 11,306 participants contributed to the meta-analysis on the risk ratio (RR) of developing a cold whilst taking vitamin C regularly over the study period. In the general community trials involving 10,708 participants, the pooled RR was 0.97 (95% confidence interval (CI) 0.94 to 1.00). Five trials involving a total of 598 marathon runners, skiers and soldiers on subarctic exercises yielded a pooled RR of 0.48 (95% CI 0.35 to 0.64).

Thirty-one comparisons examined the effect of regular vitamin C on common cold duration (9745 episodes). In adults the duration of colds was reduced by 8% (3% to 12%) and in children by 14% (7% to 21%). In children, 1 to 2 g/day vitamin C shortened colds by 18%. The severity of colds was also reduced by regular vitamin C administration.

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Seven comparisons examined the effect of therapeutic vitamin C (3249 episodes). No consistent effect of vitamin C was seen on the duration or severity of colds in the therapeutic trials.

The majority of included trials were randomised, double-blind trials. The exclusion of trials that were either not randomised or not double-blind had no effect on the conclusions.

Authors' conclusions

The failure of vitamin C supplementation to reduce the incidence of colds in the general population indicates that routine vitamin C supplementation is not justified, yet vitamin C may be useful for people exposed to brief periods of severe physical exercise. Regular supplementation trials have shown that vitamin C reduces the duration of colds, but this was not replicated in the few therapeutic trials that have been carried out. Nevertheless, given the consistent effect of vitamin C on the duration and severity of colds in the regular supplementation studies, and the low cost and safety, it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them. Further therapeutic RCTs are warranted.

PLAIN LANGUAGE SUMMARY

Vitamin C for preventing and treating the common cold

The common cold is a major cause of visits to a doctor in high-income countries and of absenteeism from work and school. There are over 200 viruses which can cause the common cold symptoms including runny nose, congestion, sneezing, sore throat, cough, and sometimes headache, fever and red eyes. Symptoms vary from person to person and cold to cold. Since the common cold is usually caused by one of the respiratory viruses, antibiotics are useless and therefore other potential treatment options are of substantial public health interest.

Vitamin C has been proposed for treating respiratory infections since it was isolated in the 1930s. It became particularly popular in the 1970s when Nobel laureate Linus Pauling concluded from earlier placebo-controlled trials that vitamin C would prevent and alleviate the common cold. Over two dozen new trials were undertaken thereafter. Vitamin C has been widely sold and used as a preventive and therapeutic agent.

This review is restricted to placebo-controlled trials testing 0.2 g/day or more of vitamin C. Regular ingestion of vitamin C had no effect on common cold incidence in the ordinary population, based on 29 trial comparisons involving 11,306 participants. However, regular supplementation had a modest but consistent effect in reducing the duration of common cold symptoms, which is based on 31 study comparisons with 9745 common cold episodes. In five trials with 598 participants exposed to short periods of extreme physical stress (including marathon runners and skiers) vitamin C halved the common cold risk. The published trials have not reported adverse effects of vitamin C.

Trials of high doses of vitamin C administered therapeutically, starting after the onset of symptoms, showed no consistent effect on the duration or severity of common cold symptoms. However, only a few therapeutic trials have been carried out and none have examined children, although the effect of prophylactic vitamin C has been greater in children. One large trial with adults reported benefit from an 8 g therapeutic dose at the onset of symptoms, and two therapeutic trials using five-day supplementation reported benefit. More trials are necessary to settle the possible role of therapeutic vitamin C, meaning administration immediately after the onset of symptoms.

BACKGROUND

Description of the condition

The term 'the common cold' does not denote any precisely defined disease, but this illness is familiar to most people. Typically symptoms of the common cold consist of some combination of nasal discharge and obstruction, sore throat, cough, lethargy and malaise, with or without fever. The common cold is the leading cause of acute morbidity and of visits to a physician in high-income countries, and a major cause of absenteeism from work and

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school.

The common cold is usually caused by respiratory viruses (rhino, corona, adeno, parainfluenza, influenza, respiratory syncytial), which overall have some 200 serotypes (Eccles 2005; Eccles 2009; Gwaltney 2005; Heikkinen 2003). Thus, the term 'the common cold' does not refer to a single entity but to a group of diseases caused by numerous unrelated aetiological agents. The most frequent agent causing the common cold is rhinovirus, which is found in 30% to 50% of sufferers. In a third of participants with cold symptoms, the aetiology remains undefined even when extensive virological tests are used. It is not clear to what extent this latter group is explained by the low sensitivity of the tests, unidentified viruses, or similar symptoms arising from non-viral aetiology, such as allergic or mechanical irritation of the airways. Different respiratory viruses have different symptom profiles, but the patterns are not consistent enough to validate aetiological conclusions from the patients' symptoms.

Although the great majority of common cold episodes are caused by the respiratory virus group, the symptom-based definition of the 'common cold' also covers some diseases caused by other viruses (varicella, measles, rubella, cytomegalo, Epstein-Barr) and some bacterial infections. For example, since streptococcal pharyngitis cannot be differentiated from viral pharyngitis on clinical grounds, it can also be included within the broad definition of the common cold. Symptoms of illnesses caused by *Mycoplasma pneumoniae (M. pneumoniae)* and *Chlamydia pneumoniae (C. pneumoniae)* may also be similar to the symptoms caused by the respiratory viruses. The manifestations of the common cold are so typical that usually the clinical diagnosis of the common cold can be made reliably by adult patients themselves. Allergic and vasomotor rhinitis can sometimes mimic the common cold, but these conditions can usually be easily differentiated (Heikkinen 2003).

In common cold trials an operational definition of the common cold is used for logistic reasons; for example, based on the duration and the set of symptoms to yield an explicitly defined outcome. However, such limits are biologically arbitrary. There is no exact minimum duration or combination of symptoms which is meaningful when drawing a conclusion as to whether the symptoms should be explained by a viral infection, or by allergic or mechanical irritation of nasal airways or throat.

The use of antibiotics for a typical acute common cold episode is useless since the vast majority of colds are caused by viruses. Nevertheless, according to some surveys about 50% of common cold patients in the USA received antibiotics (Gonzales 1997; Mainous 1996). In this respect, the alternative treatment options for the common cold are of substantial public health interest.

Description of the intervention

Numerous animal studies with different species have shown that vitamin C affects resistance to diverse infections by viruses and bacteria (Hemilä 2006a; Hemilä 1997c). Therefore this vitamin might play a similar role in infections in human beings. Since the early 1940s, a number of controlled trials have been carried out to examine the possible effects of vitamin C on the common cold.

In 1970, the publication of Linus Pauling's book *Vitamin C and the Common Cold* generated huge public interest which persists today (Pauling 1970a). Pauling had won Nobel Prizes in Chemistry (1954) and Peace (1962), and his book had a great influence. Pauling 1971a also carried out a meta-analysis in which he combined the P values derived from four placebo-controlled trials by Fisher's method and found that there was strong evidence that vitamin C decreased the 'incidence of colds' (P = 0.003). In a second meta-analysis, Pauling 1971b focused on 'days of illness per person' in the best two trials (Cowan 1942; Ritzel 1961) and by combining the P values by Fisher's method led him to conclude that "the null hypothesis of equal effectiveness of ascorbic acid and placebo [on total morbidity] is rejected at the level P less than 0.001."

Ritzel 1961 had reported a brief randomised trial of children at a ski school in the Swiss Alps in which he administered 1 g of vitamin C daily and found significantly reduced incidence and duration of colds in children who were administered vitamin C. Pauling 1971a put much weight on the Ritzel trial. On the basis of Ritzel's trial, Pauling proposed that mega-dose supplementation might profoundly influence both the incidence and severity of the common cold over all the population. Pauling also presented data suggesting that human diets might not provide sufficient intake of vitamin C for best health (Pauling 1970b; Pauling 1976a).

Pauling's advocacy of vitamin C led to numerous careful trials in different countries in the following decade, the largest of which were performed on healthy adult volunteers in Canada (Anderson 1972; Anderson 1974a; Anderson 1975a). The evidence emerging from all the published trials was confusing (Anderson 1977), but generally failed to support Pauling's hope that vitamin C would be a panacea.

In a meta-analysis, Chalmers 1975 calculated an unweighted average of the treatment effect in seven placebo-controlled trials and found that colds in vitamin C groups were 0.11 ± 0.24 (standard error (SE)) days shorter which is not a statistically or clinically significant difference. In a qualitative review on vitamin C and the common cold published in the same year, Dykes 1975 also concluded that vitamin C had no effect on colds.

However, it has subsequently been pointed out that the influential reviews by Chalmers 1975 and Dykes 1975 contain serious errors (Hemilä 1995; Hemilä 1996c; Hemilä 2006a). Hemilä 1995 showed that after extraction of correct data from the trial reports, correction of errors in calculations, and restriction to trials in which at least 1 g/day of vitamin C had been used, as Pauling had proposed, Chalmers 1975 would have calculated an eight times higher estimate of the vitamin C effect: 0.93 ± 0.22 (SE) days reduction in the duration of colds. Furthermore, both Chalmers 1975 and Dykes 1975 placed considerable weight on the double-blind, placebo-controlled trial carried out by Karlowski 1975a at

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the National Institutes of Health (NIH), which concluded that a statistically significant benefit of vitamin C supplementation was simply explained by the placebo effect. However, it has been shown that the placebo effect explanation in the Karlowski 1975a paper was not consistent with their own data (Chalmers 1996; Hemilä 1996a; Hemilä 1996d; Hemilä 2006a; Hemilä 2006c).

Hemilä 1997b claimed that the highly cited reviews of Chalmers 1975 and Dykes 1975 and the trial by Karlowski 1975a quelled interest in real, but modest effects of vitamin C on the common cold after the mid-1970s. Hemilä 1997a pooled the results of the six largest trials using ≥ 1 g/day of vitamin C found no effect on the common cold incidence (pooled risk ratio (RR) 0.99; 95% confidence interval (CI) 0.93 to 1.04), which refuted Pauling's proposal as to the prophylactic effect of gram-dose vitamin C for the general population. However, four trials with UK males found a moderate reduction in common cold incidence with vitamin C (pooled RR 0.70; 95% CI 0.60 to 0.81), which was explained by the particularly low dietary vitamin C intake in the UK rather than high doses of supplements. Also, three trials with participants under heavy acute physical stress found a reduction in the incidence of colds with vitamin C (pooled RR 0.50; 95% CI 0.35 to 0.69) (Hemilä 1996b). Thus, it is possible that vitamin C has an effect on common cold incidence in restricted subpopulations.

Although regular vitamin C supplementation at doses of ≥ 1 g/day has consistently decreased the duration or alleviated the symptoms of the common cold, there was substantial heterogeneity in the results (Hemilä 1994). A further meta-analysis found a trend for trials with children to show greater benefit than trials with adults, and another trend for trials with ≥ 2 g/day to show greater benefit than trials with 1 g/day, suggesting dose-dependency (Hemilä 1999a).

How the intervention might work

Dozens of studies have found that vitamin C may affect, for example, phagocytosis and chemotaxis of leucocytes, replication of viruses, and production of interferon (Hemilä 2006a; Hemilä 1997c; Thomas 1978; Webb 2007). Vitamin C is an efficient water-soluble antioxidant and the effects on the immune system can be explained by the protection against oxidative stress generated during infections (Akaike 2001; Castro 2006; Hemilä 1992). Phagocytes have a specific transport system by which the oxidised form of vitamin C (dehydroascorbic acid) is imported into the cells, where the reduced form of vitamin C is regenerated (Nualart 2003; Wang 1997). If the major role of vitamin C in the immune system is that of a physiological antioxidant protecting various host cells against oxidative stress during an infection, it could have important effects in certain conditions even though the mechanisms are apparently non-specific. Furthermore, heavy physical stress generates oxidative stress (Ji 1999) and the antioxidant role of vitamin C can thus also explain its effects on respiratory symptoms in physically stressed people. Dozens of animal studies found that vitamin C reduces the incidence and severity of bacterial and viral infections indicating that the vitamin has physiological effects on infections, and not just on laboratory measures of the immune system (Hemilä 2006a).

For brief notes on the history of this Cochrane Review, see Appendix 1. Links to the publications cited in this section, for which full-text versions are available, can be found at www.mv.helsinki.fi/home/hemila/CC/.

Why it is important to do this review

The common cold causes enormous morbidity worldwide and the search for simple and effective preventive or therapeutic agents has been elusive. Even if vitamin C might have modest effects in restricted population groups, that could be important from a public health point of view.

OBJECTIVES

To find out whether vitamin C reduces the incidence, the duration or severity of the common cold when used either as a continuous regular supplementation every day or as a therapy at the onset of cold symptoms.

METHODS

Criteria for considering studies for this review

Types of studies

We included placebo-controlled trials. We did not restrict to randomised controlled trials.

Types of participants

Trials of children and adults of either gender and any age were considered eligible.

Types of interventions

The intervention considered was orally administered vitamin C of at least 0.2 g daily for a single day or for a period. The limit of 0.2 g/day was selected as a choice of convenience. If a trial with a lower dose finds a negative result, the negative findings can be attributed to the low dose. Thus, trials with large doses are more critical for testing Pauling's proposal that gram doses of vitamin C would reduce morbidity due to common cold infections. On

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the other hand, under certain conditions vitamin C doses lower than 0.2 g/day might have effects (*see* Discussion: Possible role of marginal vitamin C deficiency). Thus, our selection criterion for dose does not mean that all excluded trials are irrelevant to the question of the effects of vitamin C. All trials that used a vitamin C dose lower than 0.2 g/day are listed and briefly described in the Characteristics of excluded studies table.

In a few instances the placebo included a low dose of vitamin C; Carr 1981a used 70 mg/day and a few others used 50 mg/day or less. This was done to ensure that participants were not 'vitamin C deficient', recognising that dietary intake of vitamin C is highly variable. Thus, the goal of these investigators was to test the effects of large doses for properly nourished participants.

We may include studies in which vitamin C has a co-intervention if the control group has only the co-intervention so that the only difference is vitamin C administration.

Types of outcome measures

Primary outcomes

1. 'Incidence' of colds during regular supplementation was assessed as the proportion of participants experiencing one or more colds during the study period.
2. 'Duration' was the mean number of days of illness of cold episodes.

Secondary outcomes

1. 'Severity' of these episodes was assessed in two ways: a) days confined indoors, or off work or off school per episode and b) symptom severity scores.
2. 'Evidence of possible medication side effects' was available from seven large regular supplementation studies, with the number of participants reporting possible medication side effects in the intervention and control groups.

Search methods for identification of studies

Electronic searches

For this 2012 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 11, part of *The Cochrane Library*, thecochranelibrary (accessed 29 May 2012), which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 2010 to November week 3, 2012), Embase.com (January 2010 to November 2012), CINAHL (January 2010 to November 2012), LILACS (January 2010 to November 2012) and Web of Science (January 2010 to November 2012). See Appendix 1 for details of previous searches.

We used the following search strategy to search CENTRAL and MEDLINE. The search strategy was adapted to search EMBASE (Appendix 2), CINAHL (Appendix 3), LILACS (Appendix 4) and Web of Science (Appendix 5).

MEDLINE (OVID)

1 Common Cold/
2 common cold*.tw.
3 Rhinovirus/
4 rhinovir*.tw.
5 coryza.tw.
6 "acute rhinitis".tw.
7 ((viral or virus*) adj2 rhinit*).tw.
8 or/1-7
9 exp Ascorbic Acid/
10 ascorb*.tw,nm.
11 (vitamin* adj5 c).tw.
12 or/9-11
13 8 and 12

There were no language or publication type restrictions in the literature searches.

Searching other resources

The review authors screened the reference lists incorporated in two systematic reviews of the literature published by Briggs 1984 and Kleijnen 1989 (for the search strategy of the latter, *see* Kleijnen 1992) and the references in all identified studies. Furthermore, one of the review authors (HH) has a research involvement spanning three decades in this topic and has assembled a personal reference list of papers published in the grey literature or listed in indexing services that preceded electronic searching.

We also searched the U.S. National Institutes of Health trials register www.clinicaltrials.gov and the WHO ICTRP www.who.int/ictrp on 29 May 2012 (*see* Appendix 6 for search details).

Data collection and analysis

Selection of studies

For the 2004 version of this review, HH and Bob Douglas (BD) searched the literature and independently assessed the titles and abstracts to identify potentially relevant articles (Appendix 1). They obtained and scrutinised full versions of all potentially eligible articles. When they disagreed on the relevance of an article, they discussed it until they reached a consensus. For the 2007 and 2009 updates, the first review author (HH) searched the literature and assessed the titles and abstracts to identify potentially relevant articles. For the 2012 update, two review authors (HH, EC) searched

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the literature and assessed titles and abstracts to identify potentially relevant articles.

Data extraction and management

For the 2004 version of this review, two review authors (HH, BD) independently extracted pertinent data from the articles selected and entered data into the Review Manager program (*see* Appendix 1) (Douglas 2004; RevMan 2011). They sought consensus when they differed in the interpretation of study findings. Only one new trial satisfying the selection criteria (Constantini 2011a; Constantini 2011b) has been published since the preceding version of this review (Hemilä 2010) and it was included in this 2012 update.

Assessment of risk of bias in included studies

Most of the included trials were double-blind. Double-blind means that the participant and others directly involved in treatment do not know to which treatment group the participant has been allocated, i.e. there must be allocation concealment. Double-blind also means that there must be blinding of participants and personnel. Finally, since the outcomes were recorded by personnel or the participant, double-blinding also implies that there is blinding of outcome assessment.

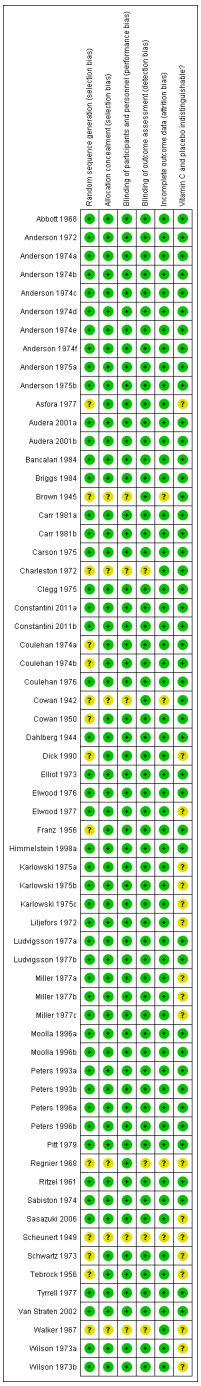
Studies are classified as randomised on the basis of the study reports, but only a few studies described the actual method of randomisation.

Chalmers 1975 proposed that the benefits of vitamin C supplementation on the common cold might be caused by "the result of the power of suggestion." His proposal was based on the Karlowski 1975a trial, in which placebo consisted of lactose which is sweet and differs by taste from ascorbic acid which was used in the vitamin C capsules. Therefore, we collected data on the reported indistinguishability of vitamin C and placebo preparations.

When the methodological description was unambiguous, one review author (HH) entered the methodological description to the 'Risk of bias' tables in Characteristics of included studies. When the description of methods was ambiguous, HH discussed the issue with the co-author (EC) to reach a consensus. The overall risk of bias is summarised in Figure 1.

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



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Measures of treatment effect

For the community trials, we selected two primary outcomes and one secondary outcome to compare vitamin C with placebo groups, resulting in five tables.

Analysis 1.1: the measure of the treatment effect is the risk ratio (RR) of 'incidence' of colds in vitamin C and placebo groups. Incidence is defined as the proportion of participants with at least one cold during the study.

Analysis 2.1 and Analysis 4.1: the measure of treatment effect is the mean difference (MD) in common cold 'duration'. Since duration of cold episodes varied appreciably across trials, we standardised the mean values and standard deviations (SD) in each group against the mean of the respective placebo group. In this way, the placebo group of each trial gets a value of 100%, and therefore the difference between the vitamin C and placebo group is the effect of vitamin C in percentages.

Analysis 3.1 and Analysis 5.1: there are two measures of effect on 'severity': a) the difference in the mean number of days that the patient was absent from work or school or confined to bed; and b) the difference in the mean symptom severity score derived from patient kept records.

In analysing dichotomous data with only a few cases in the trial groups, the mid-P value is the most appropriate method to calculate the P values for the differences in the treatment groups (Hemilä 2006a) and was used when comparing groups with small numbers of cases. Two-tailed P values are used in this review.

Unit of analysis issues

In four of the trials (Anderson 1974a; Anderson 1975a; Audera 2001a; Karlowski 1975a) more than one vitamin C group was compared with a single placebo group. Where multiple active arms were analysed in the same meta-analysis, the vitamin C arms were combined as one entry which appears in the figures, identified as the lowest lettered trial that the entry contained.

Miller 1977a and Carr 1981a studied twins and the comparison is paired. The SD values used in this meta-analysis are calculated from the SE and P values, respectively, of reported paired tests, so the two trials get proper weight in pooling.

Dealing with missing data

Some trials presented the mean duration or severity of colds, but not the respective SD. In some trials the P value for the difference of interest was reported and the SD was calculated from it. In the Anderson 1972, Anderson 1974a and Anderson 1975a trials, Fieller's theorem was used to estimate the SD for individual common cold episodes from the SD values presented in papers that were based on a per person experience. In the other trials with missing SD, we estimated SD as identical with the mean of the treatment group. This is based on our analysis that for trials reporting the SD, the ratio of SD to mean is on average 0.7 so that our ratio of 1.0 used in the SD imputation is somewhat conservative. The consequence of this is that we are putting slightly reduced weight in our estimates of effect on these trials with missing SD values, compared to the average.

Assessment of heterogeneity

We assessed heterogeneity using the Chi^2 test and the I^2 statistic (Higgins 2003; Higgins 2011). The Chi^2 test is known to be poor at detecting true heterogeneity among studies. While a statistically significant result indicates heterogeneity, a non-significant result is not evidence of no heterogeneity. The I^2 statistic examines the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of about 50% for I^2 indicates a moderate level of heterogeneity.

Data synthesis

We used the Review Manager (RevMan 2011) software to pool the results of the three outcomes of the included trials. A pooled fixed-effect RR of the probability of experiencing at least one cold while taking vitamin C was computed for 'incidence'. We computed a pooled fixed-effect MD in common cold 'duration' to derive an estimate of the percentage of days of illness by which vitamin C reduced the average common cold.

We considered separately two different approaches to the assessment of severity in the meta-analysis by treating the two measures of severity as separate subgroups. We computed a standardised mean difference (SMD) for the two subgroups and for all the trials for which severity data were available. The SMD calculation method leads to quantitative results but the estimates do not have any relevant clinical interpretation. Rather the primary statistical result of the SMD method is the P value for the combined set.

Subgroup analysis and investigation of heterogeneity

We considered three factors as possible explanations for heterogeneity observed across the results of these trials. These were vitamin C dosage, age of the participants (children and adults), and the presence or absence of heavy, short-term physical stress.

Sensitivity analysis

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We undertook sensitivity analyses in Analysis 1.1 and Analysis 2.1 to test the robustness of our conclusions regarding the methodological quality of the trials, in which we excluded all studies which were not randomised and double-blind.

In seven trials in Analysis 2.1 ('Duration of colds in regular supplementation trials') we imputed the SD values assuming that SD is equal to the mean of the group (Briggs 1984; Coulehan 1974a; Coulehan 1974b; Coulehan 1976; Peters 1996a; Peters 1996b; Pitt 1979). When we excluded these seven trials in a sensitivity analysis of Analysis 2.1, the pooled results indicated a slightly greater effect of vitamin C: for adults 8.6% (4% to 13%); for children 14.6% (7% to 22%). Thus, inclusion of the trials with imputed SD values does not lead to an increase in the estimate of benefit, but leads to a slight reduction in the calculated benefit.

We also tested whether the exclusion of the Anderson 1974a trial might affect the estimates of Analysis 1.1 and Analysis 2.1. That trial had two placebo groups and we selected for our comparisons the placebo group #4 which was close to the vitamin C groups on the basis of baseline data (*see* Hemilä 2006a and Results section 4). Exclusion of the Anderson 1974a trial had minimal effects on the pooled estimates (not shown).

RESULTS

Description of studies

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

Results of the search

The 2012 MEDLINE (Ovid) search identified 17 results, EMBASE 58, CENTRAL 6, CINAHL 20, LILACS 0, Web of Science 13, Clinicaltrials.gov 3 and WHO Trials Register (ICTRP) 1 search results. With duplicates removed there were 90 search results. One new trial satisfying our inclusion criteria was identified in the 2012 search (Constantini 2011a) and two new trials were added to the excluded trials list (Maggini 2012; Schmidt 2011).

Included studies

Sixty-three separate comparisons of vitamin C against placebo, reported in 44 publications, met our selection criteria. Eleven of these publications presented the results of two to six different study comparisons. Included in the selected papers are the four trials identified originally by Pauling 1971a to justify his proposals for mega-dose regular supplementation and therapy (Cowan 1942; Franz 1956; Ritzel 1961; Wilson 1969). We have used the Wilson 1973a final report of his boarding school trials rather than the preliminary communication which Pauling 1971a had available to him.

In Anderson 1974a, Anderson 1975a, Audera 2001a and Karlowski 1975a more than one active arm is compared with a single placebo arm. This explains why the total number of participants is less in the placebo groups than in the vitamin C groups. The 63 included trials which have contributed data to this review fall into four groups.

1. Forty-three community regular supplementation trial arms which evaluated the effects of regular daily supplementation with vitamin C (i.e. vitamin C each day over the study irrespective of the presence of colds) on reducing the incidence or duration or severity of naturally occurring colds.
2. Ten community therapeutic trial arms that evaluated the therapeutic effects of high-dosage vitamin C after natural common cold symptoms had commenced.
3. Seven community trials did not report data suitable for our meta-analysis and these trials are presented qualitatively.
4. Three laboratory trials (Dick 1990; Schwartz 1973; Walker 1967) in which volunteers were intentionally exposed to known viruses after vitamin C or placebo administration. As they are qualitatively different from the community-based trials on natural common cold infections, they are not included in the meta-analyses but are presented qualitatively.

Brief details of the circumstances, dosage and quality assessment of the trials are available in the Characteristics of included studies table. Links to the trial reports and translations can be found at www.mv.helsinki.fi/home/hemila/CC/.

Excluded studies

We excluded 25 studies. The major reasons for exclusion were the lack of placebo control (12 trials) and vitamin C dose < 0.2 g/day (seven trials). For details, please see the Characteristics of excluded studies table.

Risk of bias in included studies

Allocation

Most of the identified trials were randomised controlled trials (RCTs) (Figure 1). Most of the studies also had allocation concealment (Figure 1).

Blinding

Most of the identified trials blinded participants and personnel and the outcome was assessed by either of the two so that the outcome assessment was also blinded (Figure 1).

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Incomplete outcome data

In many trials there were no drop-outs, and in those trials in which there were, the number of drop-outs was not substantially different between the study groups.

Selective reporting

When there are one or a few trials with a positive finding on a poorly justified outcome, the possibility of publication bias is an important concern. In our review we have two large groups of trials with the same well-justified primary outcomes: incidence and duration of colds (Analysis 1.1 and Analysis 2.1). We do not see any basis to speculate that the consistency in these two outcomes could be explained by selective reporting. There is no unambiguous definition for severity which we classify as a secondary outcome, and there might be more problems with selective reporting on that outcome (Analysis 3.1). However, severity has a lower priority in our review and the findings are consistent with the effect on duration (Analysis 2.1).

Other potential sources of bias

The great majority of the trials reported that vitamin C tablets (usually ascorbic acid) and placebo tablets (usually citric acid) were indistinguishable (Figure 1 and Characteristics of included studies table). Thus there is no basis to assume that difference in taste or appearance between the tablets could have generated substantial bias in the trials.

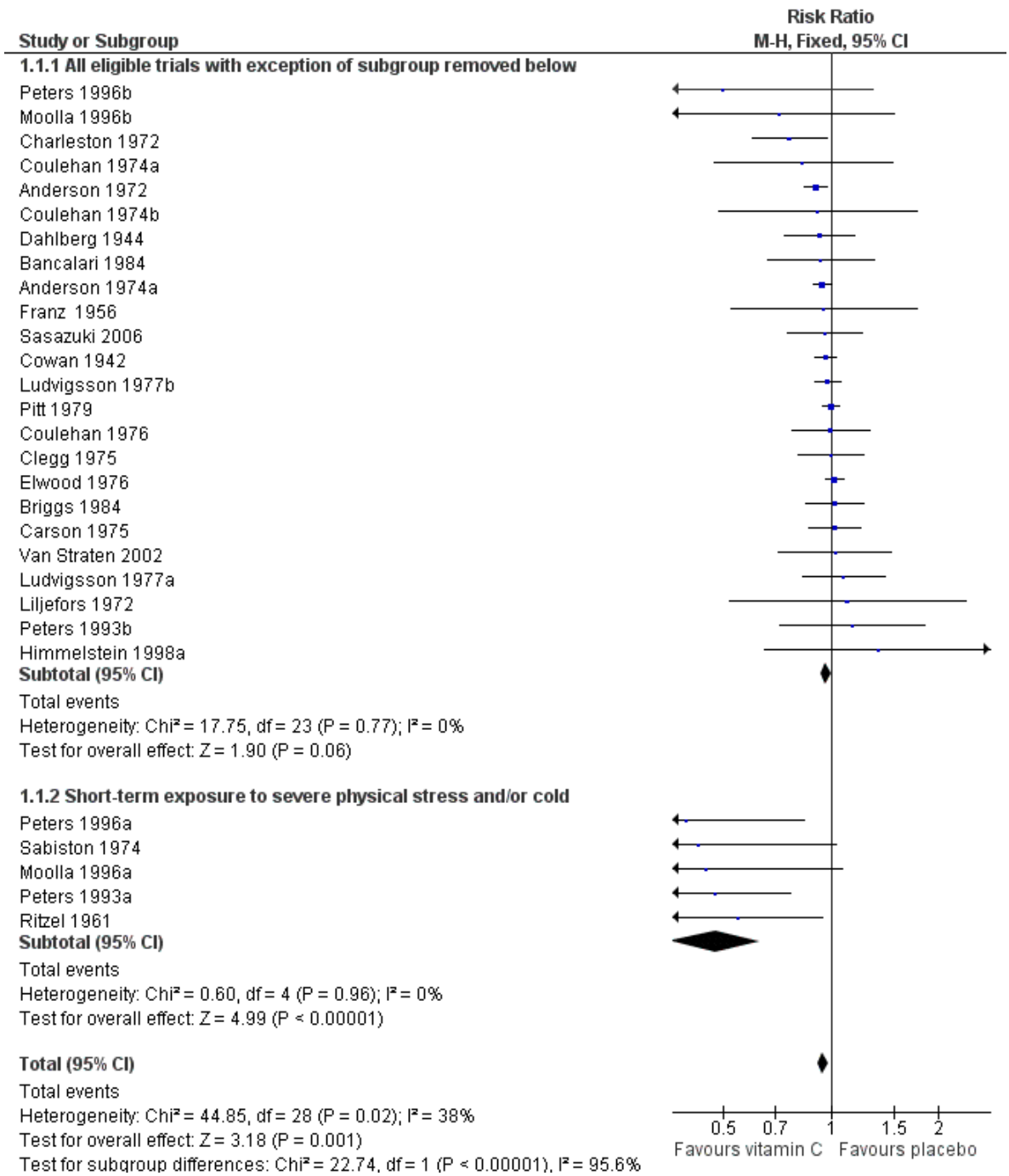
Effects of interventions

1. Community regular supplementation trials: incidence of colds

Analysis 1.1 (Figure 2) presents the meta-analysis of the risk ratio of at least one cold developing for a participant while on regular vitamin C supplementation. Regular supplementation means that vitamin C was administered each day over the study period. The entry in the meta-analysis for Anderson 1974a represents four separate trial arms (Anderson 1974a; Anderson 1974b; Anderson 1974c; Anderson 1974d) in which different vitamin C dosages ranging from 0.25 to 2 g/day were compared with one placebo group. Thus the 29 entries in Figure 2 represent 32 vitamin C arms in trials.

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Figure 2. Forest plot of comparison: 1 Incidence of colds while taking ≥ 0.2 g/day vitamin C regularly, outcome: 1.1 Proportion of participants developing ≥ 1 cold episodes during the trial



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The 29 entries represent 11,306 participants, of whom 6105 used vitamin C for periods ranging from two weeks to five years. The pooled risk ratio (RR) for all trials was 0.95 (95% confidence interval (CI) 0.92 to 0.98). Although the overall difference between vitamin C and placebo participants is statistically highly significant (P = 0.001), indicating a biological effect of vitamin C, the narrow CI precludes any clinically relevant effect over wide population groups.

Heterogeneity of results

Among all the studies included in Analysis 1.1 there is substantial heterogeneity, as indicated by the Chi^2 test (P = 0.02) and the rather high I^2 statistic (38%). Heterogeneity refutes the notion that vitamin C is universally equivalent to placebo.

Five of the 29 comparisons recorded statistically significant (P < 0.05) protection favouring the vitamin C group: Peters 1996a (RR 0.39), Peters 1993a (RR 0.50), Ritzel 1961 (RR 0.55), Charleston 1972 (RR 0.77) and Anderson 1972 (RR 0.91). Four other trials recorded a non-significant RR < 0.80 (Moolla 1996a; Moolla 1996b; Peters 1996b; Sabiston 1974). None of the 29 comparisons significantly favoured the placebo.

Of the eight relatively small trials with RR < 0.8, three were with marathon runners (Moolla 1996a; Peters 1993a; Peters 1996a), two with sedentary controls for marathon runners (Moolla 1996b; Peters 1996b), one with students in a skiing school in the Swiss Alps (Ritzel 1961), one with Canadian army troops on subarctic operations (Sabiston 1974), and one with staff and students at Glasgow University, UK (Charleston 1972).

The bottom of Analysis 1.1 shows a subgroup of five studies which involved marathon runners, skiers and Canadian soldiers in a subarctic exercise. Division of the 29 trials to the two subgroups resulted in two distinct groups of trials which were significantly different from each other in their pooled estimates of effect. Furthermore, the two subgroups were homogeneous within the two pools, as indicated by the high P values in the Chi^2 test, and the zero values for the I^2 statistic.

Subgroups: general community trials and heavy acute physical stress trials

Based on 24 entries with 10,708 participants from the general community who had no heavy short-term physical stress, the narrow CI, which is located close to the zero effect, refutes the possibility that regular vitamin C supplementation could reduce the average incidence of colds in the general community: RR 0.97 (95% CI 0.94 to 1.00) (Analysis 1.1; Figure 2).

When the general community meta-analysis was restricted to 17 entries with vitamin C dose ≥ 1 g/day, the prophylactic benefit of vitamin C supplementation was also refuted (RR 0.98; 95% CI 0.95 to 1.01; based on 6661 participants).

In the Karlowski 1975a trial, the dose of vitamin C was the highest, 3 g/day. This study is not included in Analysis 1.1 because the number of participants who caught a cold during the trial was not reported; instead the total number of cold episodes per group was reported. Nevertheless, 3 g/day vitamin C had no effect on the number of common cold episodes, with RR 0.93 (95% CI 0.73 to 1.20) (Hemilä 1997a).

In five trials with participants undergoing heavy acute physical activity in the subgroup at the bottom of Analysis 1.1, vitamin C halved the incidence of colds: RR 0.48 (95% CI 0.35 to 0.64) (Figure 2, Analysis 1.1.2). All of these five studies were randomised and double-blind. In three of these studies, the vitamin C dose was less than 1 g/day so that the benefit in this subgroup cannot explained by particularly high vitamin C doses, but by the extraordinary conditions of the participants.

Two trials had participants exposed to long-term physical stress. Pitt 1979 examined 674 US marine recruits for two months and Constantini 2011a studied 39 competitive young swimmers for three months. Neither of these trials found effect of vitamin C on common cold incidence.

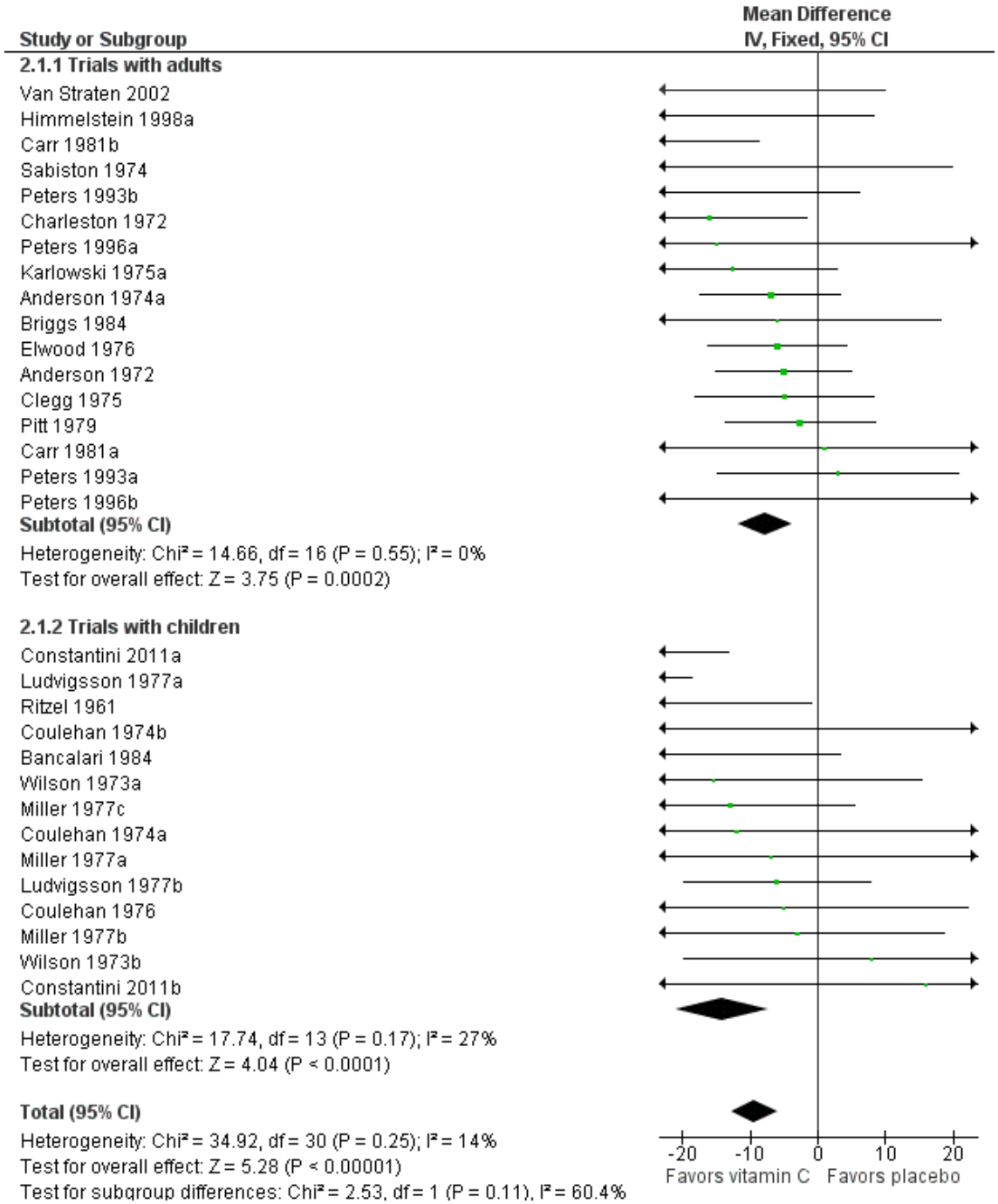
To test the effect of study quality on the findings in Analysis 1.1, we undertook a sensitivity analysis in which we removed five trials that were either not randomised or not double-blind from the general community meta-analyses and this had no effect on the estimate (RR 0.98; 95% CI 0.94 to 1.01). All trials with participants under heavy acute physical stress were randomised and double-blind. Thus, the effect of study quality as assessed by randomisation and double-blinding did not change the estimates of the two subgroups of Figure 2.

2. Community regular supplementation trials: duration of colds

Analysis 2.1 (Figure 3) presents the effect of vitamin C on the duration of colds which occurred while participants were taking vitamin C regularly, each day over the study. These trials are divided into two subgroups: adults and children. The division into child and adult trials was carried out for two reasons: a) children have a substantially higher incidence of colds reflecting differences in the immune system maturity, and b) children are on average smaller so that a fixed dose corresponds to a greater dose per weight.

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Figure 3. Forest plot of comparison: 2 Duration of the colds occurring when on regular ≥ 0.2 g/day vitamin C, outcome: 2.1 Duration of common cold symptoms (placebo group duration 100%)



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For adults there were 17 entries representing 21 trial arms (four separate trial arms in Anderson 1974a and two in Karlowski 1975a) and 7215 episodes of illness, and for children there were 14 trial comparisons including 2530 episodes of illness.

A consistent benefit was seen in the duration of colds. For children, the pooled effect was a 14.2% (7.3% to 21%) reduction in common cold duration, and for adults the pooled effect was a 7.7% (3.7% to 12%) reduction in cold duration. The Chi^2 test for trial heterogeneity was not significant in either of the subgroups.

In five of the 31 comparisons (Carr 1981b; Constantini 2011a; Charleston 1972; Ludvigsson 1977a; Ritzel 1961) the effect of vitamin C was statistically significant within the trial. In the Constantini 2011a trial, common cold duration was significantly shorter in male swimmers, but not in female swimmers, there being a statistically significant interaction between vitamin C effect and sex.

Five comparisons (Carr 1981a; Constantini 2011b; Peters 1993a; Peters 1996b; Wilson 1973b) recorded a point estimate favouring the placebo. Wilson 1973b used only 0.2 g/day vitamin C, which is the smallest dose in the analysis. Carr 1981a examined twins living together, whereas the Carr 1981b trial examined twins living apart; it is possible that the substantially divergent result in these twin groups is related to the living conditions - those living together might have exchanged or confused their tablets. The Peters 1996b trial was very small and the CI is very wide.

The great majority of the trials in Analysis 2.1 used 1 g/day of vitamin C and therefore a systematic examination of possible dose-dependency across the trials was not feasible. In the child subgroup, we used sensitivity analysis to test the possibility that low-dose vitamin C trials might dilute the pooled estimate. When we removed the trials using < 1 g/day of vitamin C (Miller 1977b; Miller 1977c; Wilson 1973a; Wilson 1973b), the pooled estimate of benefit was increased to a 18.1% (9% to 27%) reduction in the duration of colds in children suggesting that the 14.2% estimate for all studies of children may be biased downwards because low-dose trials are included. In the adult subgroup, the estimate of effect was essentially unchanged, 8.0% (3.8% to 12%), when the < 1 g/day vitamin C trials were removed (Peters 1993a; Peters 1993b; Peters 1996a; Peters 1996b); these are small trials with doses of 0.5 to 0.6 g/day.

In sensitivity analyses, we removed the studies which were not randomised and double-blind. Exclusion of two trials from the adult subgroup had no material effect on the estimated benefit of 7% (3% to 11%), and exclusion of two trials from the child subgroup similarly had no substantial effect on the estimated benefit of 14% (7% to 21%). Thus, excluding four trials with lower quality had no effect on the conclusions of Figure 3.

In summary, this meta-analysis of the duration of colds occurring while participants were on regular vitamin C supplementation demonstrated a statistically highly significant, but modest, benefit to the vitamin C supplemented participants which was greater in children than in adults.

3. Community regular supplementation trials: severity of colds

Analysis 3.1 presents the effect of vitamin C on the severity of common cold episodes occurring during regular vitamin C supplementation. Two measures of the severity of the common cold were available.

Subgroup 1 in Analysis 3.1 consists of seven entries of 10 vitamin C study arms in which severity was measured by 'days confined to home' or 'days off work or school'. This included 5066 common cold episodes in adults and children. The large-scale trials by Anderson 1972 and Ludvigsson 1977b reported statistically significant reductions in 'days confined to house per episode' with vitamin C supplementation. Subgroup 1 found a quantitatively modest, but statistically highly significant reduction in common cold severity. This subgroup exhibited significant heterogeneity between the studies as measured by the Chi^2 test and I^2 statistic.

Subgroup 2 in Analysis 3.1 presents the results of symptom severity scores in nine trials with 2143 episodes. The large-scale trial by Pitt 1979 found a statistically significant, but small, 5% reduction in the severity score. There is a statistically highly significant reduction in common cold severity also in subgroup 2. There is no heterogeneity in this subgroup.

The measures of 'severity' that have been used in the included trials are variable. We calculated the standardised mean difference (SMD) which normalises the difference between the vitamin C and placebo groups to the units of standard deviations. Therefore the pooled results of Analysis 3.1 are not practically useful, rather the significance level is of main importance in this analysis; P = 0.0004 for the studies that assessed days confined to home or off work or school, and P = 0.002 for studies which used severity scores, and P < 0.00001 when the two subgroups were combined. Although the benefit with respect to days confined to home or off work or off school is statistically significant, it is modest in absolute terms.

4. Community therapeutic studies: duration of colds when treatment commenced after common cold symptoms began

Analysis 4.1 presents the findings of therapeutic trials, which means that vitamin C administration was started after the cold symptoms occurred. This meta-analysis contains seven entries that incorporate data from 10 different trial arms involving 3249 cold episodes where participants initiated supplementation at the onset of cold symptoms. Audera 2001a, Anderson 1974e and Anderson 1975a contain two vitamin C arms.

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The pooled result for these therapeutic trials did not exhibit a difference of vitamin C from placebo in the variety of therapeutic protocols that were used. The large trial by Anderson 1974e found a statistically significant but modest benefit but this was counterbalanced by the negative results in the other trials.

The Anderson 1974e entry combines two arms with different dosages. Anderson 1974e administered 4 g/day and Anderson 1974f administered 8 g/day on the first day of illness only. The mean duration of illness episodes for those in the 4 g/day arm was 3.17 days, while that for 8 g/day arm was 2.86 days compared with the duration in the placebo group #4 of 3.52 days. However, this trial was bedeviled by the fact that the investigators originally intended to compare results with two separate placebo groups. One of the two placebo groups (#6) had statistically significant baseline differences when compared with the six vitamin C groups. The comparisons presented here are with the placebo group #4 that was close to the vitamin C groups with respect to the baseline data (*see* Hemilä 2006a). If comparisons had been made with the placebo group #6 or a combination of the two placebo groups as the investigators had originally intended, the benefits would have been minimised as the mean episode duration for the placebo group #4 was 3.52 days, and for placebo group #6 was 2.83 days. Nevertheless, notwithstanding the placebo group problem, the proportion of 'short colds', that lasted for only a single day was significantly larger in the 8 g/day group (46%; 222 out of 483) compared with the 4 g/day group (39%; 164 out of 417) (P = 0.046), consistent with a greater benefit with the higher dose compared with the lower dose.

Tyrrell 1977, Elwood 1977 and Audera 2001a failed to show an effect on duration. Tyrrell evaluated males and females separately using a dosage of 4 g/day for the first 2.5 days of illness (total 10 g), Elwood evaluated males and females separately using a dosage of 3 g/day for the first 3.3 days of illness (total 10 g), and Audera evaluated 1 and 3 g/day over the first 3 days (total 3 g and 9 g).

In summary, the therapeutic trials do not provide consistent evidence that the duration of colds could be reduced with the protocols that have been tested in the vitamin C trials. The benefit from the use of an 8 g single dose immediately after the onset of cold symptoms is interesting but indicates the need for further research rather than implying practical conclusions.

5. Community therapeutic studies: severity of cold episodes when treatment commenced after common cold symptoms began

Analysis 5.1 has four entries which represent seven trial arms that included 2708 separate common cold episodes for which cold severity was assessed. Audera 2001a, Anderson 1974e and Anderson 1975a contain two vitamin C arms.

As with the regular supplementation studies, we separated the measures of severity into two subgroups: a) days confined to home, off work or school, and b) symptom severity scores, and we analysed these subgroups separately and together.

In subgroup 1, the only comparison which found a significant benefit to those taking vitamin C was that for Anderson 1975a. In that study, participants took 1.5 g/day for the first day of the common cold and 1 g/day for the following four days (total 5.5 g). Anderson 1974e and Tyrrell 1977 found no meaningful difference between vitamin C and placebo. The pooled effect for subgroup 1 shows a marginally significant benefit of vitamin C.

The only trial in subgroup 2, Audera 2001a, found no difference between vitamin C and placebo.

6. Community trials with no data suitable for our meta-analyses

Table 1 shows the findings in seven trials which did not report suitable data for our meta-analysis. Two of them were regular supplementation trials and five were therapeutic trials. All these are placebo-controlled trials which used $\geq$ 0.2 g/day of vitamin C. The main findings of these trials are described in Table 1.

In two therapeutic trials the authors claimed to be able to identify the vitamin C and placebo participants from the clinical progress of the patients (Asfora 1977; Regnier 1968). One therapeutic trial found a marginally significant effect on the duration of "nose colds" (Brown 1945), and two therapeutic trials reported no difference between vitamin C and placebo (Abbott 1968; Tebrock 1956).

In a regular supplementation trial, Elliot 1973 found a significant effect of vitamin C on the morbidity for sore throats and productive coughs, but the study was carried out in a Polaris submarine so that the conditions were special. Scheunert 1949 reported less respiratory morbidity in persons administered higher doses of vitamin C compared with lower doses, but the study is poorly reported and methodologically unsatisfactory.

7. Laboratory trials with artificially infected volunteers

Table 2 presents three laboratory trials which were volunteer transmission studies.

Walker 1967 and Schwartz 1973 instilled virus into the noses of volunteers who had been pre-treated with vitamin C or placebo. Dick 1990 used a more natural mechanism for the transmission of a rhinovirus: their experimental volunteers were housed for a week and worked closely with other volunteers who had been previously infected by nasal instillation of rhinovirus.

Dick 1990 found that fewer vitamin C treated volunteers became infected and the cumulative symptom severity score and mucus weights were significantly less (P = 0.03), but virus shedding was similar in both groups. Schwartz 1973 found reduced common cold severity in the vitamin C group (P < 0.02 at day 4), but no effect on symptom duration, whereas Walker 1967 did not observe any benefit to those who took vitamin C.

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8. Adverse effects from high-dose vitamin C intake

Seven large trials recorded data on symptoms which participants attributed to the medication they were using.

Over the trials, data were recorded for a total of 2490 recipients who had used ≥ 1 g/day of vitamin C compared with 2066 who took a placebo. Altogether 5.8% of the vitamin C recipients reported adverse symptoms which they attributed to the medication compared with 6.0% of those who were taking placebo (data not shown). No serious symptoms were reported.

DISCUSSION

Despite the variation in methodology and the substantial heterogeneity in results from this large number of trial results carried out over a 70-year period, certain rather strong conclusions can be drawn.

Common cold incidence

Trials within the general community

An earlier meta-analysis pooled the results of the six largest trials in which ≥ 1 g/day of vitamin C had been administered regularly over the study period and found no effect of vitamin C on the incidence of colds with a narrow confidence interval (CI) (risk ratio (RR) 0.99; 95% CI 0.93 to 1.04) (Hemilä 1997a). This earlier meta-analysis pooled the number of common cold episodes occurring during the trial, whereas this Cochrane meta-analysis used the number of participants catching at least one cold as the measure of common cold incidence. Nevertheless, this second outcome definition led to the same conclusion for the general community trials.

When the subgroup of marathon runners, skiers and soldiers on subarctic operations was excluded in this review (see below), there was strong evidence that vitamin C supplementation has no effect on the number of people who catch the common cold (RR 0.97; 95% CI 0.94 to 1.00). This estimate was based on trials in which the vitamin C dose was ≥ 0.2 g/day. However, the negative finding is not explained by the inclusion of a few trials in which vitamin C dose was low. When restricting to trials in which the vitamin C dose was ≥ 1 g/day, the estimate was essentially the same. Finally, the general community trial with the largest dose, 3 g/day of vitamin C, found no difference in the common cold incidence between the vitamin C and placebo groups (Hemilä 1997a; Karlowski 1975a).

Trials with people under heavy acute physical stress

A previous meta-analysis identified three trials with participants under severe acute physical stress, and the pooling of results found that vitamin C supplementation halved the incidence of colds in this group (Hemilä 1996b). Two later trials with marathon runners (Moolla 1996a; Peters 1996a) are included in our Cochrane Review and they have not changed the pooled estimate of effect: RR 0.48; 95% CI 0.35 to 0.64. All five trials in this group involved a brief exposure to high physical stress with or without cold stress. The doses of vitamin C were not particularly high, being between 0.25 and 1.0 g/day. Thus, the benefit in this subgroup cannot be explained by high vitamin C doses. Similar and higher doses in the general community have not affected the incidence of colds (see above).

Furthermore, in the general community the acute respiratory symptoms usually have a viral cause, but it is not obvious that similar symptoms occurring after heavy exercise are caused by a viral infection because they can also result from exercise-induced bronchoconstriction (EIB) symptoms caused by an injury to the airways because of exceptional ventilatory exertion (Anderson 2008). In three trials, vitamin C supplementation reduced the decrease in pulmonary function associated with EIB (Hemilä 2009c). Thus the common cold studies of physically stressed people might have been measuring, at least in part, the effects of vitamin C on EIB instead of viral infections. Nevertheless, although the aetiology of symptoms is not clear in the physically stressed subgroup, the beneficial effect of vitamin C on acute respiratory symptoms in this subgroup is firm.

Two trials with two to three months physical stress on the participants found no effect of vitamin C on common cold incidence (Constantini 2011a; Pitt 1979). It is thus possible that vitamin C has effects on short-term exposure to physical stress, but not on long-term physical stress.

Possible role of marginal vitamin C deficiency

Hemilä 1997a has suggested that some of the early benefits of vitamin C supplementation might be a explained by low dietary vitamin C intakes in the UK when the studies were carried out (Baird 1979; Bartley 1953; Glazebrook 1942). These trials were ruled ineligible for this review because the doses were lower than 0.2 g/day. Low dietary vitamin C intake might also explain the significant reduction in cold incidence in the Charleston 1972 UK trial which is included in Analysis 1.1.

Four UK trials also found a reduction in the incidence of recurrent colds during the study period in males (pooled RR 0.54; 95% CI 0.40 to 0.74) but not in females (Hemilä 1997a). Nevertheless, a recent UK trial found a reduction in recurrent colds in a nine-week trial in both sexes (RR 0.13; 95% CI 0.03 to 0.53) (Van Straten 2002) (*see* Hemilä 2006a). The most impressive trial in this UK group is the Baird 1979 study, which was a randomised, double-blind, placebo-controlled trial, but was excluded from our Cochrane Review because the vitamin C dose was only 0.08 g/day. Thus, methodological weaknesses cannot explain the reduction in common cold incidence in males and the highly significant modification of vitamin C effect by sex (Hemilä 1997a; Hemilä

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2008). Significant sex differences in the effect of vitamin C were also found in a recent trial with competitive swimmers so that vitamin C was effective for males but not for females (Constantini 2011a).

The large trial by Anderson 1972 found a statistically significant but small reduction in common cold incidence (RR 0.91; 95% CI 0.85 to 0.98). This trial was conducted during the winter in Toronto, Canada, and participants were selected on the basis of having had problems with colds during previous winters. A cold Canadian winter might be a partial explanation for the benefit if cold along with physical stress makes a prophylactic benefit for vitamin C more likely. Furthermore, as regards the possible interaction between vitamin C supplementation and the level of dietary vitamin C intake, the Anderson 1972 trial is important as it found that vitamin C supplementation reduced the 'total days indoors' by 48% among participants in the vitamin C group who consumed < 3 oz of fruit juice (common dietary source of vitamin C), whereas the reduction was only 22% among those who consumed more juice. A similar modifying effect with fruit juice was found in the therapeutic trial by Anderson 1975a (*see* Hemilä 2006a).

Common cold duration and severity: regular supplementation trials

Both in adults and in children, regular vitamin C supplementation resulted in a statistically highly significant reduction in the duration of common cold episodes that occurred during the prophylactic supplementation period. For adults the estimate of vitamin C effect was 8% and for children it was 14%. However, when restricting to children trials with $\geq$ 1 g/day of vitamin C, the pooled estimate was an 18% decrease in the duration of colds. Although the above findings point to a definite physiological effect from regular vitamin C supplementation on common cold duration, the practical significance of these findings is not convincing. It does not seem reasonable to ingest vitamin C regularly throughout the year if the anticipated benefit is to slightly shorten the duration of colds which occur for adults a few times per year and for children half a dozen times per year. The above estimates are not trivial, but instead of regular supplementation, it would seem much more fruitful to consider the possible benefits of therapeutic supplementation and carry out trials to test whether an equivalent benefit might be achieved in children through appropriate therapeutic supplementation.

In light of the consistent effect of vitamin C on the duration of colds, an obvious question is whether there might be dose dependency, as suggested by a previous meta-analysis (Hemilä 1999a). Across the available trials, there is more evidence for the difference between children and adults than on the variation of vitamin C effect by the dose used. Few trials have used more than 1 g/day of vitamin C in the child and adult groups separately. Nevertheless, Karlowski 1975a and Coulehan 1974a used two different doses within the same trials, that is, with the same outcome definitions. Coulehan found that for school children, 2 g/day caused about twice the benefit of 1 g/day. Karlowski found that for adults, 6 g/day was associated with a double benefit compared with 3 g/day and variance analysis showed that the linear trend over the 0 g/day, 3 g/day and 6 g/day doses was significant (Hemilä 1996a; Hemilä 1999a). Although these findings do not establish dose dependency, they support the examination of doses higher than 1 g/day and comparing different doses.

Regular vitamin C administration also led to decrease in cold severity when measured as days indoors or days off work or school, and when measured on severity score scales (Analysis 3.1).

As regards the severity of colds, the Pitt 1979 paper is of further interest. This was a randomised, placebo-controlled, double-blind trial with 674 marine recruits during an eight-week period using 2 g/day of vitamin C. There was no difference in common cold incidence and only a 2% reduction in the duration of colds and a 5% reduction in cold severity (P = 0.023) for those in the vitamin C group. However, eight recruits developed pneumonia as a sequel to their colds and only one of these was in the vitamin C group (P = 0.044, Hemilä 2004; Hemilä 2007). Thus, in addition to the common cold, vitamin C might also affect other respiratory infections either independently of colds, or as complications of colds (Hemilä 1999b). A further important finding in the Pitt 1979 trial was that, although the vitamin C tablets were shown to be indistinguishable from the placebo tablets, 6% (40 out of 674; P = 0.013) of participants correctly inferred vitamin C or placebo tablets on the basis of subjective observations, indicating that this proportion of participants could identify vitamin C purely on the basis of its physiological effects (Hemilä 2006a).

Common cold duration and severity: therapeutic trials

Since the regular supplementation trials have unambiguously shown that vitamin C affects the duration and severity of colds without changing their incidence in the general population, it would seem rational to administer vitamin C therapeutically, starting immediately after the first symptoms. However, the therapeutic trials have mostly been negative (Analysis 4.1; Analysis 5.1). The pooled estimates for the duration and severity of colds do not show any difference between vitamin C and placebo.

Technically the therapeutic trials are in several ways much more complicated than regular supplementation trials. If the timing of supplementation initiation, the duration of supplementation, or the dosage, influence the size of the benefit, false negative findings might result from inappropriate study protocols.

Cowan 1950 used a therapeutic dose of about 3 g/day in the first two days of illness with no effect on common cold duration. Elwood 1977, Tyrrell 1977 and Audera 2001a used a three-day supplementation, and none of them found benefit of vitamin C on common cold duration. However, in their therapeutic trial,

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Tyrrell 1977 found a 40% reduction (P = 0.04) in the incidence of recurrent colds in men during the trial suggesting a beneficial effect in the way of protecting against new colds (Hemilä 1997a). A five-day therapeutic trial by Anderson 1975a found a 25% reduction in 'days spent indoors per subject' because of illness (P = 0.05) in the vitamin C group (1 to 1.5 g/day). Also, using a five-day therapeutic supplementation of 3 g/day in a 2 x 2 factorial design trial, Karlowski 1975c found that colds were 0.73 days shorter (P = 0.10; Hemilä 1996a). The benefits in the five-day studies by Anderson and Karlowski suggest that two to three days might be too short a time for vitamin C to produce unambiguous benefits. However, Abbott 1968 used up to two week supplementation, yet found no therapeutic benefit of 3 g/day vitamin C. Nevertheless, it seems clear that future therapeutic trials should not use short supplementation, i.e. less than five days.

It is also possible that the rapidity of initiation of vitamin C supplementation may have an impact on the effect. Asfora 1977 gave the same participants either vitamin C (6 g/day for five days) or other medications (aspirin, etc.) during different common cold episodes, but not in a double-blinded design. When treatment started within 24 hours of the onset of symptoms, the mean duration of vitamin C treated colds was 3.6 days, whereas the duration was 6.9 days with the other medications (Hemilä 2006a). However, if vitamin C was initiated later than 24 hours following the onset of symptoms, there was no meaningful difference between the groups. Regnier 1968 concluded from his therapeutic study that "the sooner the better" and "vitamin C administration is not effective when started on the third or fourth day or later in the viral infection." Anderson 1974f found a benefit from an 8 g vitamin C dose compared with a 4 g dose when administered only on the first day of illness, which is also consistent with the possibility that rapid initiation with high doses might be essential.

In several therapeutic trials, tablets were given to participants to be taken at home so they could start taking them as soon as they experienced the first symptoms of what they anticipated would be a cold (Anderson 1975a; Audera 2001a; Cowan 1950; Elwood 1977; Tyrrell 1977). In the Karlowski 1975c trial "if a cold developed, the volunteers were instructed to return to have their symptoms and clinical observations recorded and to receive supplemental study drug to be taken" and thus there was an unknown delay between the onset of symptoms and the initiation of treatment. Tebrock 1956 carried out their trial "on participants reporting to several outpatient industrial clinics under the supervision of the physicians conducting the study" indicating a delay between symptom onset and treatment. In the briefly described Abbott 1968 trial, it seems that the tablets were administered by the doctors taking part in the trial and the average time between symptom onset and treatment initiation remains unknown. Consequently, even though the time between symptom onset and treatment initiation may influence the benefit of vitamin C, the data on this factor are limited.

The larger effect observed using 8 g compared with 4 g as a single dose in the Anderson 1974f trial and the dose dependency in the Karlowski 1975a trial (Hemilä 1996a; Hemilä 1999a; Hemilä 2006a) suggest that future therapeutic trials with adults should use doses of at least 8 g/day. Similarly, the greater reported benefit of 2 g/day than 1 g/day in the prophylactic Coulehan 1974a trial suggests that therapeutic trials with children should use doses of at least 2 g/day.

None of the therapeutic trials examined the effect of vitamin C on children, although children have a substantially higher incidence of the common cold. Furthermore, the effect of regular vitamin C on the duration of colds has been substantially greater in children, up to 18% reduction in duration by 1 g or 2 g/day, compared with adults (8%), which also motivates therapeutic trials in particular with children. Finally, although a tablet is a practical and the most common form of administering vitamin C, it is worth noting that administering vitamin C powder directly into the nose has also been proposed (Gotzsche 1989).

Nevertheless, while the pooled results of our therapeutic trials do not justify routine vitamin C supplementation for the average person as a therapy for the common cold, the regular supplementation trials have shown unambiguously that vitamin C has a physiological effect on the duration and severity of colds. Furthermore, the results of controlled trials and the pooled results of trials apply to the average of the groups. We expect different sizes of vitamin C effects in different people, some having greater and some having smaller benefits than the average. Thus, given that vitamin C is safe and inexpensive, it does not seem unreasonable to test the effect of vitamin C on an individual basis as a therapy for the common cold soon after the onset of symptoms.

Trials with no data suitable for our meta-analyses

Seven studies did not report data suitable for our meta-analyses (Table 1). The findings in these trials were inconsistent. Although these trials should not be ignored, they do not add substantially to the findings of our meta-analyses discussed above.

Laboratory studies

Three experimental studies have examined the effect of vitamin C on experimentally induced common cold infections (Table 2). These trials which differed in their method of exposing volunteers to the infecting virus, are instructive. The study by Dick 1990, which has only been reported in conference proceedings, paid careful attention to the severity of the colds experienced by those who acquired them from fellow volunteers, who had been inoculated with a known rhinovirus. They also found that in these more natural circumstances of acquiring the virus, fewer, but not significantly fewer, volunteers on vitamin C developed cold symptoms but demonstrated similar viral shedding to the placebo group. The

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fragmentary descriptions of the Dick studies indicate a biological effect of vitamin C on experimentally caused colds. Schwartz 1973 found a reduction in common cold severity in the vitamin C group, also indicating a biological effect.

Findings in the excluded studies

Exclusion of a trial does not mean that the trial is necessarily uninformative. For example, we used a limit of 0.2 g/day for vitamin C as a pragmatic choice. If a trial with a lower dose finds a negative result, the negative findings can be attributed to the low dose. However, if a low dose does cause an effect, the effect may be explained, for example, by a particularly low dietary intake level (see above). Similarly, if a trial that has no placebo finds no difference between the intervention and control groups, it is not reasonable to explain the lack of difference by the placebo effect. Finally, since we were interested specifically in vitamin C, we excluded multiple antioxidant trials from our meta-analyses. However, if a multi-antioxidant formula has no effect on the common cold, it seems justified to conclude that there is a lack of effect by each constituent of the supplement (i.e. the finding is negative also for vitamin C if it is one of the components). In contrast, if a multi-antioxidant does have a beneficial effect, we cannot draw specific conclusions since the effect can be caused by any single antioxidant or the combination of several of them together. Therefore, the excluded trials can yield meaningful information. We do not summarise the findings of the excluded studies, but encourage the reader to look at those trials themselves.

Heterogeneity in the effects of vitamin C

A major finding of Analysis 1.1 was statistically significant heterogeneity in the effect of vitamin C supplementation on common cold incidence, indicating that vitamin C may influence common cold in some particular conditions.

Furthermore, Anderson 1972 found about an 8% increase in the proportion of participants who were 'not ill during the trial', 'not confined to the house' and 'not off work' in the vitamin C group. Accordingly, about one participant in 12 benefited from vitamin C supplementation in this particular setting (number needed to treat to benefit (NNTB) 12; Hemilä 2006a). Participants in this Canadian trial were asked not to enrol in the trial unless they normally experienced at least one cold in the wintertime and in this respect the participants do not represent the average population. Coulehan 1974a studied Navajo school children and found a 16% higher proportion of children in the vitamin C group who were 'never ill on active surveillance' by a medically trained clerk or school nurse (NNTB 6; Hemilä 2006a). Thus, these two trials indicate that some individual participants of the two studied populations may have benefited, even though there is strong evidence that regular vitamin C does not affect the average incidence of colds in the general community (Figure 2).

In close parallel with vitamin C, lipid-soluble vitamin E is interesting as these two antioxidants interact. Vitamin C reduces the oxidised form of vitamin E under *in vitro* conditions (Hemilä 2006a) and modifies the vitamin E effect on mortality of older males (Hemilä 2009b). Therefore heterogeneity in the vitamin E effect on common cold incidence (Hemilä 2006b) and on pneumonia incidence (Hemilä 2011) is relevant when considering the plausible heterogeneity of vitamin C effects on respiratory infections.

If the effects of vitamin C vary substantially between different subpopulations, the heterogeneity of the effect means a need for a careful consideration of goals when planning new trials. Assuming heterogeneity, further trials should try to identify and characterise the population groups or living conditions in which vitamin C might be beneficial, rather than re-examining the effects on ordinary Western people for whom the numerous trials already published have not found any substantial overall benefits from daily supplementation. Also, the notion that various factors may modify the effects of antioxidants is fundamentally important in restricting broad generalisations from individual trials, irrespective of whether the finding is positive or negative, and whether or not the trial is large and carefully conducted.

Potential for bias in the common cold trials

Even though shortcomings in the design and conduct of trials can lead to erroneous conclusions, a recent meta-analysis of 276 randomised controlled trials found that double-blinding and allocation concealment, two quality measures that are frequently used in meta-analyses, were not associated with treatment effects (Balk 2002). Furthermore, there is evidence that the importance of the placebo effect has been substantially exaggerated (Hrobjartsson 2010).

Nevertheless, we consider that given the expected small effects of vitamin C and the greatly subjective outcome definitions, only placebo-controlled trials can yield information of adequate rigour to meet the objectives of our review. Although we required only placebo control as an inclusion criterion, essentially all of the trials we identified were double-blind and randomised (Figure 1). Sensitivity analyses showed that our conclusions were not affected by the few trials that were methodologically less satisfactory.

Chalmers 1975 proposed that the effect of vitamin C on the common cold might be explained by "the result of the power of suggestion." As a support to this proposal he referred to the Karlowski 1975a trial in which the placebo was made of lactose which is sweet and thus it could be distinguished by taste from ascorbic acid which was used in vitamin C capsules. However, it was shown that Karlowski's findings cannot be logically explained by the breaking of the blind code (Hemilä 1996a; Hemilä 2006a). Furthermore, in the great majority of other trials, placebo has contained

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citric acid which cannot be distinguished from ascorbic acid by taste and in most trials the indistinguishability of the vitamin C and placebo preparations was explicitly stated (Figure 1). Thus, Chalmers' proposal is refuted by the indistinguishability of vitamin C and placebo preparations in numerous double-blinded trials.

Some aspects of this Cochrane Review were commented on recently by two groups of commentators, to which Hemilä replied (Shamseer 2008).

Safety of vitamin C

None of the vitamin C common cold trials that reported on adverse effects found evidence that vitamin C might be harmful in doses that were tested.

In general, vitamin C is considered safe in doses up to several grams per day. Although there has been speculation about the potential harm of large doses, it has been shown to be unfounded (Dykes 1975; Hemilä 2006a). For example, while 0.01 g/day of vitamin C protects against scurvy, in a recent pharmacokinetic study participants were administered up to 100 g of vitamin C intravenously within a few hours without any reported adverse effects, indicating the safety of such a very large dose in healthy people (Padayatty 2004).

Bee 1980 proposed 10 to 15 g/day for treating colds and Cathcart 1981 reported that he had orally administered over 30 g/day vitamin C to common cold patients. Such reports indicate the safety of such high doses, even though uncontrolled observations do not provide valid evidence of benefit. There are few reports of severe harm caused by high-dose vitamin C administration, but they can usually be attributed to some other coinciding medical condition. For example, the death of a 68-year old African American man was not attributed to intravenous injection of 80 g of vitamin C on two consecutive days *per se* but to his coincident glucose-6-phosphate dehydrogenase deficiency (Campbell 1975).

Linus Pauling's contribution

Among the four trials included in the Pauling 1971a meta-analysis, the largest dose, 1 g/day, was used by Ritzel 1961. Pauling based his optimistic quantitative expectations on this rather small and short trial, which was randomised, double-blind and placebo-controlled. Ritzel found significant reduction in the incidence (- 45%) and duration (- 31%) of colds, and Pauling calculated a combination of the duration and incidence, which he labelled 'integrated morbidity', referring to the total sickness days per person during the trial.

The 'integrated morbidity' was reduced by 61% in the Ritzel trial, and Pauling 1971a used this finding to extrapolate the effect of vitamin C to a broader community. The present analysis suggests that 'integrated morbidity' is not a good outcome measure, since the effects on incidence and duration/severity seem to have quite different patterns, though in the case of the Ritzel study, they moved together.

Ritzel carried out his trial with school children in a skiing school in the Swiss Alps, and such children are not a representative selection of the general population. In our analysis, Ritzel's trial is included in the group of five trials with participants exposed to short physical stress (Figure 2) which highlights the special character of this trial. Thus, it was not a misjudgement by Pauling 1971a to put the greatest weight on this trial, but his error was to extrapolate the findings to the general population (Hemilä 1997b; Hemilä 2006a).

Pauling pointed out various errors in the influential review by Dykes 1975, but did not contribute thereafter to the vitamin C and common cold field (Pauling 1976b; Pauling 1976c).

Pauling's vigorous advocacy was undoubtedly the stimulus for the wave of methodologically good trials, which now enable us to understand better the rather confusing role that vitamin C plays in the defence against the common cold. Significant uncertainties still persist, which further research should clarify.

AUTHORS' CONCLUSIONS

Implications for practice

The lack of effect of regularly administered vitamin C on the incidence of the common cold in the general population throws doubt on the usefulness of this practice. In special circumstances, where people are engaged in extreme physical exertion or exposed to significant cold stress, or both, vitamin C supplementation seems to have a beneficial prophylactic effect, but caution should be exercised in generalising this finding.

The regular supplementation trials found that $\geq$ 0.2 g/day vitamin C reduced common cold duration by 8% in adults and by 14% in children, and 1 to 2 g/day vitamin C reduced common cold duration by 18% in children. The practical relevance of these findings is not clear. In our opinion, this level of benefit does not justify long-term supplementation in its own right. So far, therapeutic supplementation has not been shown to be effective. Nevertheless, given the consistent effect of vitamin C on common cold duration and severity in the regular supplementation studies, and the low cost and safety, it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them.

Implications for research

It does not seem worthwhile to carry out further regular supplementation trials in the general population. However, the findings in marathon runners, skiers, swimmers and soldiers operating in subarctic conditions warrant further research.

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None of the therapeutic trials carried out so far have examined the effect of vitamin C on children, even though the regular supplementation trials have found substantially greater benefit for children than for adults. Furthermore, the incidence of the common cold in children is substantially higher in children compared with adults. Therefore, therapeutic trials are warranted in particular in children.

The findings in the Anderson 1974a study on the greater benefit of a single 8 g dose compared with a 4 g dose on the first day of the common cold, and the findings of the Karlowski 1975a trial on the greater benefit of 6 g/day compared with 3 g/day, suggest that doses in further therapeutic trials with adults should be at least 8 g/day.

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Harri Hemilä took charge of the review in 2004. In 2012 Professor Douglas decided to retire from updating the review. We (Hemilä and Chalker) are very grateful to Professor Douglas for his role in the initiation and update of this review.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Abbott 1968

Methods	Double-blind RCT, treatment trial
Participants	Family members of 78 UK general practitioners. Males and females were in equal numbers; 52% were from 21 to 50 years. 147 vitamin C; 123 placebo (p 442)
Interventions	3 g/d vitamin C as effervescent tablets (1 g 3 times per day) was "started as soon as coryza symptoms appeared and continued for as long as necessary, up to a total of fourteen days"
Outcomes	Sore throat, stuffy nose, sneezing, watery nasal discharge, headache, aching back and limbs (Table 1)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"similar placebo tablets were prepared"

Anderson 1972

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 months
Participants	Canadian adults, both sexes. 407 vitamin C; 411 placebo. Recruitment specified previous cold proneness in the winter months

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Anderson 1972 (*Continued*)

Interventions	1 g/d vitamin C and 3 g/d extra for the first 3 days of illness
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	[Vitamin C tablets:] "The taste of this formulation was well matched by a placebo preparation...The effectiveness of the matching was established by asking 30 individuals to taste both tablets ..."

Anderson 1974a

Methods	Double-blind RCT. Duration 3 months. 4 regular supplementation, 2 treatment and 2 placebo arms This entry reports a regular supplementation arm
Participants	Canadian adults, both sexes. Data for this arm include 277 vitamin C; 285 placebo
Interventions	1 g/d vitamin C and 4 g/d at onset of illness on the 1st day only
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	Problems with the placebo group #6; see p 40 (Table 16) in Hemilä 2006a. Therefore comparison in this review is restricted to the placebo group #4 which had close baseline values for "usual days indoors" and "usual days off work" and "contact with children" consistent with the baseline values in the 6 vitamin C groups

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Anderson 1974a (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	Tablets: "taste test carried out with the help of a number of colleagues demonstrated that they were reasonably well matched in flavour, texture and appearance"

Anderson 1974b

Methods	See Anderson 1974a. Regular supplementation arm
Participants	275 vitamin C
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	

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Anderson 1974b (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	

Anderson 1974c

Methods	See Anderson 1974a. Regular supplementation arm
Participants	308 vitamin C
Interventions	2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	

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Anderson 1974d

Methods	See Anderson 1974a. Regular supplementation arm
Participants	331 vitamin C
Interventions	0.25 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	

Anderson 1974e

Methods	See Anderson 1974a. Therapeutic arm
Participants	275 vitamin C
Interventions	4 g/d vitamin C on the 1st day of illness only
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

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Anderson 1974e (*Continued*)

Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	

Anderson 1974f

Methods	See for Anderson 1974a. Therapeutic arm
Participants	308 vitamin C
Interventions	8 g/d vitamin C on the 1st day of illness only
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	

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Anderson 1974f (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	

Anderson 1975a

Methods	Double-blind RCT. Therapeutic trial. Duration 15 weeks. 2 active and 1 placebo arm This arm used vitamin C tablets
Participants	Canadian adults, both sexes. 150 vitamin C; 146 placebo
Interventions	0.5 g weekly and 1.5 g/d on the 1st day of illness and 1 g/d for the next 4 days
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)
Notes	Indistinguishability of treatments: (p 824) "three types of medication were used: a 500-mg tablet containing sodium and calcium ascorbate in an approximate 2:1 ratio, a placebo tablet of the same appearance and taste, and a capsule containing 500 mg of ascorbic acid in sustained-release form. ... It was not possible to obtain placebo capsules that were truly indistinguishable from the active sustained-release form because the contents of the capsules (ascorbic acid pellets) proved prohibitively expensive to imitate. The explanatory notes provided to the subjects were therefore deliberately phrased to give the impression that, as with the tablets, half of the capsules contained a placebo preparation. This subterfuge was successful ... "

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	See Notes above

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Anderson 1975b

Methods	See Anderson 1975a. This arm used vitamin C capsules	
Participants	152 vitamin C	
Interventions	See Anderson 1975a	
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	

Asfora 1977

Methods	Initiated as a double-blind trial. Therapeutic trial	
Participants	Participants with age range between 14 and 89. 42 vitamin C; 41 placebo	
Interventions	6 g/d vitamin C for 5 d (total 30 g)	
Outcomes	Clinical progress (Table 1)	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Asfora 1977 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"preparations were given to alternate patients"
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

Audera 2001a

Methods	Double-blind RCT. Therapeutic trial
Participants	Australian adults of both sexes. 47 vitamin C; 42 placebo
Interventions	1 g/d vitamin C for 3 days. Placebo group received 30 mg/d vitamin C daily for 3 days
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

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Audera 2001a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"tablets with identical appearance and packaging"

Audera 2001b

Methods	See Audera 2001a
Participants	50 vitamin C
Interventions	3 g/d vitamin C for 3 days
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	

Bancalari 1984

Methods	Double-blind RCT. Regular supplementation trial. Duration 84 days
Participants	Chilean school children, male and female, age 10 to 12 years. 32 vitamin C; 30 placebo
Interventions	2 g/d vitamin C

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Bancalari 1984 (*Continued*)

Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"vitamin C tablets and the placebo tablets were identical in colour, taste, size and consistency"

Briggs 1984

Methods	Double-blind RCT. Regular supplementation trial. Over 8 winters for 3 or 6 months of commitment by each volunteer	
Participants	Australian adults, male and female. 265 vitamin C; 263 placebo	
Interventions	1 g/d vitamin C plus 4 g/d when respiratory symptoms occurred. Placebo group received 50 mg/d plus 200 mg/d when ill	
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)	
Notes	SD for duration was not published and it was estimated as SD = mean	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Briggs 1984 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"identical opaque gelatin capsules (dark brown) and ... similar acidic taste, but lacking vitamin C activity. Citric acid was selected"

Brown 1945

Methods	Placebo-controlled alternative-allocation trial. Therapeutic trial
Participants	US college students. 179 vitamin C, 119 placebo; 206 with nose colds and 92 with throat colds
Interventions	1 g vitamin C at first examination at the start of the cold and then 1 g 24 hours later
Outcomes	"Colds that did not develop" meaning that the cold lasted only a day. In contrast, those who still had symptoms on the next day were considered to have a cold. (Table 1)
Notes	Alternate allocation is not consistent with the distribution of participants in the vitamin C and placebo groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"alternately"
Allocation concealment (selection bias)	Unclear risk	?
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"given... without knowledge on the subjects' part that placebos were being given." Indicates single-blinding

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Brown 1945 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Subjects' observed outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	?
Vitamin C and placebo indistinguishable?	Low risk	"citric acid as a placebo"

Carr 1981a

Methods	Double-blind RCT. Regular supplementation trial. Duration 100 days. Identical twins: one group living together and the other living apart. This deals with those living together
Participants	Australian males and females age range 14 to 64 years (mean 25 years). 51 twin pairs living together
Interventions	1 g/d vitamin C. Both groups received a multi-vitamin tablet containing 70 mg/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	SD for duration was not published and the SD was calculated from the P value

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"matching of the active and placebo tablets was checked for both appearance and taste"

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Carr 1981b

Methods	See Carr 1981a. This deals with those living apart
Participants	44 twin pairs living apart
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"matching of the active and placebo tablets was checked for both appearance and taste"

Carson 1975

Methods	Double-blind RCT. Regular supplementation trial. Duration 40 days
Participants	UK adults. 121 vitamin C; 123 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1)
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

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Carson 1975 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"tablets or matching lactose dummies"

Charleston 1972

Methods	Single-blind, not randomised. Regular supplementation trial. Duration 15 weeks
Participants	Staff and students of the University of Strathclyde, UK. 47 vitamin C; 43 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	?
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	?

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Charleston 1972 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"placebo similar in appearance but containing lactose and 5% citric acid"

Clegg 1975

Methods	Double-blind RCT. Regular supplementation trial. Duration 15 weeks	
Participants	Scottish students. 67 vitamin C; 70 placebo	
Interventions	1 g/d vitamin C	
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"The placebo and ascorbic acid tablets were organoleptically indistinguishable"

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Constantini 2011a

Methods	Double-blind RCT. Regular supplementation trial
Participants	Male competitive swimmers in Israel. 12 vitamin C; 10 placebo
Interventions	1 g/day vitamin C for 3 months
Outcomes	Incidence of colds. Duration of colds (Analysis 2.1), severity of colds (Analysis 3.1)
Notes	Trial is divided into males and females since there was significant heterogeneity in vitamin C effect (P = 0.003)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly selected plastic bottle"
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"identical in appearance"

Constantini 2011b

Methods	Double-blind RCT. Regular supplementation trial
Participants	Female competitive swimmers in Israel. 9 vitamin C, 8 placebo
Interventions	1 g/day vitamin C for 3 months
Outcomes	Incidence of colds. Duration of colds (Analysis 2.1), severity of colds (Analysis 3.1)
Notes	Trial is divided into males and females since there was significant heterogeneity in vitamin C effect (P = 0.003)

Risk of bias

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Constantini 2011b (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	

Coulehan 1974a

Methods	Double-blind, alternate allocation. Regular supplementation trial. Duration 14 weeks
Participants	USA. Students at a Navajo Indian school. Older residential students. 131 vitamin C; 128 placebo
Interventions	2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	SD for duration was not published and it was estimated as SD = mean Personal communication (13 September 1995), about table 4: "... you are right, it is quite obvious that there is a typographical error. What I am referring to in those columns is the number of children without days of sickness, rather than the number of days as such. The title of Table 4 is correct, but the labelling of the columns is incorrect."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocation was "alternatively, from an alphabetical listing by classroom to one of two study groups"
Allocation concealment (selection bias)	Low risk	Double-blind

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Coulehan 1974a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"Placebos were formulated from citric acid to be indistinguishable in taste and appearance from the vitamin C tablets"

Coulehan 1974b

Methods	See Coulehan 1974a
Participants	Younger residential students. 190 vitamin C; 192 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	SD for duration was not published and it was estimated as SD = mean

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	?
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	

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Coulehan 1976

Methods	Double-blind RCT. Regular supplementation trial. Duration 18 weeks in one school and 15 weeks in another
Participants	USA. Children at 2 Navajo Indian residential schools, age 6 to 15 years. Both sexes. 428 vitamin C; 428 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	SD for duration was not published and it was estimated as SD = mean

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"placebo tablets were formulated with citric acid to be identical in appearance and taste with ascorbic acid pills"

Cowan 1942

Methods	Placebo-controlled, allocation method not clear. Regular supplementation trial. Duration 28 weeks
Participants	US college students. 208 vitamin C; 155 placebo
Interventions	0.2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1)
Notes	SD for duration was not published and it was estimated as SD = mean

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Cowan 1942 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The students were assigned alternately and without selection to an experimental and to a control group." However, the discrepancy in the size of trial arms is not consistent with alternate allocation, see above (208 versus 155)
Allocation concealment (selection bias)	Unclear risk	?
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single-blinded: "... placebo tablets of the same size, shape, appearance and taste as the ascorbic acid tablets. These students, of course, did not know that they were serving as controls."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The students (who were blinded) were instructed to report whenever a cold developed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	?
Vitamin C and placebo indistinguishable?	Low risk	"... placebo tablets of the same size, shape, appearance and taste as the ascorbic acid tablets. These students, of course, did not know that they were serving as controls."

Cowan 1950

Methods	Probably double-blind RCT. Alternate allocation. Therapeutic trial
Participants	US college students. 76 vitamin C; 77 placebo
Interventions	0.67 g of vitamin C for every 4 hours, with a maximum of 10 doses (total 6.7 grams); i.e. about 3 g/d for 2 days
Outcomes	Duration (Analysis 4.1)
Notes	-

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Cowan 1950 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"The medicaments were given out in strict rotation to the students as they enrolled"
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"Placebo (citric acid to simulate the taste of ascorbic acid, lactose, cornstarch, sugar, talc and stearic acid)"

Dahlberg 1944

Methods	Double-blind RCT. Regular supplementation trial. Duration 57 days
Participants	Swedish army. 1259 vitamin C; 1266 placebo
Interventions	0.2 g/d vitamin C during the first 24 days; 50 mg/d thereafter
Outcomes	Incidence Analysis 1.1
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

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Dahlberg 1944 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"Control tablets, to which a suitable amount of citric acid had been added, to disguise any difference in taste"

Dick 1990

Methods	Double-blind, placebo-controlled trial. Brief abstract report of 3 experimental regular supplementation studies using intense exposure to infected volunteers	
Participants	USA, adult volunteers. 24 vitamin C; 24 placebo	
Interventions	2 g/d vitamin C	
Outcomes	Shown in Table 2. Not included in meta-analyses	
Notes	3 abstracts, no full paper	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	?
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

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Elliot 1973

Methods	Double-blind RCT. Regular supplementation trial
Participants	Members of the crew of a Polaris submarine; 37 vitamin C, 33 placebo
Interventions	2 g/d vitamin C for 10 weeks
Outcomes	Incidence of runny nose or sneezing. Man-days of morbidity for hoarseness, sore throats, non-productive coughs and productive coughs (Table 1)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"Both AA and placebo [citric acid] capsules looked identical and when opened the contents were similar in taste and appearance"

Elwood 1976

Methods	Double-blind RCT. Regular supplementation trial
Participants	Wales, young mothers. 339 vitamin C; 349 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

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Elwood 1976 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"tablets ... These contained either 1 g ascorbic acid in an effervescent base or a matching placebo"

Elwood 1977

Methods	Double-blind RCT. Therapeutic trial
Participants	Wales, young mothers. 145 colds treated with vitamin C; 119 with placebo
Interventions	4 g/d vitamin C daily for the first 2.5 days of illness
Outcomes	Duration (Analysis 2.1) Colds were classified either as simple or chest colds
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

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Elwood 1977 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

Franz 1956

Methods	Double-blind. Regular supplementation study. 2 x 2 factorial: vitamin C and flavonoids. Duration 3 months
Participants	Medical students and student nurses. 44 vitamin C; 45 no vitamin C
Interventions	0.2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1)
Notes	In the vitamin C group 93% (13/14) of colds were cured or improved in 5 days versus 53% (8/15) in the no vitamin C group (P = 0.03; see p 14 Hemilä 2006a)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Groups were assigned in rotation"
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	Tablets: "all looked and tasted alike"

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Himmelstein 1998a

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 months
Participants	US sedentary people. 23 vitamin C; 25 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	A parallel trial with marathon runners is excluded from our analysis, because the drop-out rate was very high and divergent in the trial arms (Himmelstein 1998b)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"Placebo (similar looking and tasting tablets containing lactose)"

Karlowski 1975a

Methods	Double-blind RCT. 2 x 2 factorial: regular supplementation and therapeutic vitamin C. Duration 9 months. We compared 3 different arms with the placebo arm. This is regular supplementation arm
Participants	USA, employees of the NIH. 44 vitamin C; 46 placebo
Interventions	3 g/d vitamin C
Outcomes	Duration (Analysis 2.1)

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Karlowski 1975a (*Continued*)

Notes	The authors believed that the benefits observed were attributable to the breaking of the patient blind: "we discovered that some of the volunteers had tasted the contents of their capsules and professed to know whether they were taking the ascorbic acid or the placebo". However, their interpretation was later shown to be erroneous, *see* Hemilä 1996a, Hemilä 2006a, Hemilä 2006c

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	See Notes

Karlowski 1975b

Methods	See Karlowski 1975a. This is regular supplementation plus therapeutic arm
Participants	57 vitamin C
Interventions	3 g/d vitamin C and 3 g/d therapeutic from the onset of cold for 5 days
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	

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Karlowski 1975b (*Continued*)

Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

Karlowski 1975c

Methods	See Karlowski 1975a. This is therapeutic only arm
Participants	43 vitamin C
Interventions	3 g/d therapeutic vitamin C from the onset of cold for 5 days
Outcomes	Duration (Analysis 4.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	

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Karlowski 1975c (*Continued*)

Vitamin C and placebo indistinguishable?	Unclear risk	?

Liljefors 1972

Methods	Double-blind RCT. Cross-over regular supplementation trial. Duration 2 + 2 weeks. In the first 2 weeks 25 participants received vitamin C and 18 placebo. As participants became ill they were removed from the trial and 3 people withdrew. In the second period, 18 received placebo and 8 vitamin C
Participants	Swedish army males. 33 vitamin C; 33 placebo
Interventions	2 g/d vitamin C for 2 weeks
Outcomes	Incidence (Analysis 1.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

Ludvigsson 1977a

Methods	Double-blind RCT. Regular supplementation trial. Duration 7 weeks
Participants	Swedish school children. 80 vitamin C; 78 placebo
Interventions	1 g/d vitamin C. Placebo contained 30 mg/d vitamin C

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Ludvigsson 1977a (*Continued*)

Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)	
Notes	Pilot study to Ludvigsson 1977b	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"fizzy tablet which contained 1000 mg vitamin C; in the other group the fizzy tablet looked and tasted the same"

Ludvigsson 1977b

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 months	
Participants	Swedish school children. 304 vitamin C; 311 placebo	
Interventions	1 g/d vitamin C. Placebo contained 10 mg/d vitamin C	
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised

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Ludvigsson 1977b (*Continued*)

Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"fizzy tablet which contained 1000 mg vitamin C; in the other group the fizzy tablet looked and tasted the same"

Miller 1977a

Methods	Double-blind RCT. Regular supplementation trial. Identical twins. Duration 5 months
Participants	US school children. 12 twin pairs "high body weight"
Interventions	1 g/d vitamin C. Placebo contained 50 mg/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	

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Vitamin C and placebo indistinguishable?	Unclear risk	?

Miller 1977b

Methods	See Miller 1977a
Participants	12 twin pairs "medium body weight"
Interventions	0.75 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

Miller 1977c

Methods	See Miller 1977a
Participants	20 twin pairs "low body weight"
Interventions	0.5 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	-

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Miller 1977c (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

Moolla 1996a

Methods	Double-blind RCT. Regular supplementation trial. Duration 6 weeks before and 2 weeks after the race
Participants	South Africa. Ultra marathon runners. 13 vitamin C; 19 placebo
Interventions	0.25 g/d vitamin C
Outcomes	Incidence (Analysis 1.1)
Notes	1/4 of those who reported respiratory symptoms in the vitamin C group, and 8/13 of those who reported respiratory symptoms in the placebo group, reported that their respiratory symptoms were severe (P = 0.08)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind

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Moolla 1996a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"placebo was identical in form to the ascorbic acid"

Moolla 1996b

Methods	See Moolla 1996a
Participants	Sedentary controls for marathon runners. 11 vitamin C; 19 placebo
Interventions	0.25 g/d vitamin C
Outcomes	Incidence (Analysis 1.1)
Notes	0/6 of those who reported respiratory symptoms in the vitamin C group and 4/7 of those who reported respiratory symptoms in the placebo group reported that their respiratory symptoms were severe (P = 0.02)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	

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Moolla 1996b (*Continued*)

Vitamin C and placebo indistinguishable?	Low risk	"placebo was identical in form to the ascorbic acid"

Peters 1993a

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 weeks before and 2 weeks after the race
Participants	South Africa. Ultra marathon runners. 43 vitamin C; 41 placebo
Interventions	0.6 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"identical looking and tasting placebo containing citric acid"

Peters 1993b

Methods	See Peters 1993a.
Participants	Sedentary controls for marathon runners. 34 vitamin C; 39 placebo
Interventions	0.6 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)

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Peters 1993b (*Continued*)

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"identical looking and tasting placebo containing citric acid"

Peters 1996a

Methods	Double-blind RCT. Regular supplementation trial. Duration 21 days prior to the race
Participants	South Africa. Ultra marathon runners. 44 vitamin C; 47 placebo
Interventions	0.5 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	SD for duration was not published and it was estimated as SD = mean

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

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Peters 1996a (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"tablets of similar appearance"

Peters 1996b

Methods	See Peters 1996a.
Participants	South Africa. Family controls for marathon runners. 41 vitamin C; 45 placebo
Interventions	0.5 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"tablets of similar appearance"

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Pitt 1979

Methods	Double-blind RCT. Regular supplementation trial. Duration 8 weeks
Participants	USA marine recruits. 331 vitamin C; 343 placebo
Interventions	2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	SD for duration was not published and it was estimated as SD = mean

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"the placebo tablets were formulated from citric acid and were indistinguishable in appearance and taste from the vitamin C tablets"

Regnier 1968

Methods	Initiated as a double-blind trial, but changed to a single-blind
Participants	The number of participants for the double-blind part is not reported. In the single-blind stage, 22 subjects were included "The majority were adults whose ages ranged from 30 to 50, with the extremes being five children younger than 12" (p 949)
Interventions	For the double-blind part: "ascorbic acid alone, ascorbic acid plus bioflavonoids, flavonoids only and, fourthly, a lactose placebo with the two 'vitamins' present either alone or together in 0.2 g quantities". In the single-blind stage, 0.6 g of vitamin C was administered every 3 h

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Regnier 1968 (*Continued*)

Outcomes	Clinical progress (Table 1)	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Allocation method not described
Allocation concealment (selection bias)	Unclear risk	?
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Initiated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	?
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	?
Vitamin C and placebo indistinguishable?	Unclear risk	"lactose placebo"

Ritzel 1961

Methods	Double-blind RCT. Regular supplementation trial. Duration 2 weeks	
Participants	Children attending ski school in Swiss Alps. 139 vitamin C; 140 placebo	
Interventions	1 g/d vitamin C	
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)	
Notes	SD for duration was not published and the SD was calculated from the P value	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind

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Ritzel 1961 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"The placebo was indistinguishable from the 1-gm ascorbic acid tablet"

Sabiston 1974

Methods	Double-blind RCT. Regular supplementation trial. Duration 2 to 3 weeks
Participants	Canadian male military recruits during subarctic winter exercises. 56 vitamin C; 56 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	Personal communication from Manny Radomski (12 September 2009): "Tent group commanders [who were responsible for distributing the pills and recording the distribution] did not know what was in the vials... We [the authors] collected the data by symptoms on T-scan cards. We did not 'break the code' until after all cards had been assessed."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

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Sabiston 1974 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	Personal communication (Radomski 12 September 2009): "Vitamin C and placebo were in identical capsules, so taste did not enter into the equation... In our pre-briefing to the troops, we believe that we told the troops that they would all be getting vitamin C but at different doses."

Sasazuki 2006

Methods	Double-blind RCT. Regular supplementation trial. Duration 3.5 years
Participants	Japanese males and females, mean age 57 years. 140 vitamin C; 133 placebo
Interventions	0.5 g/d vitamin C. Placebo contained 50 mg/d vitamin C
Outcomes	Incidence (Analysis 1.1) ITT results are shown
Notes	Additional data provided by authors Duration and severity of colds were reported, but they were recorded on the period after supplementation had been stopped, with no rationale described for such a comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

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Scheunert 1949

Methods	Prophylactic trial
Participants	1066 factory workers in Germany between November 1942 and June 1943
Interventions	Different doses of vitamin C were administered to 4 study groups (range 0.02 to 0.3 g/d) so that the lowest dose arm(s) might be used as the control group. Duration of the study was 244 days
Outcomes	The common cold [Erkältungskrankheiten] was one of the outcomes and "The percentage monthly duration of people sick with the common cold" is listed (Table 1)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	?
Allocation concealment (selection bias)	Unclear risk	?
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	?
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	?
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	?
Vitamin C and placebo indistinguishable?	Unclear risk	?

Schwartz 1973

Methods	Double-blind experimental regular supplementation study with nasal instillation of virus after 2 weeks of pre-treatment
Participants	Male US prison volunteers. 11 vitamin C; 10 placebo
Interventions	3 g/d vitamin C
Outcomes	Shown in Table 2. Not included in meta-analyses
Notes	-

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Schwartz 1973 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	?
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

Tebrock 1956

Methods	Double-blinded alternative-allocation trial. Therapeutic trial
Participants	Adults from outpatient industrial clinics, and some college, seminary and private patients. 956 vitamin C, 960 placebo
Interventions	0.2 g/d vitamin C or/and flavonoids in a 2 x 2 factorial design for 3 days
Outcomes	Running nose, sneezing, hoarseness, cough, malaise, headache, postnasal drip, sore throat (Table 1)
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"assigned in rotation" to 8 groups
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

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Tebrock 1956 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

Tyrrell 1977

Methods	Double-blind RCT. Therapeutic trial	
Participants	UK, both sexes. 274 episodes treated with vitamin C; 329 placebo	
Interventions	4 g/d vitamin C for the first 2.5 days of illness	
Outcomes	Duration (Analysis 4.1) and severity (Analysis 5.1)	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	"the tubes with 'placebo treatment', contained inert substances of identical appearance and taste"

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Van Straten 2002

Methods	Double-blind RCT. Regular supplementation trial. Duration 60 days
Participants	UK, both sexes. 84 vitamin C; 84 placebo
Interventions	1 g/d vitamin C. Ester-C ascorbate, a form that, according to authors, "allows cells to efficiently absorb and retain high levels of vitamin"
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1)
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Low risk	Tablets: "ascorbate 500 mg or a matched placebo"

Walker 1967

Methods	Experimental regular supplementation study in which healthy volunteers were intranasally inoculated with viruses. Duration 3 days before and 6 days after nasal instillation of virus
Participants	UK adults both sexes. 47 vitamin C; 44 placebo
Interventions	3 g/d vitamin C
Outcomes	Shown in Table 2. Not included in meta-analyses
Notes	-

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Walker 1967 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	?
Allocation concealment (selection bias)	Unclear risk	?
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	?
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	?
Incomplete outcome data (attrition bias) All outcomes	Low risk	Laboratory study
Vitamin C and placebo indistinguishable?	Unclear risk	?

Wilson 1973a

Methods	Double-blind RCT. Regular supplementation trial. Duration 9 months
Participants	UK boarding school girls. 70 vitamin C; 58 placebo
Interventions	0.2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)
Notes	Complicated classification system makes comparison with other trials difficult

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

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Wilson 1973a (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

Wilson 1973b

Methods	See Wilson 1973a	
Participants	UK boarding school boys. 88 vitamin C; 86 placebo	
Interventions	0.2 g/d vitamin C	
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1)	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Vitamin C and placebo indistinguishable?	Unclear risk	?

g/d: grams per day
h: hours
mg/d: milligrams per day
SD: standard deviation

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ITT: intention-to-treat
NIH: National Institutes for Health
RCT: randomised controlled trial

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

Study	Reason for exclusion
Audera 2001c	Vitamin C was administered with flavonoids. Thus the comparison was not on vitamin C specifically. There was no difference between placebo and 3 g/day vitamin C + flavonoid groups. 2 other arms are included in our analyses (Audera 2001a; Audera 2001b)
Baird 1979	Low dose. 362 UK students aged 17 to 25 years were studied for 72 days in a double-blind RCT of regular supplementation. A daily drink contained either synthetic orange juice without ascorbic acid, synthetic juice with 0.08 g/d of ascorbic acid added, or natural orange juice with 0.08 g/d of ascorbic acid added. There was a highly significant reduction in common cold incidence among males (RR 0.63; 95% CI 0.50 to 0.78) but not in females (RR 1.24; 95% CI 0.95 to 1.61) (Hemilä 1997a and Hemilä 2006a). The heterogeneity between sexes was highly significant (Hemilä 2008). The benefit of low-dose vitamin C supplementation may be explained by low dietary vitamin C intake in the UK (Hemilä 1997a)
Barnes 1961	No placebo comparison. A trial in the USA. A multivitamin preparation that included 0.2 g/d vitamin C was given to 23 members (10 boys, 13 girls) of a basketball team for 7 weeks; medication being received from the coaches. The cold outcomes were compared with those of 16 people (8 boys, 8 girls) of the same age and background. The controls reported to the coaches daily. Days sick from cold were counted in each group. The study took place over 8 weeks during which the basketball players took medication on an average of 43 days. The only usable outcome was "mean days per person" in the vitamin C group 1.48 (SD 2.65) and in the control group 6.87 (SD 8.57). However, there are serious doubts about the comparability of the controls who were apparently not basketball players
Bartley 1953	Low dose. "The volunteers did not know to which group they belonged, nor did the physicians responsible for the clinical investigations. All the volunteers were given each day 7 supplementary tablets of identical taste and appearance, some containing vitamin C, others being dummies" (p 8). 3 participants received 0. 07 g/d vitamin C and a total of 14 cold episodes were recorded among them in the follow up, 4 participants were administered 0.01 g/d vitamin C (18 colds), and 6 persons were administered no vitamin C (30 colds) . The geometric mean length of colds in vitamin C deprived participants was 6.4 days, and in non-deprived participants 3.3 days, and the authors concluded "such evidence as there is definitely confirms the hypothesis that the absence of vitamin C tended to cause colds to last longer" (p 43)
Bendel 1955	No placebo comparison and the control group was not parallel. 120 children at a summer camp for 2 weeks were given 0.2 g/d vitamin C daily and their cold experience was compared with that of participants in an earlier camp
Bergquist 1943	Low dose. A Swedish trial involving supplementation with only 0.03 g/d vitamin C
Bessel-Lorck 1958	No placebo comparison. Berlin school children in a skiing camp. Abridged summary: "26 subjects received 1 g of vitamin C daily during the first 9 days. Under this regimen only one student became sick. In 20 participants the regular supplementation did not begin until the 9th day. At this point in time 9 students were already sick with upper respiratory infections; and 3 others became infected within the first 3 days after the trial began. All

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(*Continued*)

	of those who were sick were treated with 2 g of vitamin C per day. Within just 24 hours a rapid improvement in the general condition was evident so that elevated physical demands were met without particular difficulty. All participants displayed a significant increase in their capacity to perform physical activities while being treated with vitamin C." The Bessel-Lorck paper is available as a translation. This trial motivated Ritzel 1961 to carry out his RCT (see Analysis 1.1.2)
Bibile 1966	This was cited by Kleijnen 1989, but we have been unable to retrieve a copy through library orders
Boines 1956	No placebo comparison. Study of poliomyelitis sufferers
Chavance 1993	Low dose. Double-blind RCT of 0.09 g/d vitamin C in elderly participants. No benefit was demonstrated
Cuendet 1946	No placebo comparison. 200 children in 3 mountain parishes took vitamin C supplements up to 0.3 g/d
Dyllick 1967	No placebo comparison. Cohort workplace study involving 200 recipients of 1 g/d of vitamin C whose respiratory experience was compared with those not receiving vitamin C
Fogelholm 1998	Vitamin C in combination with other antioxidants. Finnish study involving 75 athletes. RCT of 1 g/d vitamin C with 0.3 g/d vitamin E and 0.09 g/d ubiquinone versus an undescribed placebo. Methodologically strong study but was excluded from the meta-analyses because there were 3 antioxidants in the active preparation which were each hypothesised to be potentially beneficial
Glazebrook 1942	Low dose. 1500 boys at a UK boarding school during World War II. The participants were allocated as administrative units and not on an individual basis. Vitamin C (0.05 to 0.3 g/d) was added to cocoa and milk in the kitchen to a group of 335 boys. Although ineffective powder was not added to the drinks of the control group, the control drinks served functionally as a placebo. The number of participants who had colds was 17% lower in the vitamin C group (72/335 versus 286/1100; P = 0.10, Hemilä 2004) and the number of participants admitted to hospital because of the common cold was 23% lower (59/335 versus 253/1100; P = 0.04, Hemilä 2011)
Gormly 1977	No placebo comparison. 14 males of 29 members of a 1-year Antarctic expedition took 1 g/d vitamin C throughout their stay. Their health outcomes were compared with the remaining group who did not take vitamin C, and no difference was observed between the 2 groups
Gorton 1999	No placebo comparison and the control group not parallel. A technical training facility in Chile was the site of this cohort study with 250 trainees who were given 3 g/d vitamin C during their 10-day course. The vitamin C group was compared with a control group of 463 students who had been monitored in a somewhat similar way during the previous year (sic)
Himmelstein 1998b	There was an extreme and divergent drop-out rate in the Himmelstein 1998b trial. They started with 52 marathon runners in 2 groups, but 42% (22 of 52) of the vitamin C group, and 75% (38 of 52) of the placebo group dropped out during the trial (P = 0.003)
Hopfengärtner 1944	Low dose. Long-term hospital baby study in which supplementation of 0.05 g/d vitamin C was used
Hunt 1994	Not focused on the common cold. Double-blind RCT. 57 elderly UK patients suffering from acute bronchitis or pneumonia who were admitted to hospital for treatment were administered 0.2 g/d of vitamin C (see Hemilä 2007)

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(*Continued*)

Kimbarowski 1967	No placebo comparison. 216 Russian soldiers were hospitalised because of influenza A. 114 were administered 0.2 g/d vitamin C. There were 2 cases of pneumonia in the vitamin C group in comparison with 10 cases in the control group. Thus this trial found a lower incidence of complications of viral respiratory infection (Hemilä 2004; Hemilä 2007)
Koytchev 2003	No placebo comparison. Double-blind RCT involving 1167 participants. 4 arms, colds treated with 0.9 g/d vitamin C plus or minus antihistamine and antipyretics
Maggini 2012	Vitamin C in combination with zinc. 1 g/d vitamin C and 10 mg/d zinc for 94 participants. The combination decreased the duration or rhinorrhoea
Masek 1974	Low dose. Two large studies of Czech coal miners comparing 0.1 g/d vitamin C and placebo over a period of 4 or 8 weeks. Excluded both on the basis of low dose and inadequacy of data for inclusion in meta-analyses. The trials were neither randomised nor blind. Authors claimed benefits to the active recipients
Niemi 1951	Low dose and no placebo comparison. Finnish study with military recruits. 1036 people were observed during a 3-month period. 516 were administered 0.1 g/d vitamin C. No benefits of vitamin C
Peters 1940	No placebo comparison. Short-term baby supplementation study
Schmidt 2011	Vitamin C in combination with vitamin D, folic acid and selenium. Double-blind, placebo-controlled RCT with 192 patients with recurrent colds. Authors claimed benefits to the active recipients

g/d: grams per day
RCT: randomised controlled trial
RR: risk ratio
SD: standard deviation

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DATA AND ANALYSES

Comparison 1. Incidence of colds while taking ≥ 0.2 g/day vitamin C regularly

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants developing ≥ 1 cold episodes during the trial	29	11306	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.92, 0.98]
1.1 All eligible trials with exception of subgroup removed below	24	10708	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.94, 1.00]
1.2 Short-term exposure to severe physical stress and/or cold	5	598	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.35, 0.64]

Comparison 2. Duration of the colds occurring when on regular ≥ 0.2 g/day vitamin C

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of common cold symptoms (placebo group duration 100%)	31	9745	Mean Difference (IV, Fixed, 95% CI)	-9.38 [-12.86, -5.90]
1.1 Trials with adults	17	7215	Mean Difference (IV, Fixed, 95% CI)	-7.72 [-11.76, -3.69]
1.2 Trials with children	14	2530	Mean Difference (IV, Fixed, 95% CI)	-14.19 [-21.07, -7.31]

Comparison 3. Severity of the colds occurring when on regular ≥ 0.2 g/day vitamin C

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Indicators of common cold severity	16	7209	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.17, -0.07]
1.1 Mean days indoors or off work or school	7	5066	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.17, -0.05]
1.2 Mean symptom severity score	9	2143	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.22, -0.05]

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Comparison 4. Duration of the colds after therapeutic ≥ 0.2 g/day vitamin C

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of common cold symptoms (placebo group duration 100%)	7	3249	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-8.20, 2.39]

Comparison 5. Severity of the colds after therapeutic ≥ 0.2 g/day vitamin C

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Indicators of common cold severity	4	2708	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.15, 0.01]
1.1 Mean days indoors or off work or school	3	2569	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.16, -8.25]
1.2 Mean symptom severity score	1	139	Std. Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.21, 0.51]

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Analysis 1.1. Comparison 1 Incidence of colds while taking ≥ 0.2 g/day vitamin C regularly, Outcome 1 Proportion of participants developing ≥ 1 cold episodes during the trial.

Review: Vitamin C for preventing and treating the common cold

Comparison: 1 Incidence of colds while taking ≥ 0.2 g/day vitamin C regularly

Outcome: 1 Proportion of participants developing ≥ 1 cold episodes during the trial

Study or subgroup	Vitamin C n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All eligible trials with exception of subgroup removed below					
Peters 1996b	5/41	11/45		0.4 %	0.50 [0.19, 1.31]
Moolla 1996b	5/11	12/19		0.3 %	0.72 [0.35, 1.50]
Charleston 1972	31/47	37/43		1.5 %	0.77 [0.60, 0.97]
Coulehan 1974a	19/190	23/192		0.9 %	0.83 [0.47, 1.48]
Anderson 1972	302/407	335/411		12.7 %	0.91 [0.85, 0.98]
Coulehan 1974b	16/131	17/128		0.7 %	0.92 [0.49, 1.74]
Dahlberg 1944	131/1259	142/1266		5.4 %	0.93 [0.74, 1.16]
Bancalari 1984	21/32	21/30		0.8 %	0.94 [0.67, 1.32]
Anderson 1974a	922/1191	233/285		14.4 %	0.95 [0.89, 1.01]
Franz 1956	14/44	15/45		0.6 %	0.95 [0.52, 1.74]
Sasazuki 2006	68/140	67/133		2.6 %	0.96 [0.76, 1.23]
Cowan 1942	184/208	142/155		6.2 %	0.97 [0.90, 1.03]
Ludvigsson 1977b	230/304	240/311		9.1 %	0.98 [0.90, 1.07]
Pitt 1979	298/331	309/343		11.6 %	1.00 [0.95, 1.05]
Coulehan 1976	98/428	98/428		3.7 %	1.00 [0.78, 1.28]
Clegg 1975	48/67	50/70		1.9 %	1.00 [0.81, 1.24]
Elwood 1976	296/339	298/349		11.2 %	1.02 [0.96, 1.09]
Briggs 1984	125/265	121/263		4.6 %	1.03 [0.85, 1.23]
Carson 1975	85/121	84/123		3.2 %	1.03 [0.87, 1.22]
Van Straten 2002	35/84	34/84		1.3 %	1.03 [0.72, 1.48]
Ludvigsson 1977a	49/80	44/78		1.7 %	1.09 [0.84, 1.41]
Liljefors 1972	10/33	9/33		0.3 %	1.11 [0.52, 2.38]
Peters 1993b	18/34	18/39		0.6 %	1.15 [0.72, 1.82]
Himmelstein 1998a	10/23	8/25		0.3 %	1.36 [0.65, 2.84]

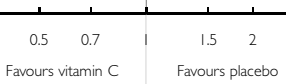


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Study or subgroup	Vitamin C n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**5810**	**4898**	◆	**96.1 %**	**0.97 [0.94, 1.00]**
Total events: 3020 (Vitamin C), 2368 (Placebo)					
Heterogeneity: Chi^2 = 17.75, df = 23 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 1.90 (P = 0.057)					
2 Short-term exposure to severe physical stress and/or cold					
Peters 1996a	7/44	19/47	←	0.7 %	0.39 [0.18, 0.84]
Sabiston 1974	6/56	14/56	←	0.5 %	0.43 [0.18, 1.04]
Moolla 1996a	4/13	13/19	←	0.4 %	0.45 [0.19, 1.07]
Peters 1993a	14/43	28/41	←	1.1 %	0.48 [0.30, 0.77]
Ritzel 1961	17/139	31/140	←	1.2 %	0.55 [0.32, 0.95]
Subtotal (95% CI)	**295**	**303**	◆	**3.9 %**	**0.48 [0.35, 0.64]**
Total events: 48 (Vitamin C), 105 (Placebo)					
Heterogeneity: Chi^2 = 0.60, df = 4 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 4.99 (P < 0.00001)					
Total (95% CI)	**6105**	**5201**	◆	**100.0 %**	**0.95 [0.92, 0.98]**
Total events: 3068 (Vitamin C), 2473 (Placebo)					
Heterogeneity: Chi^2 = 44.85, df = 28 (P = 0.02); I^2 =38%					
Test for overall effect: Z = 3.18 (P = 0.0015)					
Test for subgroup differences: Chi^2 = 22.74, df = 1 (P = 0.00), I^2 =96%					



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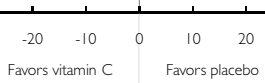
Analysis 2.1. Comparison 2 Duration of the colds occurring when on regular ≥ 0.2 g/day vitamin C, Outcome 1 Duration of common cold symptoms (placebo group duration 100%).

Review: Vitamin C for preventing and treating the common cold

Comparison: 2 Duration of the colds occurring when on regular ≥ 0.2 g/day vitamin C

Outcome: 1 Duration of common cold symptoms (placebo group duration 100%)

Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Trials with adults							
Van Straten 2002	37	58 (96)	50	100 (150)		0.5 %	-42.00 [-93.82, 9.82]
Himmelstein 1998a	14	60 (26)	12	100 (82)		0.5 %	-40.00 [-88.35, 8.35]
Carr 1981b	57	65 (75)	71	100 (75)		1.8 %	-35.00 [-61.14, -8.86]
Sabiston 1974	6	72 (50)	14	100 (50)		0.5 %	-28.00 [-75.82, 19.82]
Peters 1993b	18	75 (38)	18	100 (56)		1.2 %	-25.00 [-56.26, 6.26]
Charleston 1972	44	84 (46)	80	100 (20)		5.9 %	-16.00 [-30.28, -1.72]
Peters 1996a	7	85 (85)	19	100 (100)		0.2 %	-15.00 [-92.37, 62.37]
Karlowski 1975a	128	87.4 (51.5)	65	100 (52)		5.1 %	-12.60 [-28.07, 2.87]
Anderson 1974a	1823	93 (102)	437	100 (99)		11.2 %	-7.00 [-17.40, 3.40]
Briggs 1984	125	94 (94)	121	100 (100)		2.1 %	-6.00 [-30.27, 18.27]
Elwood 1976	627	94 (90)	690	100 (99)		11.6 %	-6.00 [-16.21, 4.21]
Anderson 1972	561	95 (92)	609	100 (82)		12.1 %	-5.00 [-15.02, 5.02]
Clegg 1975	68	95 (41)	73	100 (39)		6.9 %	-5.00 [-18.23, 8.23]
Pitt 1979	600	97.4 (100)	619	100 (100)		9.6 %	-2.60 [-13.83, 8.63]
Carr 1981a	94	101 (96)	70	100 (96)		1.4 %	1.00 [-28.70, 30.70]
Peters 1993a	14	103 (17)	28	100 (42)		3.8 %	3.00 [-14.93, 20.93]
Peters 1996b	5	136 (136)	11	100 (100)		0.1 %	36.00 [-97.05, 169.05]
Subtotal (95% CI)	**4228**		**2987**			**74.4 %**	**-7.72 [-11.76, -3.69]**
Heterogeneity: Chi^2 = 14.66, df = 16 (P = 0.55); I^2 =0.0%							
Test for overall effect: Z = 3.75 (P = 0.00018)							
2 Trials with children							
Constantini 2011a	30	53 (48)	21	100 (68)		1.1 %	-47.00 [-80.78, -13.22]
Ludvigsson 1977a	62	61 (41)	55	100 (67)		2.9 %	-39.00 [-59.44, -18.56]
Ritzel 1961	17	69 (51)	31	100 (51)		1.3 %	-31.00 [-61.17, -0.83]
Coulehan 1974b	16	71 (71)	17	100 (100)		0.3 %	-29.00 [-87.91, 29.91]

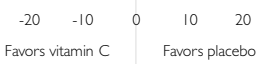


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Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bancalari 1984	38	76 (62)	46	100 (65)		1.6 %	-24.00 [-51.23, 3.23]
Wilson 1973a	160	84.5 (131)	126	100 (134)		1.3 %	-15.50 [-46.48, 15.48]
Miller 1977c	116	87 (73)	122	100 (73)		3.5 %	-13.00 [-31.55, 5.55]
Coulehan 1974a	19	88 (88)	23	100 (100)		0.4 %	-12.00 [-68.88, 44.88]
Miller 1977a	53	93 (105)	42	100 (105)		0.7 %	-7.00 [-49.51, 35.51]
Ludvigsson 1977b	423	94 (85)	398	100 (114)		6.3 %	-6.00 [-19.82, 7.82]
Coulehan 1976	98	95 (95)	98	100 (100)		1.6 %	-5.00 [-32.31, 22.31]
Miller 1977b	42	97 (50)	40	100 (50)		2.6 %	-3.00 [-24.65, 18.65]
Wilson 1973b	205	108 (150)	187	100 (132)		1.6 %	8.00 [-19.92, 35.92]
Constantini 2011b	23	116 (74)	22	100 (111)		0.4 %	16.00 [-39.37, 71.37]
Subtotal (95% CI)	**1302**		**1228**			**25.6 %**	**-14.19 [-21.07, -7.31]**
Heterogeneity: Chi^2 = 17.74, df = 13 (P = 0.17); I^2 =27%							
Test for overall effect: Z = 4.04 (P = 0.000053)							
Total (95% CI)	**5530**		**4215**			**100.0 %**	**-9.38 [-12.86, -5.90]**
Heterogeneity: Chi^2 = 34.92, df = 30 (P = 0.25); I^2 =14%							
Test for overall effect: Z = 5.28 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 2.53, df = 1 (P = 0.11), I^2 =60%							



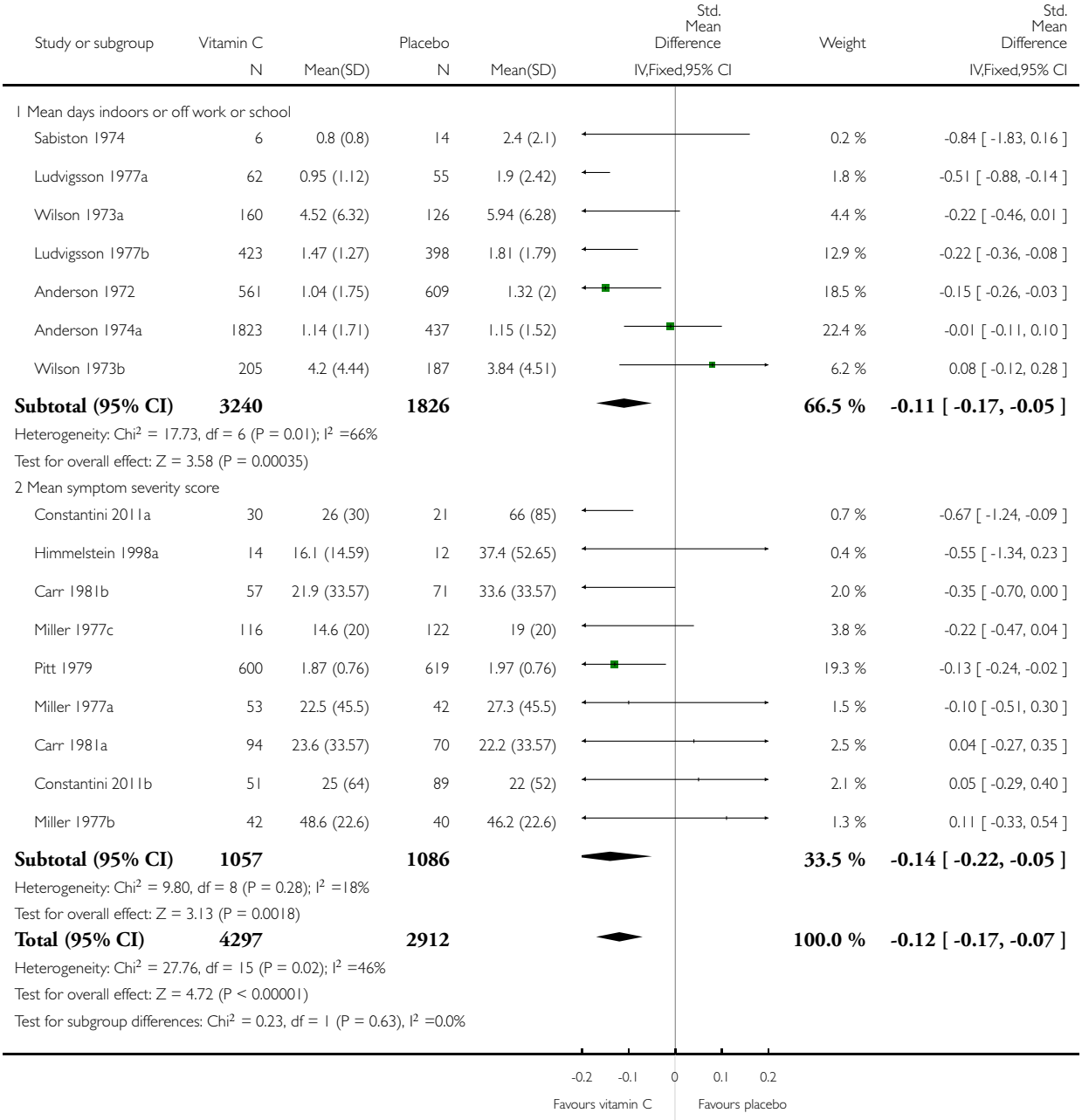
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Analysis 3.1. Comparison 3 Severity of the colds occurring when on regular ≥ 0.2 g/day vitamin C, Outcome 1 Indicators of common cold severity.

Review: Vitamin C for preventing and treating the common cold

Comparison: 3 Severity of the colds occurring when on regular ≥ 0.2 g/day vitamin C

Outcome: 1 Indicators of common cold severity



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Analysis 4.1. Comparison 4 Duration of the colds after therapeutic ≥ 0.2 g/day vitamin C, Outcome 1 Duration of common cold symptoms (placebo group duration 100%).

Review: Vitamin C for preventing and treating the common cold

Comparison: 4 Duration of the colds after therapeutic ≥ 0.2 g/day vitamin C

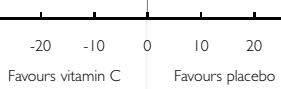
Outcome: 1 Duration of common cold symptoms (placebo group duration 100%)

Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Anderson 1974e	900	85 (91)	437	100 (99)		23.0 %	-15.00 [-26.02, -3.98]
Karlowski 1975c	56	90 (41)	65	100 (52)		10.2 %	-10.00 [-26.59, 6.59]
Anderson 1975a	419	97 (96)	213	100 (84)		13.2 %	-3.00 [-17.55, 11.55]
Elwood 1977	145	99 (75)	119	100 (51)		12.0 %	-1.00 [-16.26, 14.26]
Tyrrell 1977	274	103 (57)	329	100 (54)		35.2 %	3.00 [-5.92, 11.92]
Cowan 1950	77	110 (100)	76	100 (100)		2.8 %	10.00 [-21.69, 41.69]
Audera 2001a	97	121 (80)	42	100 (76)		3.6 %	21.00 [-6.96, 48.96]
Total (95% CI)	**1968**		**1281**			**100.0 %**	**-2.90 [-8.20, 2.39]**

Heterogeneity: Chi^2 = 10.52, df = 6 (P = 0.10); I^2 =43%

Test for overall effect: Z = 1.08 (P = 0.28)

Test for subgroup differences: Not applicable



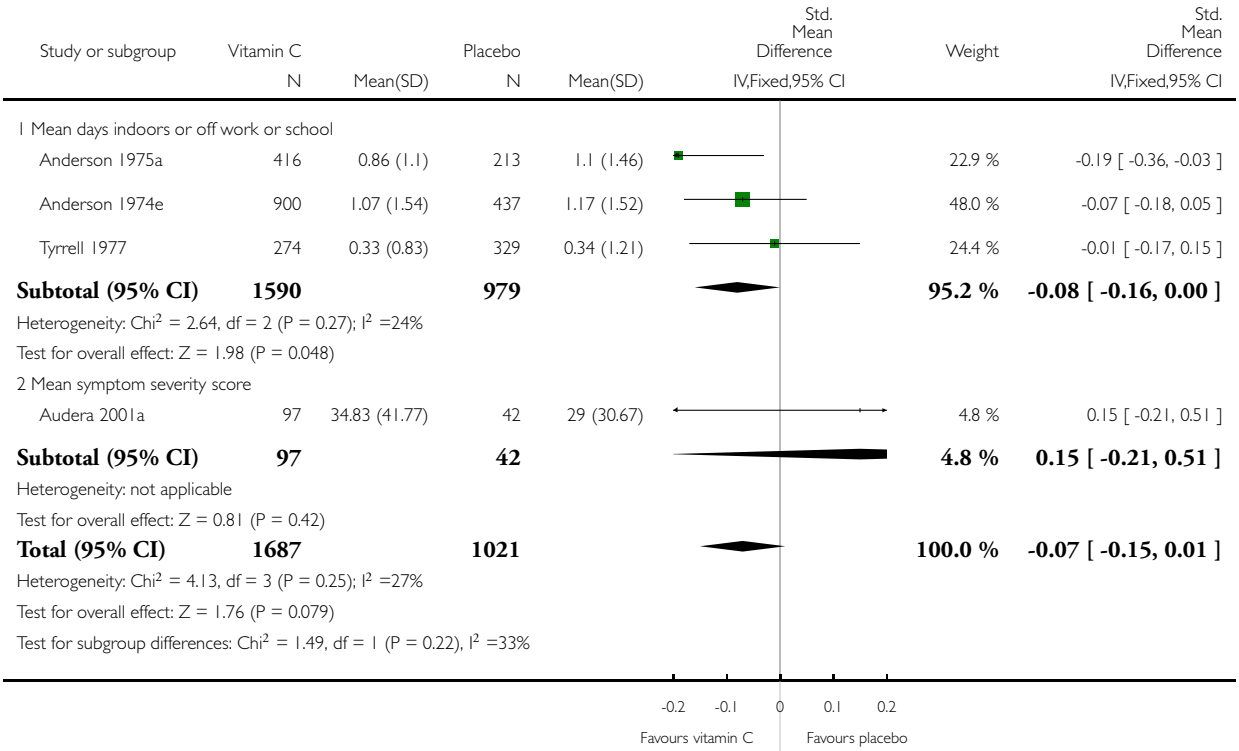
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Analysis 5.1. Comparison 5 Severity of the colds after therapeutic ≥ 0.2 g/day vitamin C, Outcome 1 Indicators of common cold severity.

Review: Vitamin C for preventing and treating the common cold

Comparison: 5 Severity of the colds after therapeutic ≥ 0.2 g/day vitamin C

Outcome: 1 Indicators of common cold severity



ADDITIONAL TABLES

Table 1. Included trials with no data suitable for our meta-analysis

Trial	Findings
Abbott 1968	Therapeutic trial. The authors write: "with regard to the comparative results with the two preparations, there were virtually no differences at all in respect of any of these individual symptoms" [p 444]. The only numerical data reported were the severity of "sore throat in patients with a common cold" [their Table 1 on p 443]. It is not clear how long a delay there was between the onset of symptoms and the initiation of treatment. "The doctors taking part in the trial were asked to treat families in order, as colds appeared during the course of the winter" [p 442]; thus it seems that the doctor gave tablets only when he or she met the patient rather than patient keeping tablets ready at home for use when symptoms started

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Table 1. Included trials with no data suitable for our meta-analysis (*Continued*)

Asfora 1977	Therapeutic trial. The author writes: "a double-blind trial was conducted in which the preparations, numbered 1 and 8, were given to alternate patients as they presented themselves. .. When 42 patients had received substance No. 1 and 41 patients had received No. 8, there was no longer any point in continuing the double-blind trial, since in view of the clinical progress of the patients there was not the slightest doubt that substance No. 1 was vitamin C and No. 8 was the placebo" [p 224]. Thereafter the trial was continued as an open trial comparing vitamin C with other drugs
Brown 1945	Therapeutic trial. Of the 206 "nasal colds", 62% (76/123) of the vitamin C group had a cold being cured overnight whereas 37% (31/83) of the placebo participants had colds that were cured overnight (P = 0.06). There was no difference in the curing of 92 "throat colds" (35/56 versus 22/36, respectively). The great difference in the distribution of participants is not consistent with reported alternate allocation
Elliot 1973	Prophylactic trial. The authors write: "There was no consistent difference between groups in the incidence of runny nose or sneezing. Man-days of morbidity for hoarseness, sore throats, non-productive coughs, and productive coughs was 36, 107, 42 and 72 in the placebo group with only 37%, 28%, 40% and 31% as much morbidity in the ascorbic acid group. The Wilcoxon Sequence Test with a one tailed test rejected the null hypothesis of equal effectiveness of ascorbic acid and placebo for sore throats and productive coughs (P = .0155 and .0327) but not for hoarseness or non-productive coughs" [p 12] (Hemilä 2004).
Regnier 1968	Therapeutic trial. The author writes: "I initiated a double-blind study using ascorbic acid alone, ascorbic acid plus bioflavonoids, flavonoids only and, fourthly, a lactose placebo with the two "vitamins" present either alone or together in 200 mg quantities. It was shortly obvious that there was no need to continue double-blind techniques. The continued studies were done by the single blind method... " "The 22 subjects mentioned have been studied systematically and under conditions which were as controlled as is possible in a clinical investigation of an infection such as the common cold. Some acted as what are commonly termed their own controls... None of the subjects was studied for less than three years... [p 950]." "Within the first 24 hours of a typical infection which the patient recognizes as his usual early symptoms of a cold, and the sooner the better, the beginning dose of ascorbic acid or 0.6 or 0.625 g is taken every three hours" (p 950). The author reports that "in 50 colds the treatment consisted of ascorbic acid alone ... the colds were nicely suppressed in 45 [of the 50]... In 22 of 24 instances in which the lactose-filled capsules alone were taken the colds were seemingly untempered and ordinary" [p 952]
Scheunert 1949	Prophylactic trial. The common cold [Erkältungskrankheiten] was one of the outcomes and "The percentage monthly duration of people sick with the common cold [Prozentualer Monatsdurchschnitt der erkrankten Personen]" was 7.3% in the 0.02 g/d group, 7.2% in the 0.05 g/d group, 1.95% in the 0.1 g/d group, and 1.93% in the 0.3 g/d group suggesting that there were more days sick with the common cold when vitamin C doses were low. However, the data are presented ambiguously and it is a combination of incidence and duration. The methodology is not good
Tebrock 1956	Therapeutic trial. The authors conclude "the overwhelming impression gained from the study is the singular lack of effect in altering the course of the common cold by ... the ascorbic acid". A number of tables were published but they could not be used in our meta-analyses

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Table 2. Three trials with experimentally induced colds

Study characteristics	Walker 1967	Schwartz 1973	Dick 1990
Number of participants	91 healthy volunteers; 47 vitamin C and 44 placebo	21 healthy male volunteers	Altogether 48 participants. Three separate transmission experiments each involving 16 healthy volunteers (8 vitamin C; 8 placebo) housed closely for 1 week with 8 volunteers actively infected with rhinovirus
Viruses used	Rhinovirus (3 strains); 29 vitamin C and 26 placebo Influenza B (8/8) B814 virus (10/10)	Rhinovirus 44; 11 vitamin C and 10 placebo	Rhinovirus 16; 24 vitamin C and 24 placebo
Transmission method	Nasal instillation	Nasal instillation	Close contact with infected volunteers over a period of a week
Intervention	1 g/d vitamin C for 3 days before and 6 days after inoculation	3 g/d vitamin C or placebo for 2 weeks before and 1 week after inoculation	2 g/d vitamin C for 3.5 weeks before exposure to infected volunteers
Incidence outcome	18 colds developed in each group	All in both groups developed colds	19/24 in vitamin C group and 22/24 in placebo group became infected
Duration outcome	Mean duration in each group 5 days	Both groups resolved by 6 to 7 days	Not provided
Severity outcome	Mean severity score 8 for vitamin C and 7 for placebo	Severity peaked earlier for vitamin C group and resolution more advanced by day 4 (P = 0.02). Overall mean severity scores not significantly different in the 2 groups	Mean cumulative severity score and mucus weights reduced in the vitamin C recipients (P = 0.03). Severity of colds reduced by 50% (P = 0.02; Dick 1990)
Comments	Not double-blind	Double-blind. Nasal virus shedding similar in the 2 groups	Double-blind. Viral shedding similar in these 2 groups. The studies are briefly described in a series of conference abstracts but no full published paper is available

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APPENDICES

Appendix 1. History and search strategies prior to 2012

In the first **1998** edition of this Cochrane Review (Douglas 1998), an analysis was made of the 30 published trials that had been selected by two previous systematic reviewers, Hemilä 1992 and Kleijnen 1989. That selection of trials was one of convenience and was justified by the fact that all had been carried out post-Pauling in an era of relatively sophisticated trial methodology, and mainly using doses of vitamin C at the level recommended by Pauling (i.e. 1 g per day or more).

For the **2004** revised edition of this Cochrane Review (Douglas 2004), all known publications on the topic in the past 64 years were included. Some of these trials had been carried out since the original 1998 review, but also the controlled trials published before 1970 (pre-Pauling period) were added. We set the limit of daily vitamin C administration to 0.2 g/day, so that controlled trials with lower doses were not included in the review, but were listed and commented on in the excluded studies table.

Twenty-five additional trials were then added to the review, including a number of trials which evaluated the utility of vitamin C in the prevention of post-race colds among marathon runners and further explored the role of vitamin C as a therapy for colds.

For the 2004 update, we again searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2004); MEDLINE (January 1966 to June 2004) and EMBASE (1990 to June Week 23 2004). For the 2004 update, we also screened the reference lists incorporated in a series of systematic reviews of the literature published by Briggs 1984 and Kleijnen 1989 (for the search strategy of the latter, *see* Kleijnen 1992) and the references in those studies. One of the review authors (HH) has a research involvement spanning over a decade in this topic and has assembled a large personal reference list of papers published in the grey literature or listed in indexing services that preceded electronic searching. These were added to a primary database which was then systematically screened by two review authors (BD and Ron D'Souza - a previous review author) who worked together to exclude duplicate entries, preliminary reports of data more fully reported elsewhere, commentaries, editorials and other papers which did not contain unique reports of controlled or randomised clinical comparisons. These two review authors then separately reviewed hard copies or electronic abstract data on each of 84 papers, applying the selection criteria outlined above. A final list of 62 papers was selected, which contained unique data from one or more trials of vitamin C and the common cold. One of the papers (Bibile 1966 cited by Kleijnen 1989) remains unassessed as we have been unable to retrieve a copy through library orders. Twenty-six of the 61 remaining papers failed to meet the selection criteria.

This left us with 36 papers, of which 12 contained reports of two or more (up to six) unique study comparisons and an entry for each comparison was made into the 'Characteristics of included studies' table, using the letters a, b, c, d, e and f to identify different study comparisons within the one publication. The review in 2004 included data from 56 distinct trial comparisons, which was 25 more than in the original 1998 review. In four of the papers (Anderson 1974a; Anderson 1975a; Audera 2001a; Karlowski 1975a) more than one actively treated group was compared with the same placebo-treated group. To avoid the 'unit of analysis problem' for which we were legitimately criticised in the original 1998 review, where multiple active arms were considered separately in the same meta-analysis, they were combined as one entry.

For the **2007** update (Douglas 2007), we searched CENTRAL (*The Cochrane Library* Issue 4, 2006), MEDLINE (2004 to December 2006) and EMBASE (1990 to December 2006). In the 2007 update, only one new trial was identified (Sasazuki 2006).

The 2007 MEDLINE search

1 exp Common Cold/
2 common cold$.mp.
3 exp RHINOVIRUS/
4 rhinovir$.mp.
5 or/1-4
6 exp Ascorbic Acid/
7 ascorbic acid.mp.
8 vitamin c.mp.
9 or/6-8
10 5 and 9

For the 2010 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, issue 1), which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (2006 to February 2010) and EMBASE (2006 to February 2010).

See below the search strategy for MEDLINE. The EMBASE and CENTRAL searches were slightly modified to fit the databases (see Appendix 2 for EMBASE search strategy).

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MEDLINE (OVID)

1 exp Common Cold/
2 common cold$.mp.
3 exp Rhinovirus/
4 rhinovir$.mp.
5 or/1-4
6 exp Ascorbic Acid/
7 ascorb$.mp.
8 (vitamin$ adj5 C).mp.
9 or/6-8
10 5 and 9

EMBASE search run from 01 January 2006 to 03 February 2010

10. #5 AND #9
9. #6 OR #7 OR #8
8. ascorb*:ab,ti
7. (vitamin* NEAR/5 c):ab,ti
6. 'ascorbic acid'/exp
5. #1 OR #2 OR #3 OR #4
4. rhinovir*:ab,ti
3. 'human rhinovirus'/exp OR 'rhinovirus infection'/exp OR 'rhinovirus'/de
2. 'common cold':ab,ti OR 'common colds':ab,ti
1. 'common cold'/de OR 'common cold symptom'/de

There were no language or publication restrictions in the literature searches.

Appendix 2. Embase.com search strategy 2012

#11 #7 AND #10 361
#10 #8 OR #9 58878
#9 (vitamin* NEAR/5 c):ab,ti OR ascorb*:ab,ti 39136
#8 'ascorbic acid'/exp 50266
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 8168
#6 ((viral OR virus*) NEAR/2 rhinit*):ab,ti 84
#5 'acute rhinitis':ab,ti 85
#4 rhinovir*:ab,ti 3158
#3 'human rhinovirus'/de OR 'rhinovirus infection'/de 1204
#2 'common cold':ab,ti OR 'common colds':ab,ti OR coryza:ab,ti 2466
#1 'common cold'/de OR 'common cold symptom'/de 4344

Appendix 3. CINAHL (EBSCOhost) search strategy 2012

S13 S7 and S11 16
S12 S7 and S11 91
S11 S8 or S9 or S10 3342
S10 TI vitamin* N5 c OR AB vitamin* N5 c 1762
S9 TI ascorb* OR AB ascorb* 586
S8 (MH "Ascorbic Acid") 2325
S7 S1 or S2 or S3 or S4 or S5 or S6 1767
S6 TI ((viral or virus*) N2 rhinit*) OR AB ((viral or virus*) N2 rhinit*) 5
S5 TI acute rhinitis OR AB acute rhinitis 30
S4 TI coryza OR AB coryza 23
S3 TI rhinovirus* OR AB rhinovirus* 153
S2 TI common cold* OR AB common cold* 501

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S1 (MH “Common Cold”) 1400

Appendix 4. LILACS (BIREME) search strategy 2012

VHL > Search > (MH:“Common Cold” OR “Resfriado Común” OR “Resfriado Comum” OR “Coriza Aguda” OR catarro OR coryza OR rhinovir$ OR MH:rhinovirus OR “acute rhinitis” OR “viral rhinitis”) AND (MH:“ascorbic acid” OR “Ácido Ascórbico” OR “Vitamin C” OR MH:D02.241.081.844.107$ OR MH:D02.241.511.902.107$ OR D09.811.100$ OR “Vitamina C”)

Appendix 5. Web of Science (Thomson Reuters) search strategy 2012

Topic=(“common cold” or “common colds” or rhinovir* or coryza or “acute rhinitis” or “viral rhinitis” or (virus* NEAR/2 rhinitis)) AND Topic=(“ascorbic acid” or ascorb* or (vitamin* NEAR/5 c)) Refined by: Publication Years=(2011 OR 2010 OR 2012)
Timespan=1955-2012. Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC.
Lemmatization=On

Appendix 6. Trials Registers search strategy 2012

common cold AND vitamin c
ascorbic acid AND common cold

F E E D B A C K

Flaws in statistical analysis?

Summary

There appear to be several instances where there is considerable overlap between studies, but they are treated as independent studies as far as the meta-analysis is concerned. For example, the Anderson 1974, 1974a, 1974b studies seem to be treated as independent in graph (comparison 01, outcome 04), but the control groups seem identical, and 275 people in the treatment group seem the same in each study. The effect is to inflate the value of this study. Indeed, the difference between the treatment groups for Anderson 1974a, 1974b (33 new people, *all* apparently with one or more respiratory episodes) raises further issues.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

In the new edition of the review we have avoided this problem described above by combining all trial arms that were compared with the one placebo group into one trial arm for purposes of the meta-analysis
Reply supplied by the authors of the review.

Contributors

David Wooff
Comment and reply posted 28 August 2004

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Unit of analysis issues

Summary

Further to David Wooff's comment, I suspect there may be other statistical flaws in this review that could be placed under the heading, 'unit of analysis errors'.
At least one study (Lugviggson) appears to be a cluster randomised trial, yet there is no discussion of the possible over-weighting of this study when naively included in the meta-analyses.
At least two studies appear to be twin studies (Carr and Miller). Should the matching be taken into account in the analysis, in a similar way to a simple cross-over trial?
The particular meta-analysis for 'Mean symptom days per person' in the comparison 'Vitamin C 1G daily or more vs placebo' worries me considerably. Of the six studies (10 contributions) included in this analysis, I suspect that at most two are free of unit of analysis errors of various kinds. This makes it a wonderful teaching example, but for the wrong reasons.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

Ludvigsson writes explicitly "Every class was divided at random into two groups." In our opinion this statement means that Ludvigsson was taking one class and he divided the participants of that one class into to two groups 'at random,' and then he went to another class and similarly randomised the second class. We disagree that cluster randomisation applied here.
As to the two small twin trials: Miller 1977 explicitly stated that "analysis of the paired comparisons…" so we conclude their SE values in their main table are based on paired t-test, event though this is not explicitly stated in their methods; Carr 1981 explicitly stated "the results for the six summary cold variables of the paired analyses of variance between active and placebo groups are shown…" so we conclude their P-values refer to paired analyses. In any case, the mean difference between the groups is the same whether we calculate difference of means or mean of paired differences. Failure to take into account the pairing of data would mean that we would be over-conservative in our estimate of the precision of any effect, but it is unlikely that this issue would anyway have influenced our conclusions in a meaningful way.
In the current review we have not used as an outcome variable mean symptom days per person but have concentrated on mean symptom days per episode.
Reply supplied by the Authors of the review.

Contributors

Julian Higgins
Comment and reply posted 28 August 2004

Doses too small

Summary

One gram daily is a small dose. Most mammals make 3 or more grams in their livers. Any practitioner of orthomolecular medicine knows that a minimum of several grams a day is needed to surely prevent a cold, and as much as 20 grams to cure one in progress. Not one trial in your RCT's qualifies.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms

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Reply

The practitioners of orthomolecular medicine have not to our knowledge published any controlled trial evidence on which this comment is based. As we have said in the review, there is no reasonable doubt that vitamin C supplementation plays some biological role in defence, and there is tantalising evidence from the Anderson 1974 study that a single therapeutic dose of 8 grams at commencement of a cold may have had a useful therapeutic effect.

We believe there is a case for rigorous evaluation of the possibility that very large doses (of the order of 8 g daily in adults for periods up to five days after the onset of symptoms) could produce benefits that were not seen at lower doses.

In view of the greater propensity of children to catch colds and the greater benefits observed in the child prophylaxis studies, this may be the group in which to explore this approach (with an appropriately pro-rated dose for weight). We add however a caution. Although studies in which doses of 1 or 2 g daily of vitamin C have been used for several months have not produced convincing evidence of adverse effects to the volunteers, dosage of the kind discussed here needs to be carefully monitored for adverse effects - especially in children.

Reply supplied by the Authors of the review.

Contributors

Reuven Gilmore

Comment and reply posted 28 August 2004

Vitamin C for preventing and treating the colds

Summary

This paper by Hemila and Douglas is highly misleading. Two fundamental scientific errors invalidate the conclusions of their review.

Their first error is the dose range: the doses employed are too small. Treatment of disease requires pharmacological doses of vitamin C, in the range 10 to 200 g per day [Cathcart, Medical Hypotheses, 7, 1359-76]. Prevention of disease requires a minimum of 2.5 g per day, in divided doses, to establish a dynamic flow through the body. In defending their review, Hemila and Douglas cite Levine [Levine et al. JAMA, 1999, 281,1415-23] as showing that the body is saturated by a dose of 0.5 g per day: this finding has been discredited. A more recent paper by Levine and colleagues shows that the body is not saturated by doses up to 18 g per day. [Padayatty et al, Ann Intern Med, 2004, 140, 533-7]. This discrepancy has been explained in a recent book [Hickey and Roberts, Ascorbate, 2004, Lulu press].

The second error concerns the dose frequency. Since high doses of vitamin C have a half-life of about 30 minutes, single or twice daily doses do not increase plasma levels for more than a few hours [Levine et al. JAMA 1999, 281,1415-23]. Such doses provide a minimal protective effect. Given these infrequent doses, even a small positive effect implies a powerful therapeutic potential.

Douglas and Hemila have not shown that vitamin C is ineffective against the common cold, unless the doses used are both inadequate and inappropriate. They have, however, made clear that the previous 65 years of research has been based on a range of doses that are too small and too infrequent. Thus, the research to date may grossly underestimate the therapeutic value of vitamin C. Tests of appropriate dose levels and timing regimes are urgently required.

Reply

Hickey and Roberts claim that the prophylactic and therapeutic trials that have been carried out to date have used a range of doses that are too small and too infrequent. They speculate, on the basis of pharmacodynamic studies, that prevention of disease would require a minimum of 2.5 g of vitamin C per day in divided doses. If they firmly believe in their reasoning (there are good grounds for debate), they or someone else need to undertake rigorous prophylactic trials at such dosage levels.

Nevertheless, while stating that “prevention of disease requires a minimum of 2.5 g/day”, Hickey and Roberts ignore our finding that in six trials with participants under heavy physical or cold stress or both, vitamin C halved the incidence of common cold type of symptoms (our Fig 01). This benefit was seen with doses of 0.25 to 1.0 g/day which is substantially less than those speculated as minimal by Hickey and Roberts. Thus in our Fig 01 the living conditions rather than the vitamin C dosage provided the explanation to the heterogeneous trial results.

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Our review does not claim that the issue is closed. It acknowledges that vitamin C plays some biological role in defence against respiratory infections but finds no evidence that at doses up to 1 to 2 g/day vitamin C would prevent colds in the general population or reduce common cold duration enough to justify regular supplementation.
Finally, we drew attention to one study in which an 8 g therapeutic dose seemed to be beneficial and underlined the fact that no therapeutic trials have been carried out in children even though the regular supplementation trials found greater effect in children.
Harri Hemilä and Robert M Douglas

Contributors

Steve Hickey PhD. Manchester Metropolitan University
Hilary Roberts PhD
Comment and reply posted 16 November 2005

Vitamin C doses in trial

Summary

Studies which find the effects of vitamin C on the common cold inconclusive invariably use less than 1 g of ascorbic acid a day. Proponents of Vitamin C therapy consistently use 3 or more grams a day. This debate will not be resolved until both camps start testing the same dosages. Since the ascorbic acid proponents acknowledge that < 1 g a day will have little therapeutic effect, it is incumbent on researchers to analyze the effect of megadoses.
I routinely dose to bowel tolerance. 0.5 g every hour for eight hours will reach bowel tolerance for me. When I begin to become ill, I have dosed as high as 0.5 g every 20 minutes without reaching bowel tolerance. I can significantly reduce the effect of a cold in this fashion, and once was the only one functioning in my office when everyone else was sick.
My rule of thumb is 35 mg per pound of body weight per day. This must be distributed throughout the day to prevent overloading the ability of the stomach to absorb it, and to provide continuous saturation, because of the rapid decomposition of ascorbic acid once it is no longer in crystalline form. This dose is consistent with the levels of ascorbic acid produced by the liver of other mammals.
Submitter agrees with default conflict of interest statement:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Our review shows that the relation between vitamin C dosage and effect is not as simple as Sean Emerson suggests. We found statistically significant heterogeneity in the effect of vitamin C on common cold incidence. The heterogeneity was not explained by vitamin C dosage but by segregating trials with people under heavy acute physical stress to a separate group. In the latter subgroup, vitamin C halved the common cold risk, yet the doses in the trials were rather low, from 0.25 to 1 g/day. Prophylactic trials with the general population found no evidence that vitamin C would prevent colds, even though the highest prophylactic dose was 3 g/day (Karlowski 1975).
In the therapeutic trials, the dose-response is also complex. Several studies with 3 to 4 g/day failed to find therapeutic benefit (Cowan 1950, Elwood 1977, Tyrrell 1977, Audera 2001). Thus, the negative findings in therapeutic trials are not simply explained by the use of ascorbic acid in "doses less than 1 gram a day". On the other hand, Anderson 1975 found statistically significant 25% reduction in "days spent indoors per subject" with dosage of 1 to 1.5 g/day for five days. This benefit is not explained by the use of particularly high doses.
We pointed out that in the Karlowski 1975 trial 6 g/day was associated with a double benefit compared with 3 g/day. We also pointed out that Anderson 1974 reported that 8 g/day on the first day of the common cold appeared better than 4 g/day. Thus, there are scattered data suggesting dose dependency, but these findings are more relevant for planning further trials than for immediate conclusions to claim dose-dependency.
Based on the trials analysed in our review, we do not consider that regular supplementation of the ordinary people is justified. On the other hand, vitamin C is inexpensive and safe in doses of grams per day and, while waiting for new therapeutic trials, testing vitamin C for common cold treatment may be reasonable at an individual level. However, explicit evidence from well-conducted trials is required for broad recommendations to use vitamin C for treating the common cold, and such evidence is missing.

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Reply by Hemilä, Douglas, Chalker (22 August 2007)

Contributors

Sean Emerson
Comment posted 24 July 2007

Vitamin C and the common cold, 2 May 2008

Summary

Introduction

The Cochrane review provides a meta-analysis of low-dose studies of vitamin C and the common cold. Unfortunately, its authors limit the range of intakes to values that are marginally effective, and exclude clinical data on higher doses, which have been shown to provide positive results.

The review fails to understand orthomolecular claims for vitamin C in prevention and treatment of the common cold, repeated over a period of at least 50 years.[i] [ii] [iii] [iv] [v] [vi] Orthomolecular nutrition and medicine are concerned with varying the concentrations of substances such as vitamin C, which are normally present in the body, to prevent or control disease; typically, this involves large doses of nutrients. The doses Douglas *et al.* refer to as "mega-dose vitamin C supplementation" range from 200 mg, once or twice daily. These are small doses.

To avoid misunderstanding, we state the orthomolecular claims for vitamin C:

Vitamin C given at frequent intervals (< 6 hourly) and sufficiently high doses (8+ grams per day) will prevent common colds in the majority of subjects (individual variation is high).

Vitamin C, given at short intervals and very high doses to a subject with the common cold, can eliminate the symptoms and may bring about a cure within hours [1,2,3,3,5, 6,7]. Cathcart suggests 30-150 grams per day, at intervals of one hour or less.[vii] The Vitamin C Foundation recommends 8 grams every 20 minutes, from the onset of symptoms.

The dose-response relationship for the treatment claim is described as a threshold effect; unless a minimum threshold dose is reached, little or no clinical response is achieved.[viii]

Review shortcomings

Methodology

1. If a reviewer is aware of author names, experimental details, and results, she can influence the outcome of the review by unfair selection; even honest experimenters are subject to unconscious effects. In this case, the reviewers had prior knowledge of the literature on vitamin C and the common cold, and specific knowledge of the papers under consideration. The researchers were aware that selection criteria would exclude ALL clinical reports of high (orthomolecular) doses. These problems have been communicated to the authors, though their response has been unsatisfactory. A clear and objective response might provide reassurance that the potential for bias was being addressed.

2. As described in another Cochrane review, the placebo effect is irrelevant in the case of definitive and objective clinical effects. The effects claimed for vitamin C are large, objective, and definitive [6]. Orthomolecular physicians report complete, dose-related, reversal of symptoms, or rapid cure. The review required placebo controls on the basis that the authors considered "that with the expected small effects of vitamin C, and the greatly subjective outcome definitions, only placebo-controlled trials could yield information of adequate rigour." Such an expectation is based on a misconception of the claims for vitamin C. The explanation is particularly inadequate, as it restricts the doses studied to outliers of the range claimed to be effective.

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Results

3. The review does not include data for intakes of the order of magnitude described in the orthomolecular prevention or treatment claims. This objection was made by Hickey and Roberts, and Higgins, in response to an earlier version, later reinforced by Emerson. Douglas *et al.* responded tangentially and failed to explain how their data could be extrapolated to cover the doses claimed to be effective.
4. The review covers longer dose intervals than those claimed to be effective. Hickey and Roberts published this objection and again the response by Douglas and Hemilä did not indicate how their data could be extrapolated to more frequent doses.
5. The reviewers disregard the pharmacokinetics of vitamin C. The half-life for kidney excretion of high-dose vitamin C from plasma is about 30 minutes [6]. At the dose levels and intervals studied by Douglas *et al.*, there would be little, if any, consistent increase in plasma ascorbate levels or body content. The action of vitamin C depends on its ability to donate and transfer electrons: if the ascorbate has been excreted, it cannot exert this redox effect. A rigorous response is required, as this failure breaches basic principles of pharmacology.

Conclusions

6. The reviewers dismiss the observations of Cathcart and others, on the grounds that "their uncontrolled observations do not provide valid evidence of benefit". Scientifically, such experimental results are more valid than large-scale clinical trials or epidemiological studies. The scientific method involves hypothesis and refutation.[i] Easily replicable experiments, as reported by internationally-known physicians, such as Cathcart, Klenner, Hoffer, Levy, Kalokerinos, and Brighthope, have great scientific validity. If these observations were in error then, over the last half century, any physician or scientist could have refuted the claims, with little effort or cost. No such refutation exists in the literature.[6]
7. The authors failed to identify the limitations of their review. Their results relate to low doses: approximately an order of magnitude less than those claimed to be effective. The review did not specify that its results and conclusions exclude orthomolecular and other clinical claims for the effectiveness of vitamin C.
8. Taken as a whole, the review and resultant media generalisations are misleading, as they deflect attention away from the actual claims for vitamin C's effectiveness. The authors have promoted their conclusions widely under the Cochrane name, resulting in generalisations that are out of proportion to a scientific interpretation of the data. A widely-quoted press release from Douglas' university begins "vitamin C has been proven ineffective in combating the common cold in most people." Douglas claims, "vitamin C has proven not to be a magic bullet to solve the common cold".[i] We can find no evidence in the Cochrane review to support such unscientific claims,[9] let alone provide anything close to "proof".[9] The hypothesis that appropriate doses of vitamin C can prevent or cure the common cold has not been refuted and we ask that this review be withdrawn [6].

[1] Klenner F.R. (1953) The Use of Vitamin C as an Antibiotic, The Journal of Applied Nutrition, 6, 274-278.
[2] Stone I. (1972) Vitamin C Against Disease: The Healing Factor, Perigree Books.
[3] Cathcart R.F. (1981) The Method of Determining Proper Doses of Vitamin C for the Treatment of Disease by Titrating to Bowel Tolerance, Orthomolecular Psychiatry, 10(2),125-132.
[4] Lewin S. (1976) Vitamin C: Its Molecular Biology and Medical Potential, Academic press.
[5] Levy T. (2002) Vitamin C, Infectious Diseases and Toxins, Xlibris Corp.
[6] Hickey S. Roberts H. (2004) Ascorbate: The Science of Vitamin C, Lulu press.
[7] Cathcart R. (1981) Vitamin C, titrating to bowel tolerance, anascorbemia, and acute induced scurvy, Medical Hypotheses, 7, 1359-1376.
[8] Cathcart R.F. (1985) Vitamin C: the non-toxic,nonrate-limited, antioxidant free radical scavenger, Medical Hypotheses, 18, 61-77.
[9] Popper K. (1963) Conjectures and Refutations: The Growth of Scientific Knowledge. Routledge.
[10] Amanda Morgan (2005) News from The Australian National University, Tuesday 28 June.

Reply

Reply to Hickey and Roberts' comments, May 2008

Hickey and Roberts reiterate comments to which we have already replied. See the earlier discussions. Here we focus on fundamental issues related to the evaluation of medical interventions.

First, Hickey and Roberts criticise us for excluding uncontrolled observations from our systematic review. The importance of control groups in the evaluation of medical interventions is discussed in basic textbooks of clinical trials and epidemiology and also in the Cochrane Handbook (1). We do not repeat the arguments here. The Cochrane Collaboration focuses mainly on randomised controlled trials, but non-randomised controlled studies can be included when justified; however, the inclusion of uncontrolled observations is not an option (Ref. 1, Chapter 13). With their opinion that "uncontrolled observations are more valid than large-scale clinical trials

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or epidemiological studies", Hickey and Roberts challenge the whole Cochrane Collaboration and not just our review on the common cold.

Second, Hickey and Roberts state that "the placebo effect is irrelevant in the case of definitive and objective clinical effects." Even though the placebo effect has often been exaggerated, there is firm evidence of placebo effect on patient-reported continuous outcomes and on pain measured as a continuous outcome (2). Moreover, in their meta-analysis examining the role of methodology in controlled trials, Balk et al. (3) found that the lack of placebo control biased the treatment effects of paediatric trials that measured soft outcomes of respiratory diseases. Therefore, the absence of placebo leads to a high risk of bias in trials on the common cold, which is a short-lasting and non-severe disease with soft outcomes.

Third, Hickey and Roberts are not consistent in their argumentations. They state that "even honest experimenters are subject to unconscious effects", yet they ignore this wisdom when they lean on the uncontrolled observations by vitamin C enthusiasts.

Our review was largely motivated by the work of Linus Pauling, who hypothesised in the early 1970s that grams of vitamin C per day would prevent colds. We found that trials in the general community do not support Pauling's hypothesis, whereas trials with individuals under heavy acute physical stress do. The statistically highly significant effect in the latter group of trials refutes Hickey and Roberts' argument that our "results relate to low doses: approximately an order of magnitude less than those claimed to be effective." The heterogeneity we found indicates that the characteristics and conditions of people are important in determining the effect of vitamin C, whereas we do not see basis to assume that doses that are an order of magnitude higher than those used in the prophylactic trials (up to 3 grams per day) would prevent colds in the general community.

The purpose of our systematic review was not to test Hickey and Roberts' orthomolecular claims and none of the identified controlled trials directly test them. With their belief that frequent high-dose vitamin C supplementation prevents colds in all people, and their note that testing vitamin C effects requires "little effort or cost", Hickey and Roberts should consider organizing by themselves a randomised controlled trial to examine their orthomolecular claims.

1 Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available at: http://www.cochrane.org/resources/handbook/

2 Hrobjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane Database Syst Rev 2004;(2): CD003974.

3 Balk EM, Bonis PAL, Moskowitz H, Schmid CH, Ioannidis JPA, Wang C, Lau J. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomised controlled trials. JAMA 2002; 287: 2973-82.

Contributors

Steve Hickey PhD and Hilary Roberts PhD

Feedback and reply added 13 June 2008

Vitamin C for preventing and treating the common cold, 25 November 2008

Summary

I would be interested in your results if you restricted studies to those using 1.0 grams or more.

Submitter agrees with default conflict of interest statement:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

We have previously replied to overlapping feedbacks on the dose-response issue (see the other comments). In this update, we calculated the effect of 1 g/day or more on common cold incidence in the general community trials and also with this restriction there is strong evidence that prophylactic vitamin C has no effect on the average incidence of colds. None of the five trials with physically stressed people used over 1 g/day and therefore the benefit in that group is not explained by particularly high dosage.

We note that Karlowski 1975 and Coulehan 1974 used two different doses within the same trials and with the same outcome definitions. Karlowski found that for adults, 6 g/day was associated with a double benefit compared with 3 g/day, and Coulehan found that for school children, 2 g/day caused about twice the benefit of 1 g/day (Hemilä 1996a; Hemilä 1999a). Although these findings do not establish dose dependency, they are interesting and support the case for examination of higher doses in therapeutic trials.

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Harri Hemila, Liz Chalker, Bob Douglas
Added 13 November 2009

Contributors

Roger Mann M.D.

WHAT'S NEW

Last assessed as up-to-date: 29 November 2012.

Date	Event	Description
29 November 2012	New citation required but conclusions have not changed	Seven placebo-controlled trials, which were previously excluded because there were no data suitable for our meta-analyses, have been included (Table 1). Their exclusion was inconsistent with the Methods section. This change did not result in changes to our conclusions (Abbott 1968; Asfora 1977; Briggs 1984; Elliot 1973; Regnier 1968; Scheunert 1949; Tebrock 1956) . In previous versions 'prophylactic' was used to indicate the trials in which vitamin C was administered every day. 'Prophylactic' is relevant when measuring the incidence of episodes. However, that term is confusing when measuring the duration of episodes that occur during the trial. Therefore, in the 2012 version, we changed to the term 'regular supplementation' to indicate trials in which vitamin C was administered every day
29 November 2012	New search has been performed	Searches conducted. We included one new trial (Constantini 2011a; Constantini 2011b) and excluded two new trials (Maggini 2012; Schmidt 2011).

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 1998

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Date	Event	Description
2 February 2010	New search has been performed	No new trials identified in this updated search. However, one trial with marathon runners was excluded because of the high level of drop-outs and severe bias in the drop-out rate between the study arms (Himmelstein 1998b). We excluded the Audera 2001c trial arm because flavonoids were administered in addition to vitamin C. We restricted the review to purely vitamin C comparisons. The conclusions remain unchanged since the last update (Douglas 2007).
13 November 2009	Feedback has been incorporated	Feedback comment and reply added.
13 June 2008	Feedback has been incorporated	Feedback comment and reply added.
12 June 2008	Amended	Converted to new review format.
23 July 2007	Feedback has been incorporated	Feedback added.
15 November 2005	Feedback has been incorporated	Feedback added.
27 August 2004	Feedback has been incorporated	Feedback comment added.
11 June 2004	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Harri Hemilä (HH) carefully reviewed drafts of the second edition of the review (Douglas 2004), assisted in paper retrieval, proposed alterations to data presentation, checked data entries and contributed significant input to the text. After the 2004 revision, he took over responsibility for future updates of this review.

Elizabeth Chalker (EC) wrote the protocol for the first edition of the review (Douglas 1998), developed the initial search strategy, undertook the searches, organised retrieval of papers, screened papers against inclusion criteria and appraised the quality of papers for the 1998 version. She has been involved in reviewing and rewriting the text for subsequent versions of this review.

DECLARATIONS OF INTEREST

None of the other review authors have any conflict of interest to declare in this review.

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SOURCES OF SUPPORT

Internal sources

- Australian National University (until 2004), Australia.

External sources

- Commonwealth Department of Health and Ageing, Australia.

NOTES

Full-text versions of references which are available either free or at the publishers' databases can be accessed via the home page of the contact author, Harri Hemilä: www.mv.helsinki.fi/home/hemila/CC/.

Seven placebo-controlled trials which were previously excluded because there were no data suitable for our meta-analyses have been included (Table 1). Their exclusion was inconsistent with the Methods section. Their inclusion did not result in changes to our conclusions.

In previous versions "prophylactic" was used to indicate the trials in which vitamin C was administered every day. "Prophylactic" is relevant when measuring the incidence of episodes. However, that term is confusing when measuring the duration of episodes that occur during the trial. Therefore, in the 2012 version, we changed to the term "regular supplementation" to indicate trials in which vitamin C was administered every day.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Ascorbic Acid [administration & dosage; *therapeutic use]; Common Cold [*drug therapy; *prevention & control]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [drug therapy; prevention & control]

MeSH check words

Humans

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