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

Hemilä H, Chalker E

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Vitamin C for preventing and treating the common cold.
Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD000980.
DOI: 10.1002/14651858.CD000980.pub5.

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[Intervention Review]

Vitamin C for preventing and treating the common cold

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 2, 2017.
Review content assessed as up-to-date: 3 May 2016.

Citation: Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No.: CD000980. DOI: 10.1002/14651858.CD000980.pub5.

ABSTRACT

Background

Animal studies show that vitamin C (ascorbic acid) prevents and alleviates bacterial and viral infections. Vitamin C for the common cold in humans remains controversial. This review was first published in 1998, extensively revised in 2004 and updated in 2007 and 2013.

Objectives

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

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, LILACS and Web of Science from 2012 to May 2016. We also searched the US National Institutes of Health trials register and the WHO International Clinical Trials Registry Platform (www.who.int/ictrp) on 2 May 2016.

Selection criteria

We excluded trials that used less than 0.2 g per day of vitamin C and trials lacking placebo comparison. We restricted our review to placebo-controlled trials.

Data collection and analysis

Two review authors independently assessed reports and extracted data. We assessed incidence as the proportion of participants experiencing ≥ 1 colds during the study period. Duration was the mean number of days of illness due to common cold episodes. Severity of colds was measured as days indoors and off work or school or by a severity scale.

Main results

This update included three new studies (63 participants) (one of these studies reported two trials) for a total 46 studies (77 reports, 11,941 participants). We found that in the general community, ≥ 1 g/day vitamin C had no effect on common cold incidence (risk ratio (RR) 0.98; 95% confidence interval (CI) 0.95 to 1.01; I^2 statistic = 0%; 7308 participants; 20 studies; moderate quality evidence). Within-trial heterogeneity was significant in few trials. Trials involving participants doing intense physical exercise found that vitamin C had a protective effect against colds (RR 0.49; 95% CI 0.37 to 0.64; I^2 statistic = 0%; 622 participants; 7 studies; high quality evidence; number-needed-to-treat-to-benefit (NNTB) = 3 to 10).

In adults, ≥ 1 g/day vitamin C shortened cold duration by 8% (95% CI 4% to 12%; I^2 statistic = 18%; 6672 colds; 17 studies; high quality evidence), and in children by 18% (95% CI 9% to 26%; I^2 statistic = 48%; 1534 colds; 10 studies; high quality evidence).

Regular ≥ 1 g/day vitamin C administration reduced numbers of days indoors and off work and school by 13.6% (95% CI 7% to 20%; I^2 statistic = 31%; 4388 colds; 8 studies; high quality evidence), and symptom severity scores by 12.8% (95% CI 4.8% to 21%; I^2 statistic = 24%; 1730 colds; 7 studies; high quality evidence).

Therapeutic doses of 1.5 to 4 g/day vitamin C (given after cold symptoms appear) did not influence common cold duration (-2%; 95% CI -7% to +2%; 3299 colds; 12 studies; high quality evidence), but 8 g on the first day shortened colds by 19% (95% CI 5% to 32%; 718 colds; one study; high quality evidence). In therapeutic studies, the difference in the duration of days indoors and off work was 12% shorter (95% CI -25% to 0.8%; 2641 colds; 7 studies; high quality evidence).

There was no difference in frequency of adverse effects in vitamin C and placebo group participants in the largest trials.

Most included studies were randomised, double-blind trials. Excluding trials that were not randomised or double-blind had no effect on conclusions.

Authors' conclusions

The lack of effect of vitamin C on the incidence of colds in the general population indicates that routine supplementation is not justified. However, significant within-trial heterogeneity in some studies indicates that a small proportion of people might gain preventive benefits from vitamin C. Vitamin C seems to be useful for people engaged in brief periods of intense physical exercise.

Regular supplementation of vitamin C reduced cold duration and severity. The benefit found with the largest therapeutic dose has substantial practical importance if the finding is repeated.

Given the consistent effect of vitamin C administered as a supplement on cold duration and severity, and its safety and low cost, it may be worthwhile for people with colds to individually test if therapeutic vitamin C is beneficial for them. Further therapeutic RCTs are warranted.

PLAIN LANGUAGE SUMMARY

Vitamin C and the common cold

Review question

We assessed vitamin C to prevent and treat the common cold.

Background

Common cold refers to combined symptoms including blocked nose and discharge, sore throat, cough, feeling tired and unwell, with or without fever. Colds are usually caused by viruses, and in high-income countries, are the most common reason for doctor visits. Vitamin C is widely used to prevent and treat colds. This is an update of reviews previously published in 2013, 2007 and 2004.

Search date

We searched for evidence up to May 2016.

Study characteristics

We included 46 studies (77 reports) that involved 11,941 people who received at least 0.2 g/day of vitamin C; three studies (63 participants) (one of these new studies contained two trials) were added for this update. Most studies gave vitamin C regularly over the whole study period and a few gave it to treat symptoms after the onset of a cold. Some studies chose participants who were involved in strenuous activities such as skiing. Studies looked at whether regular vitamin C reduced the length of colds, could prevent colds, or reduced cold severity.

Study funding sources

Most studies were from the 1970s and funding sources were seldom reported.

Key results

Regular vitamin C doses of at least 1 g/day did not change the average number of colds in the general community, but halved numbers of colds in people involved in strenuous activities. It also shortened the length of colds in adults by an average of 0.4 days (8%) per cold, and 1 day (18%) in children. This dose reduced numbers of days indoors, off work and school by 14% and symptom severity scores by 13%.

Therapeutic doses of 2 g to 4 g/day of vitamin C did not lead to shorter colds, but 8 g of vitamin C on a single day shortened colds by 19%.

Adverse effects in vitamin C and placebo groups did not differ in the largest trials.

Quality of the evidence

Evidence quality was assessed as high in relation to regular vitamin C on length and severity of colds; therapeutic doses on length of colds, days indoors or off work; for people engaging in strenuous physical activity; and severity scales. Evidence quality was moderate for vitamin C on cold incidence in the general community.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Vitamin C compared with placebo for preventing and treating the common cold				
Patient or population: see below Settings: see below Intervention: vitamin C Comparison: placebo				
Outcomes	**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
General community trials with ≥1 g/day vitamin C Proportion of participants developing ≥ 1 cold episodes during the trial	**RR 0.98** (0.95 to 1.01)	7308 (20)	⊕⊕⊕ **moderate**[a]	
Short-term exposure to severe physical stress and/or cold Proportion of participants developing ≥ 1 cold episodes during the trial	**RR 0.49** (0.37 to 0.64)	622 (7)	⊕⊕⊕⊕ **high**	
Adults, regular ≥1 g/day vitamin C Duration of common cold symptoms (effect in %)	**-8.1%** (-12.1% to -4.2%)	6672 (17)	⊕⊕⊕⊕ **high**	
Children, regular ≥1 g/day vitamin C Duration of common cold symptoms (effect in %)	**-17.8%** (-26% to -9.5%)	1534 (10)	⊕⊕⊕⊕ **high**	
Regular ≥1 g/day vitamin C Severity of the common cold (effect in %)	**-13.3%** (-18.3% to -8.2%)	6118 (15)	⊕⊕⊕⊕ **high**	
Therapeutic 1.5 to 4 g/day vitamin C Duration of the common cold (effect in %)	**-2.4%** (-7.1% to +2.3%)	3299 (12)	⊕⊕⊕⊕ **high**	

Therapeutic 8 g/day vitamin C Duration of the common cold (effect in %)	**-19%** (-32% to -5.5%)	718 (1)	⊕⊕⊕⊕ **high**

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] We removed 1 point because of within-trial heterogeneity in certain studies indicating that an assumption of a uniform effect over the entire population seems not to be justified.

BACKGROUND

Description of the condition

The term 'common cold' does not denote any precisely defined disease, rather it is a cultural concept (Eccles 2013). Nevertheless, this illness is familiar to most people. Typical cold symptoms include combinations 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 visits to physicians in high-income countries, and is a major cause of absenteeism from work and school. The economic burden of the common cold is comparable to hypertension and stroke (Fendrick 2003).

The common cold is usually caused by respiratory viruses (rhino, corona, adeno, parainfluenza, influenza, respiratory syncytial), which together have some 200 serotypes (Eccles 2005; Eccles 2009; Heikkinen 2003; Turner 2010). Common cold refers to a group of diseases caused by numerous unrelated aetiological agents. The most common causative agent is rhinovirus, which is found in 30% to 50% of people with colds. In a third of participants with cold symptoms, aetiology is undefined even when extensive virological tests are applied. It is not clear to what extent this is explained by low test sensitivity, 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 patients' symptoms.

Although most common cold episodes are caused by respiratory viruses, the symptom-based definition of 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 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 symptoms caused by respiratory viruses.

Common cold manifestations are so typical that clinical diagnosis can usually be made reliably by adult patients. Allergic and vasomotor rhinitis can sometimes mimic the common cold, but these conditions can usually be differentiated easily (Heikkinen 2003).

In common cold trials, an operational definition 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 minimum duration or combination of symptoms which are meaningful when drawing a conclusion about whether symptoms could be explained by a viral infection, allergic or mechanical irritation of nasal airways or throat.

Using antibiotics to treat a typical acute common cold episode is useless because most colds are caused by viruses. Nevertheless, according to some surveys, about half of common cold patients in the USA received antibiotics (Barnett 2014; Mainous 1996). In this respect, alternative treatment options for the common cold have substantial public health interest. For example, high-dose zinc acetate lozenges have been shown to shorten common cold

duration by 40% (Hemilä 2011b; Hemilä 2016a).

Description of the intervention

Vitamin C was identified in the 1930s as the consequence of research to identify the cause of scurvy (Carpenter 1986). This led to the assumption that the sole physiological function of vitamin C is to prevent and treat scurvy, consequently, it is often assumed that higher doses of vitamin C cannot be beneficial if a person does not have scurvy. Assessing the role of vitamin C on diseases and conditions other than scurvy is not just an empirical question but also a conceptual issue (Goodwin 1998; Louhiala 2014).

In the early literature, vitamin C deficiency was associated with pneumonia which indicated that vitamin C may influence respiratory infections (Hemilä 2013b). After its identification there was considerable interest in the effects of vitamin C on the immune system, as illustrated by reviews that had dozens of references to empirical studies (Clausen 1934; Perla 1937; Robertson 1934). Several physicians proposed that vitamin C may be beneficial for people with the common cold (Korbsch 1938; Markwell 1941; Miegl 1957; Miegl 1958; Ruskin 1938) or pneumonia (Hemilä 2013b).

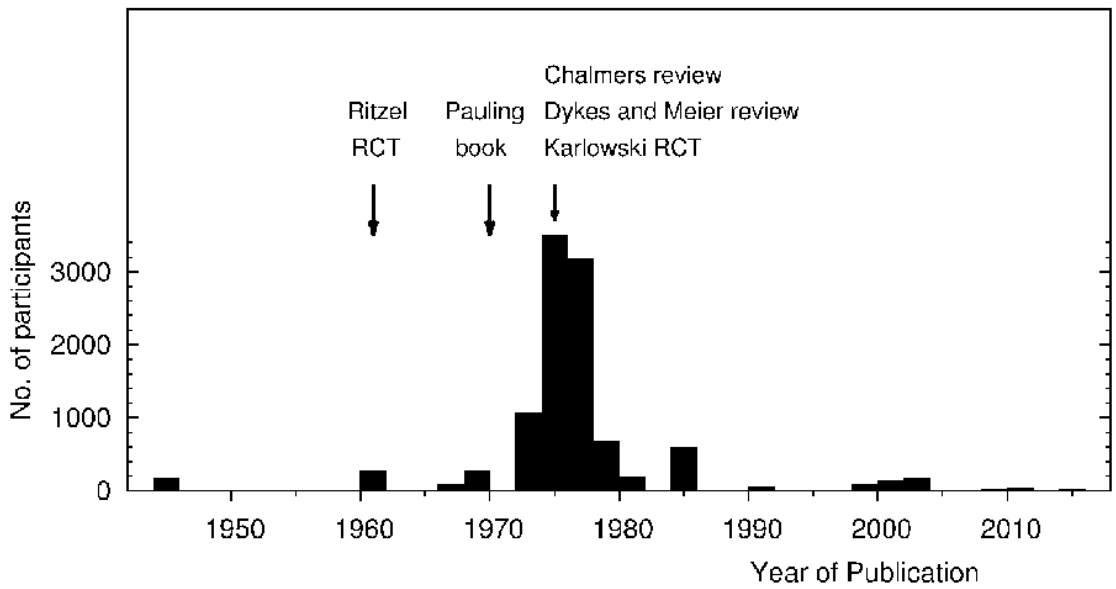
Research on vitamin C and colds

Controlled trials on vitamin C and the common cold started in the early 1940s (Bartley 1953; Bendel 1955; Bessel-Lorck 1959; Cowan 1942; Dahlberg 1944; Glazebrook 1942; Renker 1954; Scheunert 1949). Most early studies were not included in our review because vitamin C doses were low or a placebo was not used. See Characteristics of excluded studies.

Interest in vitamin C and the common cold in the 1970s was stimulated by publication of Linus Pauling's book *Vitamin C and the common cold* (Pauling 1970a). Pauling had won Nobel Prizes in Chemistry (1954) and Peace (1962), and this book was influential. Pauling meta-analysed data from four placebo-controlled trials and found strong evidence that vitamin C decreased the incidence of colds (P = 0.003; Pauling 1971a). In a second meta-analysis, Pauling 1971b focused on days of illness per person in the best two trials (Cowan 1942; Ritzel 1961) and concluded that "the null hypothesis of equal effectiveness of ascorbic acid and placebo [on total morbidity] is rejected at the P level less than 0.001."

In Pauling's considerations on vitamin C and the common cold, significant weight was placed on Ritzel 1961 (Pauling 1970a; Pauling 1971a; Figure 1). Ritzel 1961 reported a short 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 received vitamin C. On the basis of findings reported by Ritzel 1961, Pauling proposed that mega-dose supplementation might profoundly influence both incidence and severity of the common cold. Pauling also presented data suggesting that human diets might not provide sufficient intake of vitamin C for best health effects (Pauling 1970b; Pauling 1976a).

Figure 1. Numbers of participants in placebo-controlled trials in which ≥1 g/day of vitamin C was administered for any period. Numbers of participants in the studies published over two consecutive years is combined and plotted for the first of the two years.



Pauling's advocacy of vitamin C led to numerous randomised placebo-controlled trials investigating high doses of vitamin C and the common cold in different countries in the 1970s (Figure 1).

The largest vitamin C trials were performed involving adults in Canada (Anderson 1972; Anderson 1974a; Anderson 1975a). Evidence emerging from the published trials was confusing (Anderson 1977), but failed to support Pauling's hope that large doses of vitamin C would be a panacea against colds.

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 neither statistically nor clinically significant. In a qualitative review Dykes 1975 also concluded that vitamin C had no effect on colds. Furthermore, both Chalmers 1975 and Dykes 1975 placed considerable weight on the double-blind, placebo-controlled trial carried out by Karlowski 1975a which concluded that a statistically significant benefit of vitamin C supplementation was simply explained by the placebo effect (Figure 1).

However, it has been subsequently found that influential reviews by Chalmers 1975 and Dykes 1975 contained 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 ≥ 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 (SE 0.93 ± 0.22; P = 0.01) on numbers of days reduced in cold duration. The influential Dykes 1975 review also misrepresented findings of the vitamin C trials (Hemilä 1996c). It was shown that the placebo effect explanation in the Karlowski 1975a paper was inconsistent with published data (Chalmers 1996; Hemilä 1996a; Hemilä 1996b; Hemilä 2006a; Hemilä 2006c). The Kleijnen 1989 systematic review on vitamin C and the common cold also had several shortcomings (see Hemilä 2006a).

Hemilä 1996c and Hemilä 1997a argued that frequently cited reviews by Chalmers 1975 and Dykes 1975 and the randomised trial by Karlowski 1975a quelled interest in real, but modest effects of vitamin C on the common cold after the mid-1970s. Few trials on vitamin C and the common cold were initiated after 1975 (Figure 1).

Hemilä 1997b pooled the results of the six largest trials using ≥ 1 g/day of vitamin C and found no effect on the common cold incidence (pooled RR 0.99; 95% CI 0.93 to 1.04), which refuted Pauling's proposal of the prophylactic effect of gram-dose vitamin C for the general population.

Although high dose vitamin C was shown to have no effect on common cold incidence, four trials that involved men in the UK found a modest, but statistically significant, 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 by high doses of supplements (Hemilä 1997b). It is therefore possible that vitamin C influences susceptibility to the common cold in restricted groups of people, such as men with particularly low dietary vitamin C intakes.

A meta-analysis of three trials with participants under heavy short-term physical stress calculated that vitamin C halved the incidence of colds (pooled RR 0.50; 95% CI 0.35 to 0.69) (Hemilä 1996d). Vitamin C may have an effect on common cold incidence in physically stressed people.

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

Pharmacokinetics of vitamin C

When considering the potential treatment effects of vitamin C administration, it is informative to look at the relationship between vitamin C dose and its plasma concentration. When vitamin C dose is less than 0.2 g/day, there is a steep relationship between plasma vitamin C levels and the dose. For example, when the vitamin C dose increases from 0.06 to 0.2 g/day, the plasma concentration of vitamin C approximately triples (Levine 1999). The plasma vitamin C level of healthy people reaches saturation at doses of about 1 g/day. However, there is no reason to assume that the relationship between dose and plasma concentration is the same for healthy people and for patients with infections.

Vitamin C metabolism is affected by various infections, as indicated by decreased levels of vitamin C in plasma, leucocytes and urine (Davies 1979; Hemilä 2006a; Hume 1973; Hunt 1994). The changes in metabolism also indicate that vitamin C might have a treatment effect on patients with the common cold, irrespective of their dietary intake.

Safety of vitamin C

Although doses of around 0.01 g/day of vitamin C are sufficient to prevent scurvy, the safe dose extends to several grams per day (Hemilä 2006a; IOM 2000; Levine 1999). In the US nutritional recommendations, the 'tolerable upper intake level' is specified at 2 g/day for adults. However, the basis for this limit is the presence

of diarrhoea (IOM 2000), which is an adverse effect that resolves quickly with reduced vitamin C intake. Participants of a pharmacokinetic study were administered up to 100 g of vitamin C intravenously within a period of a few hours without any reported adverse effects, which may demonstrate the safety of such a large dose in healthy people (Padayatty 2004). Two large-scale trials of 0.5 g/day of vitamin C over a period of eight to nine years were conducted on 8171 female health professionals and 14,641 male physicians. No adverse effects were found, which may indicate the long-term safety of doses at this level (Cook 2007; Sesso 2008).

How the intervention might work

Vitamin C has affected random migration and chemotaxis of phagocytes (Goetzl 1974), transformation of influenza virus-infected lymphocytes (Manzella 1979), production of interferon (Siegel 1975), replication of viruses (Bissell 1980) and the gene expression of monocyte adhesion molecules (Rayment 2003). (See Beisel 1982; Hemilä 1997b; Manning 2013; Thomas 1978; Webb 2007).

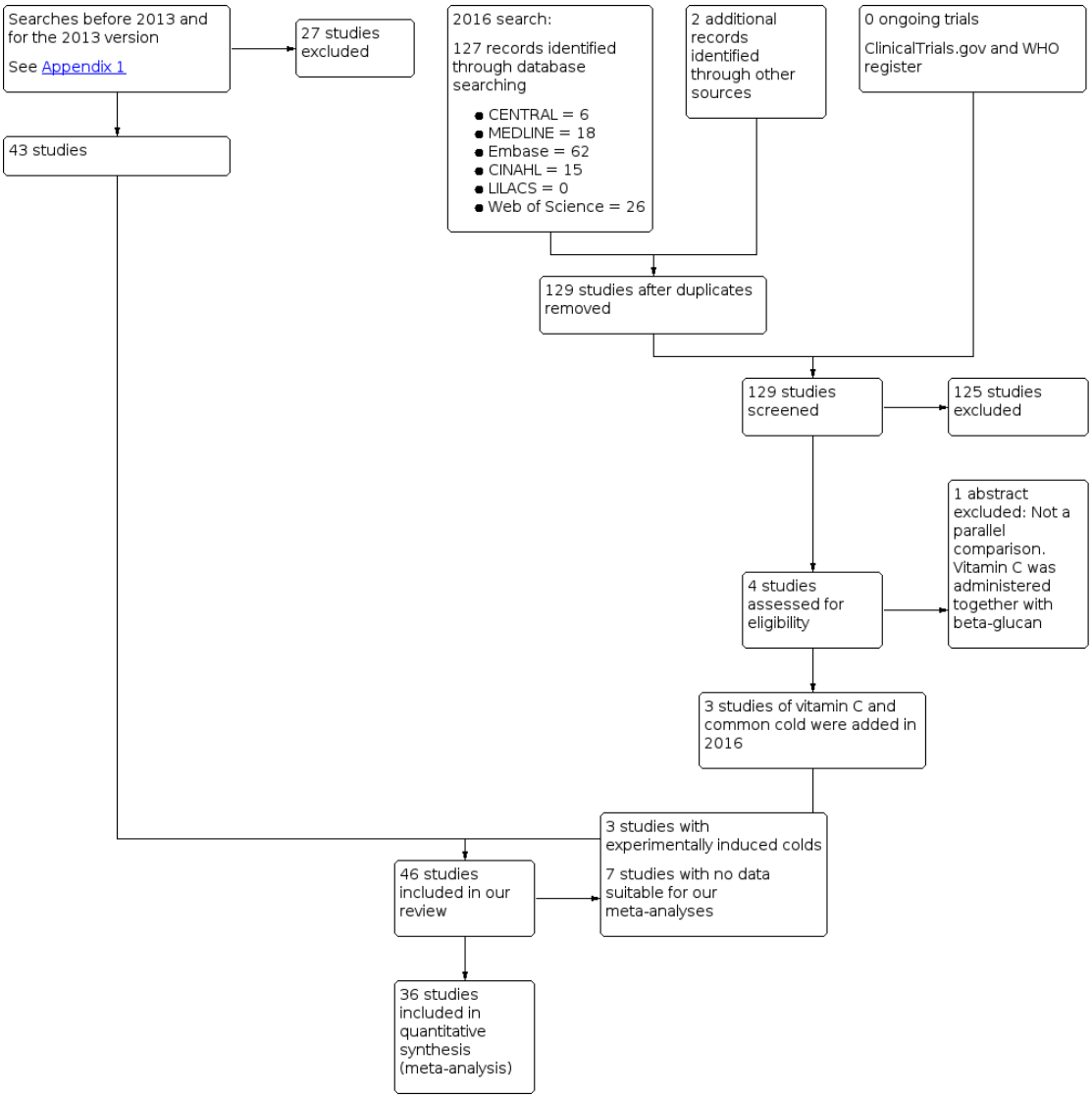
Vitamin C is an efficient water-soluble antioxidant and the effects on the immune system can be explained by the protection against oxidative stress generated during infections (Akaike 2001; Castro 2006; Hemilä 1992). Phagocytes have a specific transport system where the oxidised form of vitamin C (dehydroascorbic acid) is imported into 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 as 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.

Dozens of studies in different animal species have shown that vitamin C affects resistance to diverse infections by viruses and bacteria (Hemilä 1997c; Hemilä 2006a). Given the wide variety of animal species in which vitamin C has influenced infections it seems unlikely that vitamin C would not have similar effects in humans.

Infections lead to the consumption of vitamin C (Davies 1979; Hemilä 1997b; Hemilä 2006a; Hume 1973; Hunt 1994); therefore, higher doses of vitamin C may be beneficial during infections. Physical exertion generates oxidative stress (Powers 2011), and as an antioxidant, vitamin C may influence respiratory symptoms associated with physical exertion.

For brief notes on the history of this Cochrane Review, see Figure 2, Appendix 1. Links to cited publications are available from www.mv.helsinki.fi/home/hemila/CC.

Figure 2. Study flow diagram



Why it is important to do this review

The common cold causes significant morbidity worldwide and the search for simple and effective preventive or therapeutic agents has been elusive. Even if vitamin C has modest effects for specific populations, this may be an important public health benefit.

OBJECTIVES

To find out whether vitamin C reduces the incidence, the duration or the severity of the common cold, when used either as a daily supplementation 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 our review to RCTs.

Types of participants

We considered trials of children and adults of either sex and any age to be eligible for inclusion.

Types of interventions

We investigated orally administered vitamin C ≥ 0.2 g daily for a single day or over a period. The limit of 0.2 g/day was selected for convenience. If a trial with a lower dose finds a negative result, the negative findings can be attributed to the low dose. Trials with larger doses are more informative for testing Pauling's proposal that gram doses of vitamin C would reduce morbidity due to the common cold. On the other hand, under certain conditions, vitamin C doses less than 0.2 g/day may have an effect on the common cold (see Discussion: Possible role of marginal vitamin C deficiency). Our selection criterion for dose does not mean that all excluded trials are irrelevant to the question of whether vitamin C has an effect. All trials that used vitamin C doses < 0.2 g/day are briefly described in Characteristics of excluded studies.

In some instances, placebo groups included low dose vitamin C; Carr 1981a administered 70 mg/day, Miller 1977a, Briggs 1984 and Sasazuki 2006 administered 50 mg/day, and a few studies administered less. This approach was to ensure that participants were not vitamin C deficient, so that the treatment of marginal deficiency was not a plausible explanation if there were differences between people in vitamin C and control groups. The investigators' goal was to test the effects of large doses for properly nourished participants. However, vitamin C administered as placebo leads to the problem of contamination.

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 the episodes was assessed in two ways:
   i) days confined indoors, or off work or off school per episode; and
   ii) symptom severity scores.
2. Adverse effects.

Search methods for identification of studies

Electronic searches

For this 2016 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2016, part of the Cochrane Library (accessed May 2016), which contains the Cochrane Acute Respiratory Infections Specialised Register, MEDLINE (November 2012 to May, 2016), Embase (November 2012 to May 2016), CINAHL (November 2012 to May 2016), LILACS (2012 to May 2016) and Web of Science (2012 to May 2016). See Figure 2.

Our previous update (in 2013) used the same databases and search strategies for the period January 2012 to May 2016. See Appendix 1 for details of earlier searches.

We used the search strategy described in Appendix 2 to search CENTRAL and MEDLINE. The search strategy was adapted to search Embase (Appendix 3), CINAHL (Appendix 4), LILACS (Appendix 5) and Web of Science (Appendix 6). We also searched the US National Institutes of Health trials register and the WHO ICTRP on 2 May 2016 (Appendix 7). There were no language or publication type restrictions in the literature searches.

Searching other resources

We screened reference lists of systematic reviews by Briggs 1984 and Kleijnen 1989 (see Kleijnen 1992 for the search strategy) and references in all identified studies. One author (HH) has research involvement in this topic and has assembled a personal reference list from the grey literature or listed in indexing services that preceded electronic searching.

We contacted Drs Carillo (Carillo 2008a; Carillo 2008b) and Elwood (Elwood 1976) for further details of their trials.

Data collection and analysis

Selection of studies

Two authors (HH, EC) searched the literature and assessed titles and abstracts to identify potentially relevant articles for this update (Figure 2). The same authors undertook these processes for the 2013 update. HH searched the literature and assessed titles and abstracts to identify potentially relevant articles for the 2007 and 2009 updates.

Two authors (HH BD) searched the literature and independently assessed titles and abstracts to identify potentially relevant articles for the 2004 review (Appendix 1). The authors obtained and scrutinised full versions of all potentially eligible articles. Disagreements were resolved by discussion until consensus was achieved.

Data extraction and management

Two authors (HH, BD) independently extracted and collated data in Review Manager for the 2004 review; the authors sought consensus when interpretations differed (Douglas 2004). See Appendix 1.

The authors constructed a spreadsheet to record all original data for the 2016 update. One author (HH) entered data and both authors (HH, EC) independently checked consistency of recorded data with original reports. There were no disagreements.

Assessment of risk of bias in included studies

We assessed and reported on the methodological risk of bias of included studies in accordance with the Cochrane Handbook (Higgins 2011). We assessed random sequence generation; allocation sequence concealment; blinding (participants, personnel); blinding (outcome assessment); completeness of outcome data, selective outcome reporting; whether placebo was distinguishable from vitamin C; and contamination. We judged each item as being at high, low or unclear risk of bias as set out in the criteria provided by Higgins 2011 and provided a quote from the study report and a justification for our judgement for each item in the risk of bias table.

Studies were deemed to be at the highest risk of bias if they were scored as high or unclear risk of bias for either the sequence generation or allocation concealment domains, based on growing empirical evidence that these factors are particularly important potential sources of bias (Higgins 2011).

Two authors independently assessed risk of bias for this update; disagreements were discussed and consensus achieved. We contacted study authors for additional information as required.

Measures of treatment effect

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, Analysis 2.2, and Analysis 4.1: the measure of treatment effect is the mean difference (MD) in common cold duration. Since the duration of cold episodes varied appreciably across trials, we standardised the mean values and standard deviations (SD) in each group against the mean duration of the respective placebo group. In this way, the placebo group of each trial was set to a value of 100%, and therefore the difference between the vitamin C and placebo groups is a direct measure of the effect of vitamin C as a percentage. This approach adjusts for the variation in untreated (placebo group) colds. A recent comparison showed that the relative scale leads to less heterogeneity in meta-analyses compared with the absolute scale (calculation in days) (Friedrich 2011). The duration of colds is a type of outcome which should be analysed on the relative scale (Hemilä 2016b).

Analysis 2.3: the measure of treatment effect on common cold duration is 'days' without normalization to the 100% scales. The effect was calculated with the MD method.

Analysis 4.2 calculates the risk difference for the proportion of participants who had 1-day colds in the Anderson 1974a trial.

Analysis 3.1 and Analysis 5.1: there are two measures of effect on severity: the difference in the mean number of days that the patient was absent from work or school, or confined to bed or indoors; and the difference in the mean symptom severity score derived from patient-kept records. The measure of treatment effect is the MD in common cold severity. We standardised results in each group against the mean of the respective placebo group, so the placebo group of each trial was given a value of 100%. Hence, differences between vitamin C and placebo groups show the effect of vitamin C as percentages.

Analysis 6.1, Analysis 6.2, Analysis 6.3, and Analysis 6.4 examine within-trial subgroup difference using the MD method. Transformation of effects to percentages was not conducted because these comparisons were not between-trials.

Occurrence of adverse effects was analysed by calculating RR between vitamin C and placebo groups (Analysis 7.1).

The Anderson 1974a study had eight trial arms. Participants in six arms received vitamin C using different protocols; two were placebo arms. One of the two placebo groups (#6) had statistically significant baseline differences up to P value 0.00002 when compared with the six vitamin C groups (see Hemilä 2006a). However, the six vitamin C arms and placebo group #4 were consistent in terms of baseline data. The comparisons presented in this review are with placebo group #4 which was consistent with vitamin C groups with respect to baseline data (see Hemilä 2006a). In Anderson 1974a, participants in two arms (#7 and #8) were administered therapeutic vitamin C but not regular vitamin C, so they serve as placebo groups for comparing regular vitamin C with common cold incidence. We pooled data for participants in arms #7 and #8 with placebo group #4 participants to provide the placebo group for the regular vitamin C arms #1, #2, and #3 (Analysis 1.1).

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 treatment groups (Berry 1995; Hemilä 2006a; Lydersen 2009) and was used when comparing groups with small numbers of cases.

Two-tailed P values were used in this review.

Unit of analysis issues

In four trials (Anderson 1974a; Anderson 1975a; Audera 2001a; Karlowski 1975a), more than one vitamin C group was compared with a single placebo group. For these studies, we divided the respective placebo group for all vitamin C arms weighted with the

number of participants or common cold episodes of the vitamin C arms. This avoided double counting placebo arm participants in the analysis.

Miller 1977a and Carr 1981a studied twins and the comparison is paired. The SD values used or this meta-analysis were calculated from the published SE and P values respectively, of reported paired tests, so both trials were weighted appropriately when pooled.

In several studies participants had a few colds per person; such colds are correlated because they occurred in the same person. However, Constantini 2011a reported that duration of the third common cold episode was very weakly explained by the duration of the first and second common cold episodes (R^2 = 0.05). In most studies the average number of colds was fewer than three per person. The within-person correlation of cold duration therefore probably had no relevant influence on our analysis.

Dealing with missing data

Some trials presented 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 there. In trials that did not report SD, we imputed from the estimated ratio of SD to mean duration. We calculated the SD per mean duration of colds in 67 study groups. The first quartile was 0.49, the median was 0.57, the third quartile was 0.82, and the 80th percentile was 0.91. We selected the 80th percentile value as the ratio for imputations because it is more conservative than the median. The consequence was that on average we reduced weight on our estimates of effect for trials that did not report SD values. This imputation was applied to Analysis 2.1, Analysis 2.2, Analysis 2.3 and Analysis 4.1.

Assessment of heterogeneity

We assessed heterogeneity by considering forest plots and examining the Chi^2 test for heterogeneity. We quantified heterogeneity using the I^2 statistic (Higgins 2003). We considered an I^2 value of 50% or more to represent substantial levels of heterogeneity, but interpreted this value in light of the size and direction of effects and the strength of the evidence for heterogeneity, based on the P value from the Chi^2 test (Higgins 2011). Where heterogeneity was found in pooled effect estimates we explored possible reasons for variability by conducting subgroup analysis.

Data synthesis

We used Review Manager (RevMan 2014) 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 for common cold duration and severity to derive an estimate of the percentage effect of vitamin C on those outcomes and on the number of days the common cold became shorter.

GRADE and 'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: incidence of colds during regular supplementation; duration of common cold symptoms; and severity of common cold symptoms. We used the five GRADE (Atkins 2004) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the pre-specified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and we used GRADEproGDT software (GRADEproGDT 2015). We justified all decisions to down- or up-grade the quality of studies using footnotes, and we made comments to aid the reader's understanding of the review where necessary.

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 (size) of the participants (children versus adults), and the presence or absence of heavy, short-term physical stress.

Sensitivity analysis

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 nine trials that reported duration of colds with regular vitamin C supplementation at doses $\geq$ 1 g/day we imputed SD values assuming that SD is equal to 0.91 times the mean of the group (Anderson 1974a; Anderson 1974b; Anderson 1974c; Briggs 1984; Carr 1981a; Coulehan 1974a; Coulehan 1974b; Coulehan 1976; Pitt 1979). When we excluded these trials in a sensitivity analysis of Analysis 2.2, the pooled results indicated a slightly greater effect of vitamin C in adults: 10.5% (95% CI 5.6% to 16%), compared with 8.2% (4.2% to 12%) in Analysis 2.2, and in children: 19.5% (10% to 29%) compared with 17.8% (9.5% to 26%) in Analysis 2.2. Thus, inclusion of these trials with imputed SD values does not lead to an increase in the estimate of benefit, but leads to a slight reduction in the estimated benefit in both adults and children.

RESULTS

Description of studies

Results of the search

Our searches identified a total of 127 records for this update (Figure 2). After removal of duplicates, we assessed 110 records for possible inclusion. We found no new records from searches of Clinicaltrials.gov or WHO ICTRP.

Included studies

We added three studies to this update. One of the new studies reported two trials so that the number of new included trials was four (Carillo 2008a; Carillo 2008b; Johnston 2014; Craig 1976). The new studies involved a total of 63 participants. The 2016 review includes a total of 46 studies (a "study" being defined as the primary study report, with a total of 77 separate reports of the studies, 11,941 participants). Several of the included studies contained two or more separate trials with their own placebo groups (Carillo 2008a; Carr 1981a; Constantini 2011a; Coulehan 1974a; Cowan 1950a; Ludvigsson 1977a; Miller 1977a; Moolla 1996a; Peters 1993a; Peters 1996a; Tyrrell 1977a; Wilson 1973a). Certain other included studies had more than one vitamin C arm compared with the placebo group (Anderson 1974a; Anderson 1975a; Audera 2001a; Karlowski 1975a). Because many studies reported several separate trials, or more than one vitamin C arm, the total number of comparisons in our review is 71 (Figure 2). We use letters a, b, etc. to indicate the individual comparisons of the particular studies. See Characteristics of included studies. We contacted Drs Carillo (Carillo 2008a; Carillo 2008b) and Elwood (Elwood 1976) for further details of their trials.

Design

All included studies were placebo-controlled parallel group comparison trials.

Sample sizes

Numbers of participants ranged from 12 (Carillo 2008a) to 818 (Anderson 1972).

Setting

Most studies were undertaken in the US, UK, Canada and Australia in settings that included workplaces, universities, schools, boarding schools and military training facilities.

Participants

Participants ranged from young children to the elderly and were both male and female. Some studies selected participants who were involved in strenuous activities such as skiing or competitive swimming; two studies looked at twins living together and apart.

Interventions

All studies used at least 0.2 g/day of vitamin C. The highest doses were 8 g/day for a single day (Anderson 1974f) and 6 g/day for five days (Asfora 1977; Karlowski 1975b).

Outcomes

Studies reported the numbers, the duration, and/or the severity of colds during the follow-up period. Most data were based on published reports.

Study categories

The 46 included studies were categorised into three groups:

1. Thirty six studies of Naturally-occurring colds reported on the effects of therapeutic or regular vitamin C administration on the numbers of common cold episodes, or on the duration and severity the common cold.
2. Seven studies of Naturally-occurring colds did not report data suitable for our meta-analysis; these trials are presented qualitatively (Table 1).
3. Three Laboratory studies (Dick 1990; Schwartz 1973; Walker 1967) in which volunteers were intentionally exposed to known viruses after vitamin C or placebo administration. Because these studies are qualitatively different from the community-based studies of naturally occurring common cold infections, they were not included in our meta-analyses but are presented qualitatively (Table 2).

The time of publication of the studies

Figure 1 shows the common cold studies in which $\geq$ 1 g/day of vitamin C was administered to the vitamin group. After the Pauling 1970a book, over the 15-year period from 1970 to 1984 there were 35 published vitamin C studies, which together included 9501 participants (average 271 participants per study). In contrast, in the 25 -year period from 1990 to 2014 there were 11 studies which together included only 538 participants (average 48 participants per study). Thus, the number of studies published after 1990 is much lower than during the 1970s and 1980s. In addition, the few recent studies are much smaller than the trials published in the 1970s and in the 1980s. As a consequence of both the number of studies and the number of participants per study, the total number of participants in the 15 year period starting from 1970 is 17 times as great as the number of participants in the studies published since 1990.

Since most included studies, and all the large studies, were published in the 1970s (Figure 1), the old studies have the greatest weight in most of the analyses in this Cochrane review. In Analysis 1.1.1 only 2.3% of the total weight of the studies originates from studies published after 1990. In Analysis 2.2 only 3.3%, and in Analysis 3.1 only 1.6%, of the total weight of the included studies originates from studies published after 1990. The only meta-

analysis, which is dominated by recent studies, is Analysis 1.1.3 in which 60% of the weight is from studies published after 1990.
Terrence Anderson made a significant contribution to research on vitamin C and the common cold. He carried out three RCTs, which altogether had 3287 participants in ≥ 1 g/day of vitamin C comparisons, which is 30% of all participants in trials that have used ≥ 1 g/day of vitamin C (Anderson 1972; Anderson 1974a; Anderson 1975a). The Anderson 1972 and Anderson 1974a studies have a weight of 39% in Analysis 1.1.1 and a weight of 32% in Analysis 2.2.1. Consequently, the Anderson trials have a particularly great weight in our meta-analyses.

Excluded studies

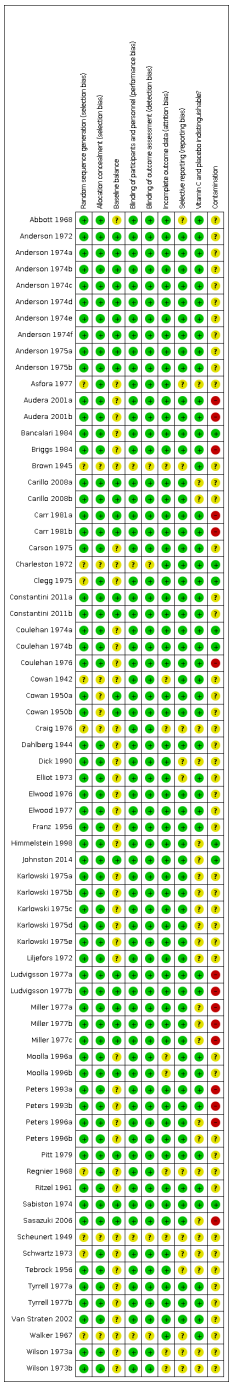
We excluded 28 studies. Reasons for exclusion included lack of placebo control (Barnes 1961; Bendel 1955; Bessel-Lorck 1959; Boines 1956; Cuendet 1949; Dyllick 1967; Gormly 1977; Gorton 1999; Kimbarowski 1967; Koytchev 2003; Miegl 1957; Miegl 1958; Niemi 1951; Peters 1940; Renker 1954); vitamin C dose < 0.2 g/day (Baird 1979; Bartley 1953; Bergquist 1943; Chavance 1993; Glazebrook 1942; Hopfengärtner 1944; Masek 1974; Niemi 1951); administration of vitamin C with other substances (Fogelholm 1998; Maggini 2012; Pico Sirvent 2013; Schmidt 2011); not a parallel comparison (Bendel 1955; Gorton 1999; Pico Sirvent 2013); not focused on the common cold (Hunt 1994); and we were unable to find the report (Bibile 1966) that was cited in one earlier review on vitamin C and the common cold (Kleijnen 1989). See Characteristics of excluded studies.
In addition to the 28 excluded studies described above, some of the included studies reported trials or trial arms that were excluded from our analyses. To avoid double counting, these studies are not listed in the Characteristics of excluded studies table. Instead the reason for the exclusion of particular trials or trial arms of included studies is described in the Notes section of Characteristics of included studies table. Audera 2001a had an arm which administered vitamin C with flavonoids and that arm was excluded. Cowan 1942 reported a trial with low vitamin C dose with multiple other vitamins and that trial was excluded. Himmelstein 1998 reported a trial with marathon runners, but there was an extreme and divergent drop-out rate which led us to exclude that trial.

Risk of bias in included studies

Allocation

The use of randomisation was reported in 61 out of 71 comparisons (low risk) (Figure 3). The majority of the studies are from the 1970s and the technical method of randomization was rarely described in the included studies. Ten comparisons did not report on the method of allocation (unclear risk): Asfora 1977; Brown 1945; Charleston 1972; Clegg 1975; Cowan 1942; Craig 1976; Regnier 1968; Scheunert 1949; Schwartz 1973; Walker 1967. Only four of the ten comparisons with unclear risk are included in our meta-analyses (Charleston 1972; Clegg 1975; Cowan 1942; Craig 1976) and they do not have a substantial weight in the estimates. The The Cowan 1942 study used 0.2 g/day of vitamin C and therefore it is not included in Analysis 1.1.1 or Analysis 2.2. Six of the ten comparisons with unclear risk were laboratory studies or did not report data suitable for our quantitative analysis.

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study



Allocation concealment was used in 63 out of 71 comparisons (low risk) (Figure 3). Eight comparisons did not report on allocation (unclear risk): Brown 1945; Charleston 1972; Cowan 1942; Cowan 1950a; Cowan 1950b; Craig 1976; Scheunert 1949; Walker 1967. Five of the eight comparisons with unclear risk are included in our meta-analyses (Charleston 1972; Cowan 1942; Cowan 1950a; Cowan 1950b; Craig 1976). They do not have a great weight in the estimates of vitamin C effect. Three of the eight comparisons with unclear risk were laboratory studies or did not report data suitable for our quantitative analysis.

Baseline balance

In 27 out of 71 comparisons, essential baseline variables were published for the compared groups and the groups were reasonably balanced.

Blinding

Blinding of participants, personnel and outcome assessment was used in 67 out of 71 comparisons (low risk) (Figure 3). Four comparisons did not report on blinding or single-blind was used (unclear risk): Brown 1945; Charleston 1972; Scheunert 1949; Walker 1967. Two of them did not report data suitable for our quantitative analysis (Brown 1945; Scheunert 1949) and one was a laboratory study (Walker 1967). The Charleston 1972 study is included in our meta-analyses, but it had only 90 participants and thus has no great weight.

Incomplete outcome data

There were no evident concerns about incomplete outcome data in 62 out of 71 comparisons (low risk) (Figure 3). Seven comparisons did not report sufficient data to conclude that there were no dropouts or that the dropout rates were similar Brown 1945; Cowan 1942; Craig 1976; Regnier 1968; Scheunert 1949; Wilson 1973a; Wilson 1973b), and in two comparisons the dropout difference was moderately large (Moolla 1996a; Moolla 1996b) (unclear risk). Two of these comparisons with unclear risk are not included in our meta-analyses (Brown 1945; Regnier 1968; Scheunert 1949). Cowan 1942, Moolla 1996b; Wilson 1973a and Wilson 1973b used vitamin C doses < 1 g/day and therefore they are not included in Analysis 1.1.1 or Analysis 2.2. Moolla 1996a is part of Analysis 1.1.3 but it has a weight of only 10% in that analysis.

Consequently, the comparisons with unclear risk that are included in our quantitative analyses have low weight in the meta-analyses.

Contamination

Contamination occurs if participants in the control group receive the same treatment as people in the intervention group. Contamination causes bias towards the null effect so the true effect may be greater than the observed effect.

In the USA, recommended dietary vitamin C intake is 90 and 75 mg/day for men and women respectively (IOM 2000), and 40 mg/day in the UK (FSA 2003). From the public health perspective, studies on vitamin C and the common cold should administer 40 to 90 mg/day of vitamin C for the placebo group and a high dose for the vitamin C group. We found that contamination occurred where vitamin C was administered intentionally to placebo arm participants, particularly high dietary vitamin C intake or self-supplementation by people in the placebo group.

We found contamination in 15 included comparisons: in 11 comparisons vitamin C was administered to placebo group participants in doses ranging from 10 to 70 mg/day (Carr 1981a). Two comparisons reported that placebo group partcipants had a vitamin C intake of about 500 mg/day from diet and self-supplementation (Peters 1993a; Peters 1996a). In a study of twins vitamin C excretion in urine was high at baseline indicating high dietary vitamin C intake: on average 225 mg/day in the placebo group (Miller 1977a). Among boys in the placebo arm, urinary vitamin C excretion increased significantly during the study by 121 mg/day (P = 0.03) whereas the increase in girls was 27 mg/day: contamination may have occurred when boys swapped their tablets. In another study with twin children, vitamin C was beneficial for twins living apart but no effect was seen among twins living together, which also may indicate swapping of the tablets by twins (Carr 1981a). Coulehan 1974a wrote that "older P[lacebo] children of both sexes had significantly higher blood ascorbic acid levels in March than in January, suggesting that some P children may have been switching tablets at times with [vitamin] C children or getting excess ascorbic acid in some other way" (p. 9).

Vitamin C and placebo indistinguishable?

Most (46) comparisons reported that vitamin C tablets (usually ascorbic acid) and placebo tablets (usually citric acid) were indistinguishable; there was no basis to assume that differences in taste or appearance generated substantial bias as speculated by Chalmers 1975 (based on Karlowski 1975a). Many studies in which vitamin C indistinguishability was not explicitly stated were small laboratory studies (Dick 1990; Schwartz 1973; Walker 1967), or were not included in meta-analyses (Asfora 1977; Regnier 1968; Scheunert 1949). No major studies other than Karlowski 1975a had concerns about vitamin C and placebo indistinguishability; however, even in the Karlowski 1975a study Chalmers 1975 speculation was found to be erroneous (Hemilä 1996a).

Selective reporting

When there are only 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 reason to speculate that the consistency in these two outcomes might be explained by selective reporting.

There is no unambiguous definition for the severity of the common cold and there might be concerns with selective reporting on that outcome (Analysis 3.1). Nevertheless, cold severity is a secondary outcome in our review and the findings are consistent with the effect on cold duration (Analysis 2.1).

Thirteen of the 71 comparisons had unclear risk of reporting bias. Three of these were laboratory studies (Dick 1990; Schwartz 1973; Walker 1967) and not directly comparable with the studies with natural common cold infections. Seven were studies with no suitable data for our quantitative analysis (Abbott 1968; Asfora 1977; Brown 1945; Elliot 1973; Regnier 1968; Scheunert 1949; Tebrock 1956). If lack of reporting quantitative data is negatively associated with the findings, then this set of trials might bias our quantitative analysis. However, only two of the seven trials were unambiguously negative for vitamin C (Abbott 1968; Tebrock 1956). Two of the seven studies in Table 1 were published in the 1940s (Brown 1945; Scheunert 1949) and the time of publication is a more reasonable explanation for poor reporting than the findings. Three studies reported a benefit fromf vitamin C, but not in a manner that we could include in our analyses (Asfora 1977; Elliot 1973; Regnier 1968). Three of the 13 comparisons with unclear risk of reporting bias were included, but Wilson 1973a and Wilson 1973b used vitamin C doses < 1 g/day and therefore they are not included in Analysis 1.1.1 or Analysis 2.2, and Craig 1976 is a small therapeutic trial.

The only included studies we identified which were not published as full journal articles were Dick 1990 and Craig 1976. However, both studies reported vitamin C to be beneficial and therefore lack of identification of them would have led to less evidence for the benefits of vitamin C, rather than the contrary.

Other potential sources of bias

Most studies were published in the 1970s when sources of funding were seldom reported. Vitamin C is inexpensive and measuring the incidence, duration and severity of colds is not costly. It seems that many studies were carried out with small budgets from universities, hospitals, or non-commercial institutions. Many studies reported that the tablets were supplied by the pharmaceutical industry.

Effects of interventions

See: **Summary of findings for the main comparison**

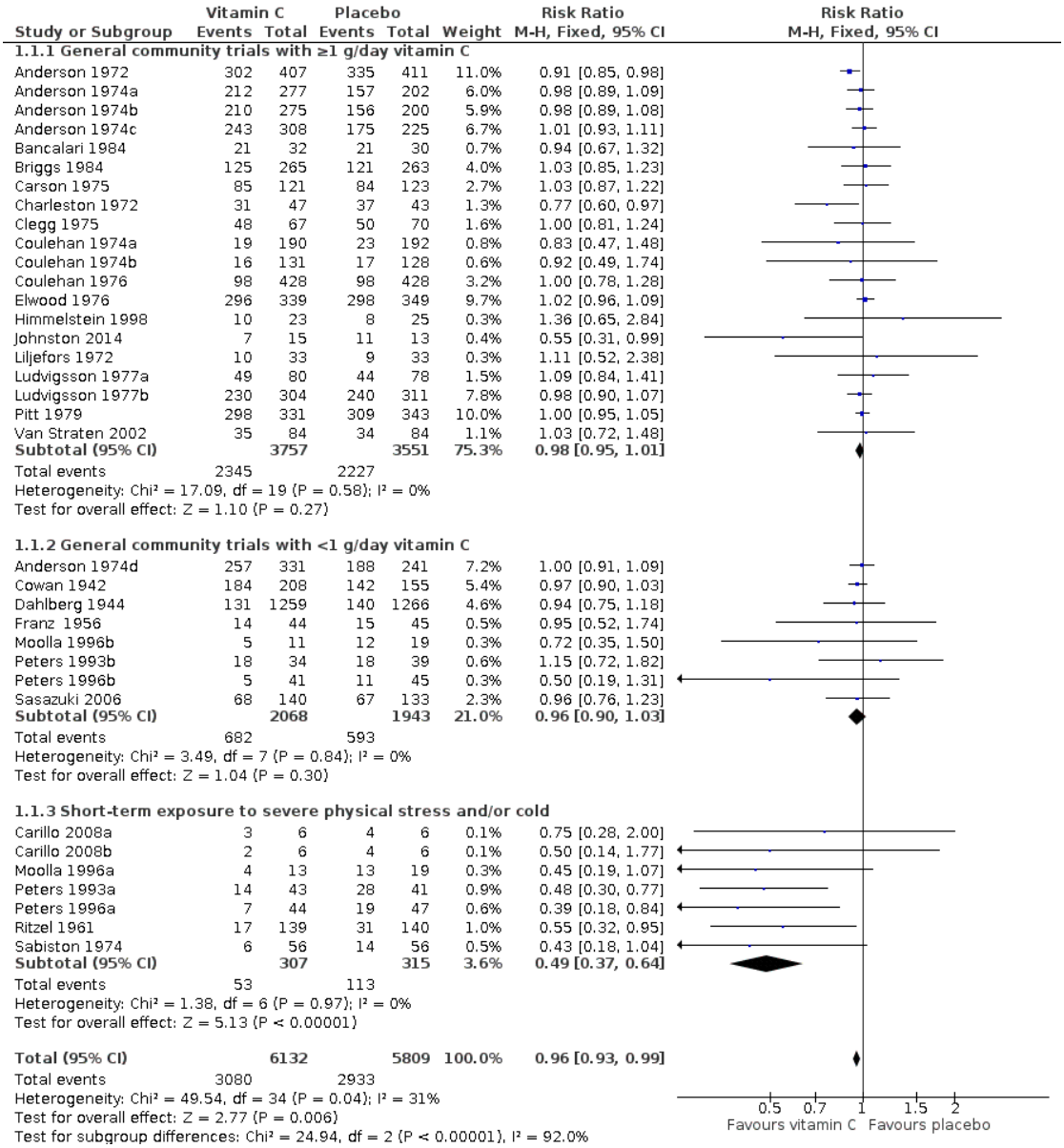
Primary outcomes: regular supplementation trials

1. Incidence of colds

We looked at the effect of regular vitamin C on numbers of people who caught at least one cold during the trial. Participants (who did not have colds) received vitamin C each day over the study period to assess the efficacy of vitamin C in preventing colds.

Analysis 1.1 (Figure 4) includes 11,941 participants, of whom 5809 were given vitamin C for periods ranging from about a week to three years. The pooled risk ratio (RR) for all 35 studies was 0.96 (95% CI 0.93 to 0.99). The overall difference between participants taking vitamin C and placebo was statistically highly significant (P = 0.006) indicating that vitamin C had a biological effect. However, the narrow 95% CI precluded any clinically relevant effect for the populations studied.

Figure 4. Forest plot of comparison: 1 Incidence of colds when on regular vitamin C, outcome: 1.1 Proportion of participants developing ≥ 1 cold episodes during the trial.



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 the episodes was assessed in two ways:
   i) days confined indoors, or off work or off school per episode; and
   ii) symptom severity scores.
2. Adverse effects.

Heterogeneity of the results

Among the 35 studies included in Analysis 1.1 there was substantial heterogeneity, as indicated by the Chi² test (P = 0.02) and a rather high I² statistic (38%). Heterogeneity refutes the notion that vitamin C is universally equivalent to placebo.

In six of the 35 studies it was found that vitamin C was effective in preventing the common cold (P < 0.05): Peters 1996a (RR 0.39), Peters 1993a (RR 0.50), Johnston 2014 (RR 0.55), Ritzel 1961 (RR 0.55), Charleston 1972 (RR 0.77) and Anderson 1972 (RR 0.91). None of the 35 studies significantly favoured the placebo.

Analysis 1.1.3 shows seven studies which involved participants under short-term physical stress. This subgroup included three of the six studies that reported significant preventive effects of vitamin C.

Pauling proposed that vitamin C doses of at least one gram were necessary to prevent the common cold. Consequently, we divided the general community studies into two groups: those with vitamin C doses ≥ 1 g/day (Analysis 1.1.1) and those with vitamin C doses <1 g/day (Analysis 1.1.2). The three subgroups were homogeneous within the three pools (I² = 0%). However, comparison of the pooled estimates of these three subgroups indicated that the differences were explained by true heterogeneity rather than random variation (I² = 92%; P = 10^{-5} in the Chi² test.

General community trials

Analysis 1.1.1 leads to RR 0.98 (95% CI 0.95 to 1.01; 7308 participants; 20 studies; I² = 0%; high quality evidence). The narrow 95% CI, which is located around the null effect, refutes the possibility that regular ≥ 1 g/day vitamin C supplementation could reduce the average incidence of colds in the general community. The eight lower dose studies also found no effect of vitamin C in Analysis 1.1.2 .

Furthermore, the nine-month Karlowski 1975a trial, in which the 3g/day dose of vitamin C was the highest, is particularly informative. 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 mean incidence of colds, with RR 0.93 (0.73 to 1.20) (Hemilä 1997b).

Three studies in Analysis 1.1.1 found a statistically significant effect on common cold incidence (Anderson 1972; Charleston 1972; Johnston 2014). See below for other findings and comments on the two earliest trials.

Heavy acute physical activity trials

Analysis 1.1.3 included seven studies with participants undergoing heavy, short-term physical activity. Vitamin C halved the incidence of colds (RR 0.49; 95% CI 0.37 to 0.64; P value 10^{-6}; 622 participants; 7 studies; I² = 0%; high quality evidence). Three studies were with marathon runners (Moolla 1996a; Peters 1993a; Peters 1996a), one with students in a skiing school in the Swiss Alps (Ritzel 1961), one with Canadian army troops on subarctic operations (Sabiston 1974), and two very small studies with participants after an exercise test (Carillo 2008a; Carillo 2008b).

All of these seven studies were randomised and double-blind. In three studies, the dose of vitamin C was < 1 g/day (Moolla 1996a; Peters 1993a; Peters 1996a) so that the benefit in this subgroup cannot be explained by particularly high vitamin C doses. Instead the benefits seem to be caused by the extraordinary conditions of the participants. Table 3 shows the number-needed-to-treat-to-benefit (NNTB) values calculated a) from the reported incidence of colds in the vitamin C and placebo groups and b) from the pooled RR estimate and the reported incidence in the placebo groups. The NNTB varied between 3 and 10.

Two trials in Analysis 1.1 included participants exposed to long-term physical stress. Pitt 1979 examined 674 US marine recruits for two months and Constantini 2011a studied 39 competitive adolescent swimmers for three months. Neither of these trials found that vitamin C had an effect on common cold incidence. The preventive effects seen in Analysis 1.1.3 seem to be restricted to short-term physical stress conditions.

To test the effect of study quality on the findings in Analysis 1.1,1 we removed four studies which were not randomised and double-blind (Charleston 1972; Clegg 1975; Coulehan 1974a; Coulehan 1974b). This had no effect on the effect estimate (RR 0.99; 0.96 to 1.02). All trials in Subgroup 3 were randomised and double-blind: the effect of study quality as assessed by randomisation and double-blinding does not change our conclusions.

Other effects of regular vitamin C in Analysis 1.1

Although the overall estimate of effect in Analysis 1.1.1 is null with a narrow 95% CI, some of the general community studies found that vitamin C had significant preventive effects on outcomes relevant to the common cold.

Anderson 1972 found that the occurrence of "not ill during the trial", "not confined to the house" and "not off work" because of common cold related symptoms were all 8 percentage points lower in the vitamin C group than in the placebo group (P = 0.01 for each; NNTB 12; Hemilä 2006a). Similarly, Coulehan 1974a found a 16 percentage point higher proportion of children in the vitamin C group who were 'never ill on active surveillance' by a medically trained clerk or school nurse (P = 0.0001; NNTB 6; Hemilä 2006a). So some individual participants of these two studied populations benefited from regular vitamin C administration, even though the 95% CI for Analysis 1.1.1 indicated no overall average effect on the general population.

Elwood 1976 found a statistically significant decrease (-18%; P = 0.03) in the incidence of "chest colds" (cough or other chest symptoms) in the vitamin C group, but no effect (+ 1%) on the incidence of "simple colds" (runny nose or sneezing) (Hemilä 1997b). Similarly, Anderson 1972 observed a moderate decrease in the incidence of "throat colds" (-21 %; 0.34 and 0.43 per subject; P < 0.01), but no effect (-2%) on the incidence of "nose colds" (Hemilä 1997b). In both of these studies the number of "nose colds" was about two-thirds of all colds, and so the possible effects of vitamin C on symptoms originating from lower airways are camouflaged if the two types of symptoms are pooled. These two large studies suggest that vitamin C supplementation might have an effect on the incidence of cold symptoms originating from lower airways.

Some studies found that vitamin C may have a significant preventive effect on people who have colds frequently. Sasazuki 2006 reported that the number of participants who had three or more colds over the three-year follow-up was significantly decreased in the vitamin C group with RR 0.36 (0.13 to 0.99). The significant preventive effect of vitamin C on common cold incidence in the Charleston 1972 study may be explained by marginal vitamin C deficiency, see Discussion. Furthermore, Charleston 1972 found that vitamin C had an even more dramatic effect on the number of people who had more than three colds over the five-month follow up with RR 0.08 (0.01 to 0.56; based on 1/47 versus 12/43).

As a further approach to detect possible subtle treatment effects of regular vitamin C that might not have been measured by the specific common cold outcomes, Miller 1977a asked the mothers of the twin children to guess which twin had received vitamin C (while the mother and the investigator were still blinded on allocation). Among 21 mothers, who felt there was a detectable effect of vitamin C, 17 correctly identified the twin who had received the vitamin (P = 0.007 in binomial distribution).

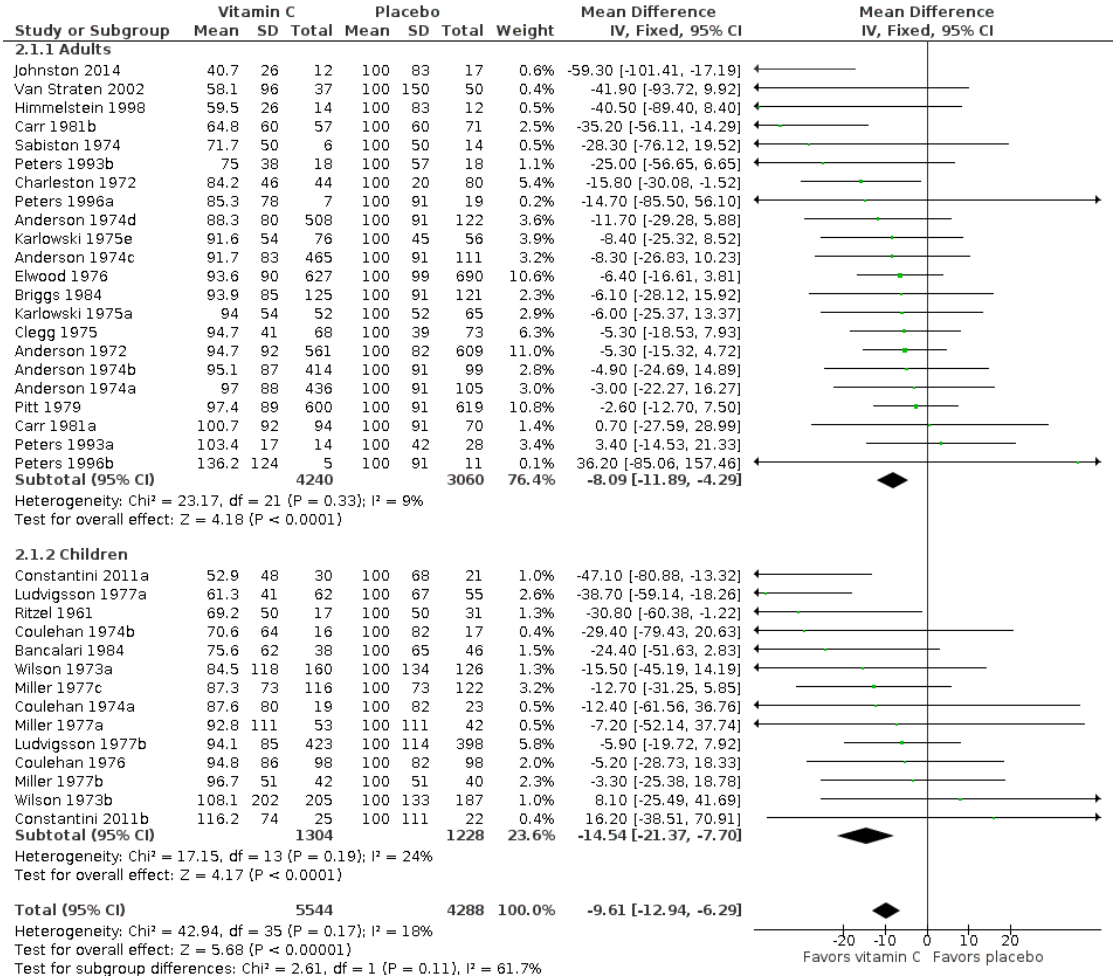
Similarly, Pitt 1979 asked participants, US Marine recruits, if they could identify the tablet by subjective observations. Placebo consisted of citric acid, and even though the vitamin C tablets were shown to be indistinguishable from the placebo tablets, 6% (40 of 674; P = 0.013) of participants correctly 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).

So, although the null effect with the narrow 95% CI in Analysis 1.1.1 should discourage routine use of vitamin C to prevent colds in ordinary people, several studies in Subgroup 1 indicate that a proportion of participants did benefit from the regular vitamin C supplementation. However, the proportion was a minority.

2. Duration of colds

Analysis 2.1 (Figure 5) presents 36 studies on the effect of vitamin C on the duration of colds which occurred while the participants were taking vitamin C regularly, each day over the study. Vitamin C shortened the duration of colds on average by 9.6% (95% CI 6.3% to 13%; P = 10^{-7}).

Figure 5. Forest plot of comparison: 2 Duration of colds occurring when on regular vitamin C, outcome: 2.1 ≥ 0.2 g/day vitamin C (effect in %).



In six studies (Carr 1981b; Charleston 1972; Constantini 2011a; Johnston 2014; 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 reduced in male swimmers, but not in female swimmers, there being a significant interaction between the vitamin C effect and sex (P = 0.003).

Five studies (Carr 1981a; Constantini 2011b; Peters 1993a; Peters 1996b; Wilson 1973b) recorded a point estimate favouring the placebo, but all of them are small studies and, on the basis of their 95% CI, all of them are also consistent with a 15% reduction in common cold duration. In addition, Wilson 1973b used only 0.2 g/day vitamin C, which is the smallest dose in Analysis 2.1, and Peters 1993a and Peters 1996b used only 0.5 to 0.6 g/day of vitamin C.

Carr 1981a examined twin children living together and reported a point estimate favouring placebo, whereas the Carr 1981b trial examined twin children living apart and reported a significant beneficial effect from vitamin C. It is possible that twins living together exchanged or confused their tablets. Furthermore, among twins living separately, the mean duration of colds was 4.86 days in the vitamin C group and 7.50 days in the placebo group, corresponding to a 35% (8.8% to 61%) reduction in common cold duration (Carr 1981b). Among twins living together, the mean duration (MD) of colds was 5.46 days in the vitamin C group and 5.42 days in the placebo group (Carr 1981a). So, among twins living together, in both study groups the duration of colds was in the middle of the durations of colds in the study groups of twins living apart, which is also consistent with swapping of tablets. In

this review, we followed the intention-to-treat (ITT) principle and so included the data for twins living together, although it seems evident that the reported 35% effect in twins living apart is a more valid estimate of vitamin C effect than the lack of effect in twins living together.

Studies of children and adults

There was no considerable heterogeneity over all the 36 vitamin C studies, but the studies were divided into two subgroups, adults and children, for two reasons: a) children have a substantially higher incidence of colds reflecting differences in immune system maturity and therefore colds are a greater problem in children (Monto 1974), and b) children are on average smaller so that a fixed dose corresponds to a greater dose per weight. Analysis 2.2 was restricted to studies which administered ≥ 1 g/day of vitamin C since they are most informative about the possible effects of high-dose supplementation.

In Analysis 2.2, the adult studies contributed 81% of the weight for the calculation of the average effect, and therefore the overall estimate of 10% reduction in common cold duration was primarily based on adult studies and reflects the effects of vitamin C on adults.

The adult studies led to a pooled effect of an 8.1% (4.2% to 12.1%; P = 6×10^{-5}; 6672 colds; 17 studies; I^2 = 20%; high quality evidence) reduction in cold duration in the vitamin C group (Analysis 2.2,1).

Studies in children led to a pooled effect of a 17.8% (9.5% to 26%; P = 3×10^{-5}; 1534 colds; 10 studies; I^2 = 33%; high quality evidence) reduction in the duration of colds in the vitamin C group (Analysis 2.2,2).

When the estimate of effect of ≥ 1 g/day of vitamin C for adults (8.3%) was directly compared with the estimate for children (17.8%), there was evidence of heterogeneity (I^2 = 76%, Chi^2 test P = 0.04 (Analysis 2.2). The effect of 1 to 2 g/day of regularly administered vitamin C seemed to be greater in children.

In sensitivity analyses, we removed four studies which were not randomised and double-blind (Charleston 1972; Clegg 1975; Coulehan 1974a; Coulehan 1974b). Exclusion of the first two from the adult studies led to an effect estimate of 8.1% (3.8% to 13%). Exclusion of the latter two from the child studies led to an effect estimate of 17.6% (9.1% to 26%). Hence exclusion of studies with less satisfactory methods had no material effect on the findings of Analysis 2.2.

Effect on duration (reduction in days)

Our primary analysis calculated the effect of vitamin C in percentages. We also calculated the effect of ≥ 1 g/day of vitamin C on the absolute scale, as a reduction in duration of the cold in days (Analysis 2.3). In adults, vitamin C shortened the duration of colds by 0.40 days (0.21 to 0.60 days; 7180 colds; 18 studies; P = 10×10^{-5}; I^2 = 2%; high quality evidence) and in children by 0.97 days (0.47 to 1.48 days; 1534 colds; 10 studies; P = 18×10^{-5}; I^2 = 46%; high quality evidence).

The reason we used the relative scale in our primary analysis (i.e. percentages) is because it adjusts for variations in untreated (placebo group) colds. For children the calculation of effect on days led to greater heterogeneity (46% versus 33%) and a larger P value (10×10^{-5} versus 3×10^{-5}) compared with the calculation on the relative scale. These differences illustrate the benefit of the percentage scale, though the difference is not dramatic.

In summary, when adults and children are regularly administered ≥ 1 g/day of vitamin C, the duration of colds that occur during supplementation are reduced on average by 8% (0.4 days) in adults, and by 18% (1.0 days) in children.

Secondary outcomes: regular supplementation trials

1. Severity of colds

Analysis 3.1 presents the effect of vitamin C on the severity of common cold episodes that occur during regular vitamin C supplementation. Two measures of the severity of the common cold were available: days at home, off work or school and severity scales. This analysis is restricted to studies that administered ≥ 1 g/day of vitamin C. Vitamin C reduced cold severity by an average of 13.2% (95% CI 8% to 18%; P = 10^{-6}; 6118 participants; 15 studies; I^2 = 24%; high quality evidence).

Analysis 3.1.1 consists of studies in which severity was measured by days at home, off work or school. On average, regular vitamin C decreased these outcomes by 13.6% (7% to 20%; 4388 colds; eight studies; I^2 = 31%; high quality evidence). There was no substantial heterogeneity among studies.

Analysis 3.1.2 presents the results on symptom severity scores, and the combined effect in the remaining vitamin C studies was a 12.8% (4.8% to 21%; 1730 colds; seven studies; I^2 = 28%; high quality evidence) reduction in common cold severity. This estimate is very close to the estimate in Analysis 3.1.1.

There was no evidence that the effects of vitamin C in Analysis 3.1.1 and Analysis 3.1.2 differ (P = 0.9, I^2 = 0%) for the difference between the subgroups.

In summary, regularly administered vitamin C, in doses ≥ 1 g/day, decreased the severity of colds that occurred during the supplementation period by 13%.

Primary outcomes: therapeutic studies

2. Duration of colds

Analysis 4.1 shows the effect of vitamin C on the duration of colds, when vitamin C administration started after the cold symptoms

began. In the therapeutic vitamin C groups, the cold episodes were shorter on average by -4.2% (-9% to 0.2%).

Analysis 4.1 shows the therapeutic trials stratified by dosage, so that low dose therapeutic studies with 1.5 to 4 g/day of vitamin C are shown as Analysis 4.1.1 and the Anderson 1974f arm with 8 g/day of vitamin C as Analysis 4.1.2. There was significant heterogeneity in estimates of these subgroups (P = 0.02; I^2 = 81%).

Doses of 1.5 to 4 g/day had no effect on cold duration with an estimate of -2.4% for the average difference between vitamin C and placebo groups (-7.1% to 2.3%; 3299 colds; 12 studies; I^2 = 0%; high quality evidence). The 8 g single day vitamin C dose shortened the duration of colds by 18.9% (5% to 32%; P = 0.006; 718 colds; one study; moderate quality evidence).

Furthermore, Anderson tested the effect of two different doses of therapeutic vitamin C. Anderson 1974f administered the 8 g/day dose only on the first day of the cold, and in the same study Anderson 1974e administered 4 g/day on the first day of the cold to another trial arm. The latter arm found a 9.8% difference between the vitamin C and placebo groups, which is close to half of the 18.8% effect in the 8 g/day arm, indicating dose dependency.

A second measure to assess the effect of vitamin C on common cold duration is by dichotomised duration. In their study, Anderson 1974a reported the number of 1-day common cold episodes and the total number of cold episodes. If a treatment increases the proportion of 1-day colds, it indicates that colds were shortened by the treatment.

In the 8 g/day arm Anderson 1974f, 46% (222/483) of colds were of only 1 day whereas others were longer. In the placebo group #4, 33% (143/437) of colds were of 1 day whereas others were longer. This means that the 8 g/day dosage for the first day of the common cold increased the proportion of 1-day colds by 13 percentage points (7 pp to 19 pp) corresponding to NNTB 7.5 (Analysis 4.2.1).

Compared with the 4 g/day therapeutic vitamin C arm, the 8 g/day arm had 6.6 percentage points (0 pp to 13 pp) higher frequency of 1-day colds, which also indicates dose dependency (Analysis 4.2.2). The Anderson 1974a had six vitamin C arms and three of them were only administered vitamin C regularly in doses of 0.25 to 2 g/day. When the 8 g/day therapeutic arm was compared with the three pooled regular vitamin C arms, the 8 g/day arm had 8 percentage points (3 pp to 13 pp; P = 0.003) higher frequency of 1-day colds, which indicates the robustness of the benefit in the 8 g/day therapeutic arm in the comparison against the other study arms with low doses of vitamin C (Analysis 4.2.3).

In summary, the therapeutic trials as a group did not provide consistent evidence that the duration of colds might be reduced with the protocols that have been tested in the vitamin C trials. However, 8 g/day of vitamin C on the first day of the common cold, administered as several small doses over the day, significantly shortened the mean duration of colds and increased the proportion of colds lasting for only 1 day. Since only one study arm has examined such a high dosage, the finding indicates need for further research, rather than implying firm practical conclusions.

Secondary outcomes: therapeutic studies

1. Severity of colds

Analysis 5.1 calculates the effect of therapeutic vitamin C on common cold severity when treatment started after cold symptoms began.

Analysis 5.1.1 consists of studies in which severity was measured by days confined to home or days off work. The severity of colds in the vitamin C groups was 11.9% lower compared with the placebo groups (95% CI -25% to 0.7%; 2641 colds; seven studies; I^2 = 0%; high quality evidence).

Analysis 5.1.2 covers the severity score findings and has only one trial with two vitamin C arms. No difference was found between vitamin C and placebo (95% CI -11% to 34%; 139 colds).

The two subgroups in Analysis 5.1 are inconsistent with the I^2 statistic of 69% yet the difference is explained by chance (P = 0.07).

In summary, seven published therapeutic studies found a 12% reduction in cold severity as measured by the pragmatic outcomes such as days confined to home or days off work, which is an estimate very close to the 13% estimate calculated from the 15 regular supplementation studies (see above). The single study reporting on the effect of vitamin C treatment on cold severity using a severity scale found no benefit. However, the study is small and the 95% CI extends up to an 11% benefit from vitamin C.

Dose-response relationship

There is no relation between vitamin C dose and the effect on common cold incidence. Three studies in Analysis 1.1.1 used low doses ranging from 0.25 to 0.6 g/day of vitamin C yet colds were prevented (Moolla 1996a; Peters 1993a; Peters 1996a), but all studies in Analysis 1.1.1 used ≥ 1 g/day of vitamin C without any overall effect. Thus, in the case of common cold incidence the dose seems to be a secondary issue to explain the effects of vitamin C, compared with the conditions of heavy short physical stress or the lack of it.

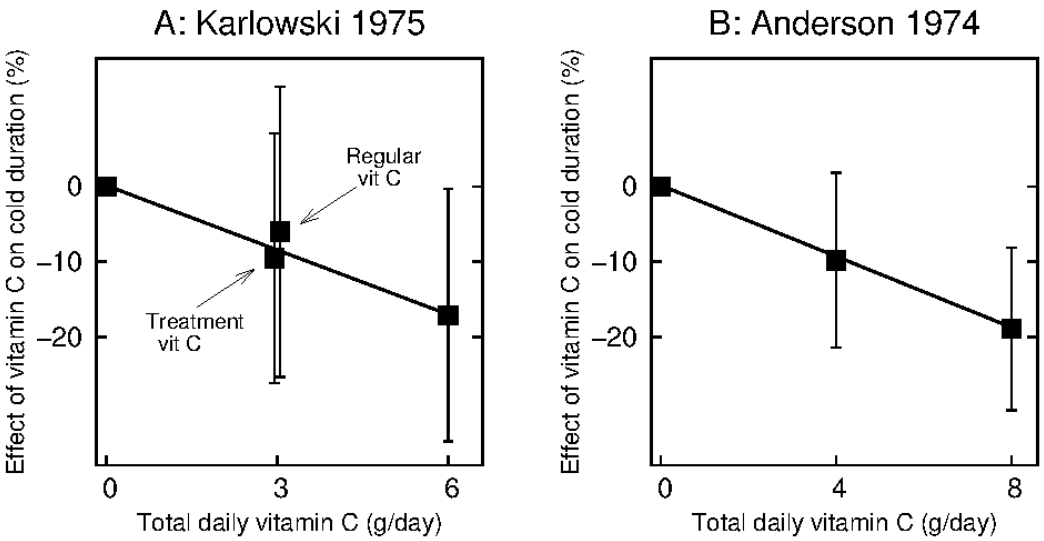
Nevertheless, vitamin C might have a dose-response effect on the duration and severity of colds when the vitamin is consumed during infection: the dosage might be more crucial under such conditions (see Description of the intervention). Although a dose-response relationship was proposed previously on the basis of comparing trials that had used 1 g/day versus ≥ 2 g/day, the comparison suffers from numerous differences between the trials (Hemilä 1999a). The most valid examination of dose-response is within a single study so that the virus distribution is similar in each trial arm and the outcome definition is identical.

Coulehan 1974a administered 1 g/day to children and observed a 12% reduction in common cold duration, and in parallel

Coulehan 1974b administered 2 g/day to other children and observed a 29% reduction in cold duration. The point estimates suggest a dose-response, however, the study was small and the 95% CIs overlap widely (Analysis 2.1).

In a 2×2 design, Karlowski 1975a randomised participants to 3 g/day regular vitamin C and to 3 g/day vitamin C treatment for five days when the participant caught a cold. They reported that "Volunteers taking placebo had colds of a mean duration of 7.14 days, while those taking 3 gm of ascorbic acid (groups 2 and 3) had colds of a mean duration of 6.59 days and those taking 6 gm had colds of a mean duration of 5.92 days. Thus, each 3-gm increment of ascorbic acid would appear to shorten the mean duration of a cold by approximately half a day." The four arms of the Karlowski trial are shown in panel A of Figure 6 with the 95% CIs of the comparison of the vitamin C groups with the placebo group (see calculation of the 95% CIs in Analysis 8.1). With inverse-variance weighting, the test for trend for a linear model gives P = 0.018. In a previous investigation, analysis of variance gave P = 0.040 for a linear trend (Hemilä 1999a).

Figure 6. Dose response relation in the Karlowski 1975 study (A) and in the Anderson 1975 study (B).



Anderson 1974a randomised participants to placebo and two vitamin C treatment arms. One treatment arm (arm #7) was administered 4 g/day of vitamin C only on the first day of the cold, and another (arm #8) was administered 8 g/day of vitamin C only on the first day of the cold. These arms are compared with the placebo arm #4 in panel B of Figure 6 with the 95% CIs of the comparison of the vitamin C groups with the placebo group. The 95% CIs are shown for the comparison with the placebo arm (see calculation in Analysis 8.2). With inverse-variance weighting, the test for trend in a linear model gives a P value of 0.013.

In summary, it seems plausible that there is a dose-response relationship in the effect of vitamin C on common cold duration in the dose range ≥ 1 g/day. Most studies in Analysis 2.2 used 1 g/day and most in Analysis 4.1 used 3 to 4 g/day of vitamin C. Therefore, the studies included in those meta-analyses might underestimate the potential effect of vitamin C if the therapeutic doses were 8 g/day and over.

Possible differences in the effects of vitamin C between subgroups

The regular supplementation study by Anderson 1972 is one of the largest that has been carried out. They found that the proportion of participants who were not confined to the house decreased by 8 percentage points in the vitamin C group (P = 0.01; Hemilä 2006a). In addition, they found that per episode the days confined to the house was 21% shorter in the vitamin C group) (Analysis 3.1). Together these combine to a 30% reduction in the days confined to the house per person (P = 0.001) (Anderson 1972). Such a large effect makes subgroup analyses informative.

Anderson 1972 reported that vitamin C decreased total days confined to house by 46% in participants who had contact with young children, but just by 17% in participants who did not have contact with young children. The difference between the two subgroups was significant (P = 0.016; Analysis 6.1). Anderson 1972 also reported that vitamin C decreased total days confined to house by 43% in participants who usually had two or more colds per winter, but just by 13% in participants who usually had zero to one cold per winter (P = 0.023 for the difference; Analysis 6.2).

In their therapeutic study, Anderson 1975a reported that vitamin C decreased total days confined to house by 40% in participants who had contact with young children, but just by 13% in participants who did not have contact with young children. So that study supports their 1972 subgroup finding, although the method of vitamin C administration was different. Anderson 1975a did not collect data about the usual frequency of colds and thus there are no data about the reproducibility of that subgroup difference. Children are a considerable source of respiratory viruses in the community and so there is probably substantial correlation between contact with children and the frequency of colds.

Constantini 2011a found a significant difference in the effect of vitamin C for boys compared with girls. However, the P value for the interaction in Analysis 6.4 is too conservative: because of the skew of the distribution of common cold duration, in the original report the interaction test was carried out on log-transformed duration and the interaction (P = 0.003).

Carr 1981a found that vitamin C had a beneficial effect on the duration of colds for twin children living apart, but not for twins living separately (P = 0.012, Analysis 6.3). This subgroup difference is probably explained by the swapping of tablets by twins living together.

In summary, the significant within-trial differences in the effect of vitamin C on the common cold indicate that there is no universal effect of vitamin C that is valid over the whole population. Instead, the size of the vitamin C effect seems to depend on various characteristics of people.

Trials with data unsuitable for meta-analyses

Table 1 shows the main findings in seven trials which did not report data suitable for meta-analysis. Two were supplementation trials and five were therapeutic trials.

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, which is one type of measure of the effects of vitamin C. Asfora 1977 wrote "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 the vitamin C and No. 8 was the placebo" (p 224). Regnier 1968 wrote "some of the subjects were able to recognize the fact that they were being treated with a placebo and refused to proceed with a useless type of therapy." (p 950). Furthemore, one therapeutic trial found a marginally significant benefit on the duration of "nose colds" (Brown 1945), whereas 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 benefit of vitamin C on the morbidity of sore throats and productive coughs, but the study was carried out in a Polaris submarine so that the conditions were special and the results cannot be directly extrapolated. In a post-World War II study in Germany, Scheunert 1949 reported less respiratory morbidity in persons administered a higher dose of vitamin C compared with a lower dose, but the study is poorly reported.

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 for those who took vitamin C.

Adverse effects from high-dose vitamin C intake

Our consideration of adverse effects is restricted to the largest studies that administered ≥ 1 g/day of vitamin C and had a follow-up period of > 50 person-years in the vitamin C group, and to the

two trials that administered the highest doses, 2 g/day of vitamin C, to children.

Anderson 1972 (102 person-years) administered 1 g/day of vitamin C and reported that "The occurrence of less severe side effects was not monitored in any detail, but at the end of the study, in answer to the question 'Did you have any unusual symptoms while you were taking the tablets?', the proportion answering yes was almost identical in the two groups (vitamin 12%, placebo 11%)." The number of cases is calculated from the percentages and shown in Analysis 7.1. In addition, Anderson reported that "Of the 182 subjects who dropped out of the study 28 did so because of suspected side effects, distributed almost equally between the vitamin (15) and placebo groups (13)" (p. 507).

Anderson 1974a (212 person-years) had an eight arm trial with two placebo groups and six vitamin C groups. Groups #1, #2 and #3 were administered 1 to 2 g/day vitamin C and their adverse effects were pooled, i.e. participants who dropped out of the study who gave side effects from the daily tablets as the reason for doing so. Groups #4, #7, and #8 received regular placebo and their adverse effects were pooled. These two groups are compared in Analysis 7.1.

Pitt 1979 (51 person-years) administered 2 g/day vitamin C for two months and reported that "approximately 15% of the recruits in each group reported symptoms that they believed were due to the pills." The number of cases is calculated from the percentages and shown in Analysis 7.1. In addition, "urticaria developed in one recruit in the vitamin C group, which subsided when the pills were withheld and recurred when he resumed taking his pills. He was instructed to stop taking his pills and was excluded from the final analysis. No other adverse effects were noted by either the recruits or the physicians seeing them at sick call" (p. 910).

When the findings of thes trials were combined, there is no evidence that vitamin C and placebo differ in their adverse effects over 365 person-years of observation time (Analysis 7.1).

Karlowski 1975a (76 person-years) administered 3 g/day of vitamin C for 9 months and reported "No important side effects could be determined in either the placebo or ascorbic acid groups" (p. 1041).

Briggs 1984 (103 person-years), Elwood 1976 (339 person-years) and Ludvigsson 1977a (76 person-years) did not report on adverse effects, which probably implies that no substantial adverse effects were observed.

Two studies administered 2 g/day vitamin C for three months to children. Bancalari 1984 wrote that "neither the medical histories conducted by the authors, nor the laboratory tests revealed any side effects of vitamin C". Coulehan 1974a wrote that "no children were eliminated because of adverse effects" (p. 7).

In summary, none of the large studies in adults that administered 1 g to 3 g/day of vitamin C, and neither of the studies with children that administered 2 g/day of vitamin C, reported substantial adverse effects from vitamin C. Urticaria in the patient mentioned by Pitt 1979 may reflect a real effect of vitamin C but the problem subsided when vitamin C as stopped. The frequency of this effect seems very low.

DISCUSSION

Most included studies were published in the 1970s; research interest declined thereafter (Figure 1). There was considerable variation in study methods and substantial heterogeneity in their results. Despite this, some robust conclusions could be drawn.

Common cold incidence

Trials in 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 CI (RR 0.99; 95% CI 0.93 to 1.04; Hemilä 1997b). Hemilä 1997b pooled common cold episodes occurring during the trial, whereas this review assessed numbers of participants who caght at least one cold as the measure of common cold incidence. Nevertheless, we arrived at the same conclusion for general community trials.

When the subgroup of people under heavy short-term physical stress was excluded, we found compelling evidence with a narrow CI that ≥ 1 g/day vitamin C supplementation had no effect on numbers of people who catch colds (RR 0.97; 95% CI 0.94 to 1.00). Karlowski 1975a administered the largest dose (3 g/day) yet found no difference in common cold incidence between the vitamin C and placebo groups (Hemilä 1997b).

Despite the narrow CI refuting any clinically meaningful average effect in the general community, some trials in the general community found evidence that vitamin C was beneficial in a subgroup of participants (see Results). Therefore, the overall negative finding should not be interpreted as evidence that no-one can benefit from regular vitamin C.

Trials with people under heavy short-term physical activity

Hemilä 1996d identified three trials with participants under severe acute physical stress. Pooling of results found that vitamin C supplementation halved the incidence of colds in this group. In this Cochrane Review, two later trials involving marathon runners (Moolla 1996a; Peters 1996a) and two very small trials with participants followed after an exercise challenge test (Carillo 2008a; Carillo 2008b); their inclusion did not change the pooled estimate of effect (RR 0.49; 95% CI 0.37 to 0.64). All seven trials in this group involved brief exposure to high physical stress with or without cold stress. The doses of vitamin C were not particularly

high (0.25 g to 1.0 g/day). The benefit for this subgroup could not be explained by high vitamin C doses. Higher doses in the general community have not affected the incidence of colds. The benefit in this subgroup seems to be explained by the exceptional conditions: heavy short-term physical activity.

The NNTB value in studies with people under heavy short-term physical stress range from three to 10 (Table 3), indicating that the prophylactic effect of vitamin C may be useful for a substantial proportion of physically active people.

Furthermore, in the general community, 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. Symptoms can also result from exercise-induced bronchoconstriction (EIB), symptoms caused by an injury to the airways because of exceptional ventilatory exertion (Parsons 2013).

In three RCTs, vitamin C supplementation halved FEV_1 decline caused by an exercise challenge test (Hemilä 2013a, Hemilä 2014). Common cold studies of physically-stressed people may have measured, at least in part, the effects of vitamin C on EIB rather than 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 is firm.

There is evidence that long-term physical activity leads to adaptation in the body (Powers 2011) and hence the effects of antioxidants may be greater for occasions involving short-term physical stress. Two trials involving participants undergoing two to three months of physical stress found no effect from vitamin C on common cold incidence (Constantini 2011a; Pitt 1979). It is therefore possible that vitamin C has beneficial effects for people undertaking short-term physical activity, but not long-term physical activity.

Possible role of marginal vitamin C deficiency on common cold susceptibility

Hemilä 1997b suggested that some early benefits of vitamin C supplementation in the UK my be explained by low dietary vitamin C intake at the time studies were conducted (Baird 1979; Bartley 1953; Glazebrook 1942). We excluded these trials from this review because vitamin C doses were less than 0.2 g/day. Low dietary vitamin C intake may also explain significant reduction in cold incidence eported by Charleston 1972, a study carried out in the UK, as one of the three studies that found significant decrease in common cold incidence with vitamin C administration (Analysis 1.1.1).

Hemilä 1997b calculated that in four UK studies involving men, vitamin C reduced common cold incidence (pooled RR 0.70; 95% CI 0.60 to 0.81) (Baird 1979; Charleston 1972; Clegg 1975; Glazebrook 1942). Another four UK trials found reductions in incidence of recurrent colds during the study period among men (pooled RR 0.54; 95% CI 0.40 to 0.74) but not in women (Hemilä 1997b). A later UK trial found a reduction in recurrent colds in a nine-week trial involving both men and women (RR 0.13; 95% CI 0.03 to 0.53) (Van Straten 2002; see Hemilä 2006a).

The most impressive trial in the UK group of studies was Baird 1979 - a randomised, double-blind, placebo-controlled trial. It was excluded because the vitamin C dose was 0.08 g/day. Dietary vitamin C intake level was estimated to be 0.05 g/day, which may explain the benefit of the low dose vitamin C supplementation. Methodological weaknesses lone did not explain the significant reduction in common cold incidence in men in Baird 1979 (RR 0.63; 95% CI 0.50 to 0.78; P = 0.004; Hemilä 1997b; Hemilä 2008).

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. Participants were selected on the basis of having had problems with colds during previous winters. Regarding the possible interaction between vitamin C supplementation and level of dietary vitamin C intake, Anderson 1972 is interesting because it found that vitamin C supplementation reduced "total days indoors" by 48% among participants in the vitamin C group who consumed < 3 oz (0.1 L) of fruit juice (common dietary source of vitamin C); whereas the reduction was 22% among those who drank more juice. A similar modifying effect with fruit juice was found in the therapeutic trial by Anderson 1975a.

Some early regular supplementation studies from Germany reported decrease in common cold incidence with vitamin C supplementation which may be explained by low dietary vitamin C intake after World War II. Scheunert 1949 was included in our review, but did not provide suitable data to enable meta-analysis. Renker 1954, Bendel 1955, and Dyllick 1967 were excluded because these studies did not use placebo. However, in addition to lack of blinding, reported benefits may also be attributed to low dietary vitamin C.

Duration and severity of colds: regular supplementation trials

Most published studies examined the effect of regular vitamin C supplementation (where vitamin C was administered every day during the study). Overall, regular vitamin C shortened cold duration by 9%.

It is plausible that the effect of vitamin C depends on dose and participants' age. There is insufficient data to perform dose-response analysis, but in a secondary analysis, we restricted studies to those in which the vitamin C dose was at least 1 g/day. We also analysed the effect of vitamin C separately on adults and children. In adults, $\geq$ 1 g/day of vitamin C shortened cold duration by 8%. In children, $\geq$ 1 g/day of vitamin C shortened cold duration by 18%. We found evidence of high level true heterogeneity between adults and children (Analysis 2.2).

Two regular supplementation studies indicate dose dependency. Karlowski 1975a and Coulehan 1974a used two different doses

within the same trial. Coulehan 1974a found that for school children, 2 g/day was associated with about twice the benefit of 1 g/day. Karlowski 1975a found that 6 g/day had double the benefit of 3 g/day in adults (Figure 6; Hemilä 1996a; Hemilä 1999a). These findings do not establish dose dependency, but support examination of doses over 1 g/day and comparing different doses.

Vitamin C doses ≥ 1 g/day decreased cold severity by 13% n average (Analysis 3.1; 15 studies). The effect estimate was essentially the same when severity was measured as "days off work or school or days indoors" compared with measuring by severity scales.

These findings point to a definite physiological effect from regular vitamin C supplementation on common cold duration and severity, yet the practical significance of these findings is not clear. For people in the general community, 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 that occur a few times per year for adults and half a dozen times per year for children (Monto 1974).

These effect estimates are not trivial, but rather than regular supplementation, it would seem much more fruitful to consider the possible benefits of therapeutic supplementation and examine if an equivalent benefit might be achieved through appropriate therapeutic supplementation. In any case, it is possible that some restricted groups of people might benefit from regular vitamin C administration. See Effects of interventions and *Complications of the common cold* in Discussion

Duration and severity of colds: therapeutic trials

Regular supplementation trials have unambiguously shown that vitamin C affects cold duration and severity without changing the incidence in the general population, and accordingly therapeutic administration of vitamin C starting immediately after the first symptoms, rather than taking vitamin C all the time.

In therapeutic trials 1.5 to 4 g/day of vitamin C did not shorten cold duration (Analysis 6.1). However, 8 g/day shortened cold mean duration by 19% and increased the proportion of short one day colds by 13 percentage points (NNTB 7.5). If confirmed, the latter effect has substantial practical importance.

Therapeutic 1.5 to 4 g/day vitamin C was associated with a 12% reduction in days indoors or days off work. This estimate is consistent with the estimate calculated from the 15 regular vitamin C supplementation studies: a 13% decrease in common cold severity. However, the only therapeutic study that measured common cold severity using a scale did not find any benefit from 3 g/day of vitamin C (Audera 2001a), which is inconsistent with the regular supplementation studies on severity scores, which found a 13% decrease with vitamin C.

Methodological problems in therapeutic trials

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

Cowan 1950a administered vitamin C over two days and found no effect on common cold duration. Elwood 1977, Tyrrell 1977a and Audera 2001a administered vitamin C over three days, and they all found that vitamin C had no effect on common cold duration. In these studies, the colds lasted for five to eight days and therefore the two to three day vitamin C administration might have been too short. Nevertheless, Tyrrell 1977a found a 40% reduction (P = 0.04) in the incidence of recurrent colds in men during the trial indicating a beneficial effect in protecting against later colds during the trial (Hemilä 1997b).

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 these five-day studies suggest that periods of two to three days might be too short for vitamin C to produce unambiguous benefits. However, Abbott 1968 used up to two weeks 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 (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 common cold 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 vitamin C and the other medications. 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 significant benefit from 8 g vitamin C when administered on the first day of illness only. This was consistent with the notion that rapid initiation with high doses may 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 1950a; Elwood 1977; Tyrrell 1977a). 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 sup-

plemental study drug to be taken" and so 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 an unknown 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. 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, data on this factor are limited.

Implications of the therapeutic trials

The larger effect observed using 8 g compared with 4 g as a single dose in Anderson 1974f and the dose dependency seen in Karlowski 1975a (Figure 6; 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 compared with 1 g/day in Coulehan 1974a, and the greater mean effect of 2 g/day compared with 1 g/day for children (Hemilä 1999a) 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 (Monto 1974). Furthermore, the effect of regular vitamin C on the duration of colds was substantially greater in children, up to 18% reduction in duration for 1 to 2 g/day, compared with the 8% effect in adults, which also should motivate therapeutic trials in particular with children. Finally, although a tablet is a practical and the most common form of administering vitamin C, administration of vitamin C powder directly into the nose has also been proposed (Gotzsche 1989).

The regular supplementation trials have shown unambiguously that vitamin C has effects on the duration and severity of colds, and it seems reasonable to extrapolate that an optimal treatment protocol with vitamin C might also have some benefit against colds.

Furthermore, the results of controlled trials and the pooled results of trials apply to the average of the groups. We expect variation in the magnitude 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 would seem reasonable for common cold patients to test soon after the onset of symptoms whether vitamin C is beneficial for them on an individual basis.

Possible sex differences in the effects of vitamin C on the common cold

In their study involving UK students, Baird 1979 found a significant difference between males and females in the effect of vitamin C on common cold incidence (P = 0.0001 for the interaction; Hemilä 2008). In their study with adolescent swimmers, Constantini 2011a found a significant difference between males and females in the effect of vitamin C on common cold duration and severity (P = 0.003 for the interaction for both outcomes) (Analysis 6.4). In both cases, vitamin C was beneficial for males, but not for females. In both studies the evidence of interaction between vitamin C effect and sex is statistically strong. In addition, Tyrrell 1977a found that therapeutic vitamin C prevented colds in males but not in females, and a meta-analysis suggested a difference between males and females in the UK (Hemilä 1997b). Although there are independent lines of evidence indicating that vitamin C is more effective for males, it is not clear how far these findings can be generalised.

Trials with no data suitable for meta-analysis

Seven studies did not report data suitable for meta-analysis (Table 1). Most of these trials are technically satisfactory and should not be dismissed.

Experimental rhinovirus infection studies

Three experimental studies have examined the effect of vitamin C on experimentally induced common cold infections (Table 2). These trials differed in method of exposing volunteers to the infecting virus. Dick 1990, which has only been reported in abstracts, paid careful attention to cold severity experienced by those who were infected by fellow volunteers and 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 people in the placebo group. The fragmentary descriptions of the Dick 1990 indicate a biological effect of vitamin C on experimentally caused colds. Schwartz 1973 found a reduction in common cold severity in vitamin C group participants, also indicating a biological effect.

Findings from the excluded studies

Exclusion of a trial does not mean it was uninformative. We used a limit of 0.2 g/day for vitamin C as a pragmatic choice. If trials with lower doses report negative results, these may be attributed to the low dose. However, if a low dose caused an effect in a methodologically valid trial, the effect may be explained, for example, by a particularly low dietary intake level corresponding to marginal deficiency. Similarly, if a trial that had no placebo found no difference between intervention and control groups, it is not reasonable to explain the lack of difference by the placebo effect. Because we

were interested in vitamin C, we excluded multiple antioxidant trials from our analyses. However, if a multi-antioxidant formula has no effect on the common cold, it seems justified to conclude 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 had a beneficial effect, we could not draw specific conclusions because effects could be caused by any single or combination of antioxidants.

Cohort studies on vitamin C and the common cold

Analysis of the regular supplementation studies indicates that vitamin C may have an effect on common cold incidence under certain specific conditions (e.g. short-term physical stress) and for restricted subgroups of people, see the Effects of interventions. However, the average effect in regular supplementation studies with the general community has been null.

We do not consider that cohort studies might capture the potential effects of vitamin C against the common cold in narrow subpopulations. Confounders are typically adjusted for in cohort studies, allowing calculation of a uniform effect across the population. However, if vitamin C has effects on specific conditions or limited subgroups of people, the assumption of a uniform effect is not valid. Randomised trials may give relevant information about subgroup differences in treatment effects as shown in Analysis 6. Similar subgroup analyses in cohort studies are much more challenging or impossible because of the close correlations between dietary variables with each other and with numerous other lifestyle factors (Smith 2007).

One cohort study reported that higher dietary vitamin C intake had a marginally significant negative association with common cold incidence in females, but not in males (Fondell 2011). However, such an association may result from residual confounding. Two other cohort studies did not find a negative association between dietary vitamin C intake and colds (Hemilä 2002; Takkouche 2002).

Complications of the common cold

Given the strong evidence that prophylactic vitamin C shortens the duration of colds and alleviates their severity, it is possible that vitamin C might influence some of the complications of the common cold. A systematic review found three studies which reported a benefit of vitamin C for people with common cold-induced asthma (Hemilä 2013c). Thus, although we do not consider that an ordinary person should take vitamin C regularly in order to protect against colds, it is possible that some asthmatics might benefit from vitamin C during periods of higher cold risk such as during winter. In their common cold studies, Anderson 1972 and Elwood 1976 found that vitamin C reduced the incidence of respiratory symptoms originating from lower anatomical regions, see section 1 in Effects of interventions. It is not clear whether those findings are explained by effects on viruses or on asthma-type irritation caused by the viruses, but they are closely associated. Other complications of common colds are bacterial respiratory infections. Pitt 1979 studied 674 marine recruits during an eight-week period using 2 g/day of vitamin C. There was no difference in common cold incidence, only a 2% shorter 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 and only one of these was in the vitamin C group (P = 0.044, Hemilä 2004; Hemilä 2013b). Similarly, Glazebrook 1942 found a 17% decrease in the incidence of the common cold with vitamin C administration, but a 100% decrease in the incidence of pneumonia (P = 0.01, Hemilä 2004). Kimbarowski 1967 studied patients with influenza A and observed an 80% decrease in the occurrence of pneumonia in them (P = 0.02, Hemilä 2004). Under some conditions, vitamin C may affect other respiratory infections as complications of colds, or independently of colds (Hemilä 1999b; Hemilä 2013b). Some early authors suggested that vitamin C might prevent sinusitis and otitis media (Miegl 1958), but to our knowledge there are no data from studies with control groups.

Heterogeneity in the effects of vitamin C

A major finding was statistically highly significant heterogeneity in the effect of vitamin C supplementation on common cold incidence ($P = 10^{-6}$ for divergence among the three subgroups and P = 0.02 overall), indicating that the effect of vitamin C on common cold incidence cannot be universally null although the point estimate over all studies is close to the null value (Analysis 1.1). Furthermore, Anderson 1972 found about an 8 percentage point 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 (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 during winter and in this respect the participants do not represent the average population. Coulehan 1974a studied Navajo school children and found a 16 percentage points 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 there was a sub-population which benefited from vitamin C, even though there is strong evidence that regular vitamin C does not affect the average incidence of colds in the general community (Analysis 1.1).

Furthermore, in the regular supplementation study, Anderson 1972 found statistically significant interaction between the effect of vitamin C on days confined indoors per person and contact with children (Analysis 6.1) and with the usual frequency of

colds (Analysis 6.2). In the therapeutic supplementation study, Anderson 1975a also found greater effect of vitamin C in people who had contact with children, but they did not collect data on the frequency of usual colds. Children are a considerable source of respiratory viruses in the community and therefore contact with children and the frequency of colds have a reasonable correlation. If the effects of vitamin C vary substantially between different subpopulations, the heterogeneity of the effect means that the goals and interpretations of new studies should be considered carefully. Further trials should try to identify and characterise the population groups or living conditions in which vitamin C may be beneficial, rather than re-examining the effects of vitamin C on common cold incidence in ordinary Western people for whom the numerous regular supplementation trials already published have not found any substantial overall preventive benefits from daily supplementation (Analysis 1.1).

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 2009). There is very strong evidence of heterogeneity in the effect of vitamin E on common cold incidence (Hemilä 2006b) and on pneumonia incidence (Hemilä 2011a). Accordingly, we should similarly expect heterogeneity in the effects of antioxidant vitamin C on respiratory infections.

The notion that various factors may modify the effects of antioxidants on infections is fundamentally important. We should avoid broad generalisations from an individual trial, irrespective of whether the finding is positive or negative, and whether or not the trial is large and carefully conducted, or not.

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 RCTs 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 to modest 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 3). 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; Hemilä 2006c). Furthermore, in most other trials, placebo contained citric acid which cannot be distinguished from ascorbic acid by taste, and in many trials the indistinguishability of the vitamin C and placebo preparations was explicitly stated (Figure 3). Chalmers' proposal was refuted by the indistinguishability of vitamin C and placebo preparations in numerous double-blinded trials.

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

From the clinical trial methodology point of view, most trials analysed were very good quality (high internal validity). In contrast, the generalisability (external validity) of the trial findings is limited, in particular, because of variations in vitamin C intakes in placebo and vitamin C groups.

Some problems in the interpretation of vitamin C studies

Vitamin C levels in the placebo and vitamin C groups

One particular problem in the meta-analysis of vitamin C trials arises from the fundamental difference between vitamin C and prescription drugs such as antibiotics. In studies on ordinary drugs, it is possible to select a control group which has no intake of the drug, rendering the interpretation of results relatively simple. In contrast, it is not possible to select control participants who have no intake of vitamin C and no vitamin C in their system. This causes confusions in the interpretation of vitamin C studies (Hemilä 2006a).

Before considering the variations in vitamin C levels in the common cold studies, we briefly summarised pharmacokinetics of vitamin C. In healthy people, plasma vitamin C levels become quite saturated with 0.2 to 0.5 g/day of vitamin C, so that there is little further increase in the plasma vitamin C level if the vitamin C dose is increased up to 2.5 g/day (Levine 1996). In contrast, when vitamin C dosage is less than 0.2 g/day, there is a steep decline in plasma vitamin C levels with a decrease in dosage. For example, when the vitamin C dose is increased from 0.06 to 0.2 g/day, the level of vitamin C in plasma is approximately tripled (Levine 1996). Average intake of vitamin C in the USA is currently about 0.1 g/day (IOM 2000 p. 154), which means that half of the population has a lower intake. Furthermore, particularly low levels of vitamin C intake are not just of historical relevance. In the UK, 25% of men and 16% of women from low-income populations had vitamin C deficiency "(< 11μmol/L in plasma) (Mosdol 2008), and in the USA, 7% of healthy middle-class participants had vitamin C deficiency (Schleicher 2009). Hence, if common

cold incidence is increased by low intake of vitamin C, this issue might be important in population groups with particularly low vitamin C intakes.

All vitamin C trials compare two different intake levels, the lower level being obtained from the diet, and usually not estimated at all. This hampers the comparison of different trials and the generalisation of their results. In some studies the dietary intake has been high. Another problem in some vitamin C studies has been the addition of vitamin C to the placebo groups. The rationalisation for this was to exclude the possibility that observed effects of large doses might be explained by treating marginal deficiency (Hemilä 2006a). These problems lead to contamination, which has been apparent in 15 of the 71 included studies (Figure 3).

For example, there is a 10-fold difference in dietary vitamin C intake between the control groups in Baird 1979 and Peters 1993a, at the levels of 0.05 and 0.5 g/day, respectively. Both are control groups of vitamin C trials, and both studies reported benefits of vitamin C administration (Table 4). Another example of a particularly high dietary vitamin C intake is Miller 1977a. At the start of the study, the participants excreted 0.2 to 0.3 g/day of vitamin C in their urine, and the level of intake must have been even higher, since not all vitamin C is absorbed by the intestines, and only part is excreted in urine.

In a reasonable vitamin C supplementation study, the level of vitamin C intake in the control group should be close to the recommendations, such as 40 mg/day which is the recommended intake in the UK (FSA 2003) or 75 to 90 mg/day which is the recommendation in the USA (IOM 2000). In this respect, the Peters 1993a and Miller 1977a studies and several other studies are not informative for a population complying with the recommendations.

Carr 1981a administered 70 mg/day and several other studies administered lower doses (Table 4). Apparently, the purpose of administering vitamin C to the placebo group was to remove the possibility that any observed benefits of high doses ($\geq$ 1 g/day) might be explained by the treatment of marginal deficiency. However, we do not agree with the viewpoint that reduction of common cold incidence in people with marginal vitamin C deficiency would be an unimportant question. As noted above, there are population groups that have particularly low vitamin C intake levels. Therefore supplementation of the placebo group may camouflage potential benefits for people who have marginally low vitamin C intakes.

Finally, the dosage in the vitamin C groups has varied dramatically. At the extreme, Karlowski 1975a and Asfora 1977 administered up to 6 g/day of vitamin C to their participants and Anderson 1974a administered up to 8 grams of vitamin C on the first day of a cold. In contrast, Cowan 1942 administered just 0.025 g/day as their lower supplementary dose and Baird 1979 administered 0.08 g/day to their vitamin C groups. However, the Karlowski 1975a and Cowan 1942 studies were shown side by side, for example, in the influential review by Chalmers 1975 without any attention being given to the 240-fold difference in the vitamin C dosage (Table 4).

These variations in the dietary vitamin C intake, in vitamin C supplementation of the placebo groups, and in doses of vitamin C administered to the vitamin C groups lead to paradoxes. For example, the placebo (sic!) group of Peters 1993a received 0.5 g/day of vitamin C in their diet, whereas the vitamin C (sic!) group in Baird 1979 received only 0.13 g/day (diet 0.05 g/day and supplement 0.08 g/day together) (Table 4). Thus, vitamin C intake in the placebo group of the former trial was four times higher than the vitamin C intake in the vitamin C group of the latter trial. Furthermore, Baird 1979 administered 0.08 g/day to the vitamin C group, whereas Carr 1981a administered 0.07 g/day of vitamin C to the placebo group. Thus, the dose was essentially the same but it was administered to the opposite groups of the vitamin C vs. placebo comparison.

The great variation in the vitamin C doses in diet (including vitamin C given to the placebo groups) and in the vitamin C dosage in the vitamin C groups probably explains part of the variation in the results of the trials. This great variation in vitamin C dosages cannot lead to false positive differences between placebo groups and vitamin C groups. In contrast, the great variations lead to less accuracy in the pooled differences so that the true differences between proper placebo and vitamin C groups are probably greater than the estimates calculated in our review.

Recently Padayatty 2014 commented: "Many studies of vitamin supplements are flawed ... because vitamin concentrations at enrolment are usually not measured. It is predictable that study populations include those with low concentrations of vitamins, subclinical deficiencies, or both and others who are vitamin replete. These groups are distinguishable only if baseline, and preferably post supplementation, vitamin concentrations are measured. Without measurement, assuming that all participants are vitamin and mineral replete is unsafe. Benefits in one group may be hidden by no effect in the other... To put the problem in perspective, studies to test antihypertensive therapy would not be done without measuring blood pressure at enrolment. To treat everyone regardless of blood pressure would be illogical. However, this strategy has been persistently pursued in evaluating vitamin supplements."

Possible non-compliance of children

Although the estimated effect of regular vitamin C supplementation for children is double the estimated effect in adults (-18% versus -8%, Analysis 2.3), it is possible that the estimates for children are biased downwards because of children switching tablets. In the Miller 1977a study with twins children, among placebo boys the urinary vitamin C excretion increased significantly during the study by 131 mg/day (by 62%; P = 0.03) whereas the increase in girls was just 27 mg/day. Probably, the twin girls obeyed the instructions better than the twin boys, who may have swapped their tablets.

Coulehan 1974a wrote that "older P[lacebo] children of both sexes had significantly higher blood ascorbic acid levels in March than in January, suggesting that some P children may have been switching tablets at times with [vitamin] C children or getting excess ascorbic acid in some other way" (p. 9).

Carr 1981a reported their results separately for twins living apart and twins living together and there was a significant interaction between the living arrangment and the effect of vitamin C (Analysis 6.3). Vitamin C was beneficial for those living apart, but not for those living together. Furthermore, the duration of colds in both the vitamin C and placebo twins living together (5.4 days), was between the durations in the placebo twins living apart (7.5 days) and vitamin C twins living apart (4.9 days), which is consistent with vitamin C doses of twins living together being between the two groups of twins living apart. Therefore the 35% decrease in common cold duration and severity among twins living apart seems a more valid estimate of effect compared with no effect among the twins living together.

Safety of vitamin C

None of the vitamin C common cold trials that reported on adverse effects have reported that vitamin C might be harmful in doses that were tested. The largest trials did not find more adverse effects in the vitamin C groups (Analysis 7.1).

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; IOM 2000 pp. 155-61). 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 1961 carried out his trial with school children in a skiing school in the Swiss Alps. Such children are not a representative selection of the general population. In our analysis, Ritzel 1961 is included in the group of seven trials with participants exposed to short-term physical activity (Analysis 1.1) which highlights the special characteristics 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 1997a; 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 for vitamin C in the 1970s was the stimulus for the wave of methodologically good trials (Figure 1), which now enable us to understand better, yet still poorly, the complex role that vitamin C plays in the defence against the common cold. Significant uncertainties still persist, which further research should clarify.

Persisting lack of interest since 1975

Regular vitamin C halved the incidence of colds in people with short-term physical endurance/activity (Analysis 1.1), and shortened the duration and alleviated the symptoms of the common cold (Analysis 2.2; Analysis 3.1) which indicates that the vitamin has genuine physiological effects against colds. Evidence from therapeutic studies is unambiguous, but 8 g/day for a single day shortened the duration of colds significantly (Analysis 4.1); furthermore there is more methodological variation in the therapeutic trials so that a delay in the treatment initiation or a short duration of treatment might lead to a false negative finding.

Most of the studies that contributed to our analyses were published in the 1970s (Figure 1) and given the strong evidence that vitamin C is effective against colds, the evaporation of interest in the topic after the middle of 1970s is puzzling. As described in the Description of the intervention section, the disappearing interest can be explained by three papers published in 1975 by Chalmers 1975, Dykes 1975, and Karlowski 1975a which concluded that vitamin C was not effective against colds. The three papers have

been cited in nutritional recommendations, in textbooks of nutrition and infections diseases, and in numerous reviews on the common cold as evidence that vitamin C is not effective against colds (Hemilä 2006a). Furthermore, the Karlowski 1975a trial has been frequently cited by statisticians, epidemiologists and clinical trialists as an example of the placebo effect in action (Hemilä 2006a). As described in the Description of the intervention section, the three papers have been shown to be erroneous, so that the evaporation of interest in the late 1970s can be explained by those erroneous papers.

This lack of interest after the Chalmers 1975 and Dykes 1975 reviews, was perpetuated by two more important reviews on vitamin C and the common cold by Truswell 1986 and Kleijnen 1989. Most studies analysed in our review were published in the 1970s and their results were available in the 1980s. The Truswell 1986 review was very short, but it was published in the New England Journal of Medicine and therefore the review was highly influential. Truswell 1986 did not present any figures or P values of the original reports, merely providing subjective comments about the trials. At the end of his mini-review, Truswell 1986 stated that "In another five combined trials there appeared to be slight amelioration of symptoms, which was not statistically significant." However, the five papers cited by him contained six trials and not five, and all the six trials reported a statistically significant benefit in at least one of the reported outcomes, see Hemilä 1996c and Hemilä 2006a. The Kleijnen 1989 review was influential ecause it was used as an example in an educational paper on systematic reviews in BMJ by Knipschild 1994. However, Kleijnen 1989 used an arbitrary scoring system for the inclusion of studies and he did not carry out any statistical analysis of the included studies, see Hemilä 2006a. Hence, the evaporation of interest in the topic did not occur because of placebo-controlled studies consistently finding negative results, instead the studies published in the 1970s found overall positive results.

Potential biases in the review process

Our searches of databases for trials meeting the criteria for our review were exhaustive and we also read reference lists of several reviews, such as Briggs 1984, which contains 413 references to papers related to vitamin C and infections, and Kleijnen 1989, which contains 73 references to papers related to vitamin C and the common cold. Although there might be unpublished trials, or trials published in journals or books which are difficult to access, it seems unlikely that we could have missed large controlled trials.

AUTHORS' CONCLUSIONS

Implications for practice

The lack of effect of regularly administered vitamin C on common cold incidence in the general population throws doubt on the usefulness of this practice. In special circumstances, in which people are engaged in extreme physical exertion, vitamin C supplementation may halve the incidence of colds, but caution should be exercised in generalising this finding. There was some evidence that vitamin C supplementation may be beneficial for people who have particularly low dietary intake of vitamin C.

The regular supplementation trials found that $\geq$ 1 g/day vitamin C reduced common cold duration by 8% in adults and by 18% in children; and that $\geq$ 1 g/day vitamin C reduced common cold severity by 13%.

The practical relevance of these findings is not clear. In our opinion, these findings do not justify regular supplementation in its own right in the general population. Nevertheless, it is possible that some people, such as those with asthma, might benefit from regular vitamin C during periods of high risk of colds, such as during winter.

The therapeutic studies providing 1 g to 4 g/day vitamin C did not find beneficial effect on common cold duration. However, a single study providing 8 g/day on the first day of the common cold found a 19% reduction in common cold duration. The latter finding indicates a need for further research, rather than implying firm practical conclusions.

Therapeutic studies found a marginally significantly 12% reduction in days confined indoors or off work which is an estimate very close to the estimate calculated from the regular supplementation trials.

Given the consistent effects of vitamin C on common cold duration and severity in the regular supplementation studies, the significant effect of therapeutic 8 g/day, and the similar effect on days indoors and off work in the therapeutic studies, it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them, especially given the safety and low cost of the vitamin.

Implications for research

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

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

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

ACKNOWLEDGEMENTS

This review was initiated in the mid 1990s by Bob Douglas and the first version published in 1998 (Douglas 1998). Bob Douglas screened the retrieved papers against inclusion criteria, appraised the quality of papers, abstracted data, entered data into Review Manager, analysed and interpreted the data, wrote the first version of the review and participated in several updates (Douglas 1998; Douglas 2004; Douglas 2007).

Harri Hemilä took charge of the review in 2004. In 2012 Professor Douglas retired from further view updates. We (Hemilä and Chalker) are very grateful to Professor Douglas for his role in initiating and updating this review.

Professor Charles McGilchrist and Dr Keith Dear provided valuable statistical advice, and Ms Robyn Savory and Ms Leonie Hoorweg undertook a range of assistant duties for Douglas 1998. Mr Bob Galloway translated a number of papers. Ron D'Souza helped to assemble the update review database and assisted Bob Douglas in re-screening all papers and quality assessment, but decided to step down 2007. Barbara Treacy prepared overviews and summaries of published studies for Douglas 1998, and participated in updates, but stepped down in 2009.

English translations of Bessel-Lorck 1959; Ritzel 1961; Kimbarowski 1967 and Bancalari 1984 were kindly arranged by Eva Wintergerst from Roche Consumer Health LTD, Kaiseraugst, Switzerland.

English translations of Korbsch 1938; Renker 1954; Bendel 1955; Miegl 1957; Miegl 1958 and Dyllick 1967 were kindly arranged by Silvia Maggini from Bayer Consumer Care AG, Basel, Switzerland.

The review authors wish to thank the following people for reviewing the 2013 update: Bahi Takkouche, Anne Lyddiat and Mark Jones; and Sarah Thorning for her help with literature searches.

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* *Indicates the major publication for the study*

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; age range 0 to ≥ 66 years, 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	There was no unambiguous outcome. The authors wrote: "The following records were made: age and sex, smoker or non-smoker, and month of onset of the cold. Assessments were then made of improvement in those of the following symptoms which were present: sore throat, stuffy nose, sneezing, watery nasal discharge, purulent nasal discharge, headache, and aching back and limbs. In addition, temperature was recorded and a note made of whether the patient was confined to bed and whether any other treatment was given. These records were made daily and a four-point scale was used to record the severity of individual symptoms." No data suitable for meta-analysis. See Table 1.
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment ... was determined by random selection." (p 442)
Allocation concealment (selection bias)	Low risk	"This was a double-blind comparison" (p 442)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"This was a double-blind comparison" (p 442)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"This was a double-blind comparison" (p 442)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates were 0% (0/147) in the vitamin C group and 0.8% (1/123) in the placebo group. One patient had to omit treatment after four days

Abbott 1968 (*Continued*)

		on the placebo, because of nausea (p 445)
Selective reporting (reporting bias)	Unclear risk	Reported poorly, no unambiguous outcome. Included in Table 1
Vitamin C and placebo indistinguishable?	Low risk	"similar placebo tablets were prepared" (p 442)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Anderson 1972

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 months
Participants	Canadian adults from a variety of occupations and age groups (mean age in vitamin group 28.8 years, range 10 to 64; mean age in placebo group 28.9 years, range 10 to 65) , both sexes (44% males in vitamin c group, 43% males in placebo group) (p 504). 407 vitamin C; 411 placebo. Recruitment specified participants should normally experience at least 1 cold in the winter months
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) (Table II, p 505)
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Subjects were allocated to vitamin and placebo in a strictly double-blind randomized manner" (p 504)
Allocation concealment (selection bias)	Low risk	"Subjects were allocated to vitamin and placebo in a strictly double-blind randomized manner" (p 504)
Baseline balance	Low risk	Table 1 shows balance for age, sex, student status, smokers, cold frequency, contact with young children, frequency in crowds, consumption of fruit juices
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Subjects were allocated to vitamin and placebo in a strictly double-blind randomized manner" (p 504); "... the code was not broken until after all the data had been

Anderson 1972 (*Continued*)

		transferred to punch cards and initial tabulations carried out." (p 504)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Subjects were allocated to vitamin and placebo in a strictly double-blind randomized manner" (p 504); "... the code was not broken until after all the data had been transferred to punch cards and initial tabulations carried out." (p 504); "[blinded] Subjects were instructed to record each day whether they were sick or well" (p 504-5),
Incomplete outcome data (attrition bias) All outcomes	Low risk	182 drop outs out of initial full complement of 1000. Almost all were contacted and most dropped out because of loss of interest or inability to remember to take tablets. (p 504) It is not clear whether the drop outs were evenly distributed between the vitamin c and placebo groups, but the relative distribution of recorded characteristics was the same as the main group (p 505). There were 28 dropouts "because of suspected side effects, distributed almost equally between the vitamin (15) and placebo groups (13)." (p 507)
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
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 ..." (p 504)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Anderson 1974a

Methods	Double-blind RCT. Duration 3 months 4 regular supplementation, 2 treatment and 2 placebo arms This entry is the regular supplementation arm #1 The other vitamin C arms are listed as Anderson 1974a-e
Participants	Canadian adults, both sexes, recruited from staff of large hospitals and business organisations (p 32) Data for this arm include 277 vitamin C; 285 placebo; 48% male; mean age 34.5 "only those persons who usually suffered at least one episode of illness between December

Anderson 1974a (*Continued*)

	and March ... were accepted." (p 32)
Interventions	1 g/d vitamin C and 4 g/d at onset of illness on the 1st day only Therapeutic tablets after onset: "16 tablets [0.5 g] (two every hour) on the first day of any illness" (p 32)
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1) (Table II, p 33)
Notes	Problems with the placebo group #6; see p 40 (Table 36) 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 "A labelling error had occurred in two of the 176 batches" (p 33) SD for duration was not published and it was imputed, see Methods Funding: Hoffmann-La Roche Ltd. supplied the tablets.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Bottles were numbered in accordance with a computer-generated list of numbers randomized in groups of eight, then given out in consecutive order as subjects registered" (p 33)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 31)
Baseline balance	Low risk	Compared with placebo group #4, Table 2 shows balance for age, sex, smoking, frequency of usual cold episodes, usual days indoors, usual days off work, contact with children, frequency in crowds, daily juice consumption
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 31)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded "subjects were asked to complete a checklist of the symptoms present on each day of illness" (p 33)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rates were 37% (163/440) in the vitamin C group and 35% (155/440) in the placebo group #4. Of the total 1171 subjects who dropped out of the study, 74

Anderson 1974a (*Continued*)

		cited side effects as the reason (p 35). One of the commonest reasons for dropping out was difficulty in swallowing the large tablets (p 34)
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"All three tablets were of a similar size and shape, and an initial 'taste test' carried out with the help of a number of colleagues demonstrated that they were reasonably well matched in flavour, texture and appearance" (p 32)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Anderson 1974b

Methods	See Anderson 1974a. Regular supplementation arm #2
Participants	275 vitamin C; 52% male; mean age 34.5
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1) (Table II, p 33)
Notes	Problems with the placebo group #6; see p 40 (Table 36) 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 "A labelling error had occurred in two of the 176 batches" (p 33) SD for duration was not published and it was imputed, see Methods Funding: Hoffmann-La Roche Ltd. supplied the tablets.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Bottles were numbered in accordance with a computer-generated list of numbers randomized in groups of eight, then given out in consecutive order as subjects registered" (p 33)

Anderson 1974b (*Continued*)

Allocation concealment (selection bias)	Low risk	"double-blind" (p 31)
Baseline balance	Low risk	Compared with placebo group #4, Table 2 shows balance for age, sex, smoking, frequency of usual cold episodes, usual days indoors, usual days off work, contact with children, frequency in crowds, daily juice consumption
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 31)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded "subjects were asked to complete a checklist of the symptoms present on each day of illness" (p 33)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rate was 38% (165/440) in the vitamin C group and 35% (155/440) in the placebo group #4
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"All three tablets were of a similar size and shape, and an initial 'taste test' carried out with the help of a number of colleagues demonstrated that they were reasonably well matched in flavour, texture and appearance" (p 32)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Anderson 1974c

Methods	See Anderson 1974a. Regular supplementation arm #3
Participants	308 vitamin C; 46% male; mean age 34.4
Interventions	2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1) (Table II, p 33)

Anderson 1974c (*Continued*)

Notes	Problems with the placebo group #6; see p 40 (Table 36) 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 "A labelling error had occurred in two of the 176 batches" (p 33) SD for duration was not published and it was imputed, see Methods Funding: Hoffmann-La Roche Ltd. supplied the tablets.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Bottles were numbered in accordance with a computer-generated list of numbers randomized in groups of eight, then given out in consecutive order as subjects registered" (p 33)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 31)
Baseline balance	Low risk	Compared with placebo group #4, Table 2 shows balance for age, sex, smoking, frequency of usual cold episodes, usual days indoors, usual days off work, contact with children, frequency in crowds, daily juice consumption
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 31)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded "subjects were asked to complete a checklist of the symptoms present on each day of illness" (p 33)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rate was 30% (132/440) in the vitamin C group and 35% (155/440) in the placebo group #4
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"All three tablets were of a similar size and shape, and an initial 'taste test' carried out with the help of a number of colleagues demonstrated that they were reasonably well matched in flavour, texture and appearance" (p 32)

Anderson 1974c (*Continued*)

Contamination	Unclear risk	There was insufficient reporting to enable assessment

Anderson 1974d

Methods	See Anderson 1974a. Regular supplementation arm #5
Participants	331 vitamin C; 45% male, mean age 34.3
Interventions	0.25 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1) (Table II, p 33)
Notes	Problems with the placebo group #6; see p 40 (Table 36) 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 "A labelling error had occurred in two of the 176 batches" (p 33) SD for duration was not published and it was imputed, see Methods Funding: Hoffmann-La Roche Ltd. supplied the tablets.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Bottles were numbered in accordance with a computer-generated list of numbers randomized in groups of eight, then given out in consecutive order as subjects registered" (p 33)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 31)
Baseline balance	Low risk	Compared with placebo group #4, Table 2 shows balance for age, sex, smoking, frequency of usual cold episodes, usual days indoors, usual days off work, contact with children, frequency in crowds, daily juice consumption
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 31)

Anderson 1974d (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded "subjects were asked to complete a checklist of the symptoms present on each day of illness" (p 33)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rate was 31% (149/480) in the vitamin C group and 35% (155/440) in the placebo group #4
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"All three tablets were of a similar size and shape, and an initial 'taste test' carried out with the help of a number of colleagues demonstrated that they were reasonably well matched in flavour, texture and appearance" (p 32)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Anderson 1974e

Methods	See Anderson 1974a Therapeutic arm #7
Participants	275 vitamin C; 46% male; mean age 34.3
Interventions	4 g/d vitamin C on the 1st day of illness only. "16 tablets [0.25 g] (two every hour) on the first day of any illness" (p 32)
Outcomes	Duration (Analysis 6.1) and severity (Analysis 5.1) (Table II, p 33)
Notes	Problems with the placebo group #6; see p 40 (Table 36) 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 "A labelling error had occurred in two of the 176 batches" (p 33) SD for duration was not published and it was imputed, see Methods Funding: Hoffmann-La Roche Ltd. supplied the tablets.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Anderson 1974e (*Continued*)

Random sequence generation (selection bias)	Low risk	"Bottles were numbered in accordance with a computer-generated list of numbers randomized in groups of eight, then given out in consecutive order as subjects registered" (p 33)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 31)
Baseline balance	Low risk	Compared with placebo group #4, Table 2 shows balance for age, sex, smoking, frequency of usual cold episodes, usual days indoors, usual days off work, contact with children, frequency in crowds, daily juice consumption
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 31)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded "subjects were asked to complete a checklist of the symptoms present on each day of illness" (p 33)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rate was 31% (125/400) in the vitamin C group and 35% (155/440) in the placebo group #4
Selective reporting (reporting bias)	Low risk	Duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"All three tablets were of a similar size and shape, and an initial 'taste test' carried out with the help of a number of colleagues demonstrated that they were reasonably well matched in flavour, texture and appearance" (p 32)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Anderson 1974f

Methods	See for Anderson 1974a Therapeutic arm #8
Participants	305 vitamin C; 44% male; mean age 35.3

Anderson 1974f (*Continued*)

Interventions	8 g/d vitamin C on the 1st day of illness only. "16 tablets [0.5 g] (two every hour) on the first day of any illness" (p 32)
Outcomes	Duration (Analysis 6.1) and severity (Analysis 5.1) (Table II, p 33)
Notes	Problems with the placebo group #6; see p 40 (Table 36) 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 "A labelling error had occurred in two of the 176 batches" (p 33) SD for duration was not published and it was imputed, see Methods Funding: Hoffmann-La Roche Ltd. supplied the tablets.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Bottles were numbered in accordance with a computer-generated list of numbers randomized in groups of eight, then given out in consecutive order as subjects registered" (p 33)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 31)
Baseline balance	Low risk	Compared with placebo group #4, Table 2 shows balance for age, sex, smoking, frequency of usual cold episodes, usual days indoors, usual days off work, contact with children, frequency in crowds, daily juice consumption
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 31)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded "subjects were asked to complete a checklist of the symptoms present on each day of illness" (p 33)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rate was 31% (135/440) in the vitamin C group and 35% (155/440) in the placebo group #4
Selective reporting (reporting bias)	Low risk	Duration of colds and severity of colds reported

Anderson 1974f (*Continued*)

Vitamin C and placebo indistinguishable?	Low risk	"All three tablets were of a similar size and shape, and an initial 'taste test' carried out with the help of a number of colleagues demonstrated that they were reasonably well matched in flavour, texture and appearance" (p 32)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

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 recruited from the staff of Toronto East General Hospital, Ontario Hydro-Electric Commission, Ontario Ministry of Transportations and Communications and University of Toronto (p 824). Both sexes in similar numbers. 150 vitamin C; 146 placebo "subjects were required ... usually to suffer at least one cold between January and April each year" (p 824)
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 6.1) and severity (Analysis 5.1) (Table II, p 825)
Notes	SD for duration was not published and it was imputed, see Methods Funding: Vitamin and placebo preparations were supplied by Hoffmann-La Roche Limited, Montrdal and Geriatric Pharmaceutical Corp.. NY

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Bottles were numbered from a list of consecutive numbers computer-randomized in groups of three and were then issued to subjects as they registered" (p 824)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 823)
Baseline balance	Low risk	Table I shows balance for age, sex, smoking, frequency of usual cold episodes, usual days indoors, usual days off work, contact with children, frequency in crowds, daily juice

Anderson 1975a (*Continued*)

		consumption
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Data from record sheets were coded and transferred to punch cards before the tablet code was broken and without knowing whether an individual had been on tablets or capsules" (p 825)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Each subject also received a calendar-type of symptom record similar to that used in the previous two trials." (p 825)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rates were 28% (57/207) in the vitamin C group and 29% (61/207) in the placebo group
Selective reporting (reporting bias)	Low risk	Duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	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 ... "
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Anderson 1975b

Methods	See Anderson 1975a This arm used vitamin C capsules (same dose as the tablets)
Participants	152 vitamin C

Anderson 1975b (*Continued*)

Interventions	See Anderson 1975a
Outcomes	Duration (Analysis 6.1) and severity (Analysis 5.1) (Table II, p 825)
Notes	SD for duration was not published and it was imputed, see Methods Funding: Vitamin and placebo preparations were supplied by Hoffmann-La Roche Limited, Montrdal and Geriatric Pharmaceutical Corp.. NY

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Bottles were numbered from a list of consecutive numbers computer-randomized in groups of three and were then issued to subjects as they registered" (p 824)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 823)
Baseline balance	Low risk	Table I shows balance for age, sex, smoking, frequency of usual cold episodes, usual days indoors, usual days off work, contact with children, frequency in crowds, daily juice consumption
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Data from record sheets were coded and transferred to punch cards before the tablet code was broken and without knowing whether an individual had been on tablets or capsules" (p 825)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Each subject also received a calendar-type of symptom record similar to that used in the previous two trials." (p 825)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rates were 27% (56/208) in the vitamin C group and 29% (61/207) in the placebo group
Selective reporting (reporting bias)	Low risk	Duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	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

Anderson 1975b (*Continued*)

		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 ... "
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Asfora 1977

Methods	Double-blind trial at the start. Therapeutic trial	
Participants	Participants included medical students, physicians, the investigators, patients of private clinics and social security members (p 224). Participants with age range between 14 and 89 years. 42 vitamin C; 41 placebo	
Interventions	6 g/d vitamin C for 5 d (total 30 g)	
Outcomes	Clinical progress (see our Table 1)	
Notes	Funding: not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"preparations were given to alternate patients as they presented themselves" (p 224)
Allocation concealment (selection bias)	Low risk	"A double-blind trial was conducted" (p 224)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A double-blind trial was conducted" (p 224)

Asfora 1977 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A double-blind trial was conducted" (p 224)
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was insufficient reporting to enable assessment
Selective reporting (reporting bias)	Unclear risk	Reported poorly, no unambiguous outcome. Included in Table 1
Vitamin C and placebo indistinguishable?	Unclear risk	There was insufficient reporting to enable assessment
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Audera 2001a

Methods	Double-blind RCT. Therapeutic trial
Participants	Staff and students of the Australian National University, "aged over 18 years, not pregnant or planning to become pregnant, on good general health, and did not take vitamin supplements regularly ... at the onset of a cold" (p359). This arm includes 47 vitamin C (38% male, mean age 40.1 years); 42 placebo (45% male, mean age 38.6 years)
Interventions	1 g/d vitamin C for 3 days. Placebo group received 30 mg/d vitamin C daily for 3 days
Outcomes	Duration (Analysis 6.1) and severity (Analysis 5.1) (Table 2, p 361)
Notes	Funding: The project was supported by a grant from Blackmores Ltd, who also provided the study medications. Blackmores Ltd were not involved in conduct or analysis of the trial or preparation of the article Audera 2001 also had a third vitamin C arm, which was excluded from our analysis for the following reason: 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Participants were randomised to receive ... A random number table was constructed ... The code was retained by the manufacturer until we were ready to analyse the results." (p 359-360)

Audera 2001a (*Continued*)

Allocation concealment (selection bias)	Low risk	"The code was retained by the manufacturer until we were ready to analyse the results." (p 359-360)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The code was retained by the manufacturer until we were ready to analyse the results." (p 359-360)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The code was retained by the manufacturer until we were ready to analyse the results." (p 359-360)
Incomplete outcome data (attrition bias) All outcomes	Low risk	400 sets of medication were distributed to 323 volunteers. 149 people returned completed respiratory event cards for 184 cold episodes. No evidence of systematic difference between the groups
Selective reporting (reporting bias)	Low risk	Duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"tablets with identical appearance and packaging" (p 360) "Only 31 participants (17%) recorded a guess about the dose of vitamin C they had taken, and 14 guessed correctly that they had taken a high dose. Seventeen guessed incorrectly that they had taken either a high or low dose." (p361)
Contamination	High risk	Placebo group received 30 mg/d vitamin C daily for 3 days

Audera 2001b

Methods	See Audera 2001a
Participants	50 vitamin C (50% male, mean age 39.9 years)
Interventions	3 g/d vitamin C for 3 days
Outcomes	Duration (Analysis 6.1) and severity (Analysis 5.1) (Table 2, p 361)
Notes	Funding: The project was supported by a grant from Blackmores Ltd, who also provided the study medications. Blackmores Ltd were not involved in conduct or analysis of the trial or preparation of the article

Audera 2001b (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Participants were randomised to receive ... A random number table was constructed ... The code was retained by the manufacturer until we were ready to analyse the results." (p 359-360)
Allocation concealment (selection bias)	Low risk	"The code was retained by the manufacturer until we were ready to analyse the results." (pp. 359-60)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The code was retained by the manufacturer until we were ready to analyse the results." (pp. 359-60)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The code was retained by the manufacturer until we were ready to analyse the results." (pp. 359-60)
Incomplete outcome data (attrition bias) All outcomes	Low risk	400 sets of medication were distributed to 323 volunteers. 149 people returned completed respiratory event cards for 184 cold episodes. No evidence of systematic difference between the groups
Selective reporting (reporting bias)	Low risk	Duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"tablets with identical appearance and packaging" (p. 360) "Only 31 participants (17%) recorded a guess about the dose of vitamin C they had taken, and 14 guessed correctly that they had taken a high dose. Seventeen guessed incorrectly that they had taken either a high or low dose." (p. 361)
Contamination	High risk	Placebo group received 30 mg/d vitamin C daily for 3 days

Bancalari 1984

Methods	Double-blind RCT. Regular supplementation trial. Duration 84 days
Participants	Chilean children all attending the same school, male and female, age 10 to 12 years, weighing between 27.5 and 33kg. 32 vitamin C (34% male, mean age 11.3 years); 30 placebo (40% male, mean age 11.8 years)
Interventions	2 g/d vitamin C

Bancalari 1984 (*Continued*)

Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1) (Abstract, p. 871)
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"students were divided into two random groups... tablets were marked with codes understood only by staff members in the Department of Applied Biochemistry of the University of Concepcion." (see translation)
Allocation concealment (selection bias)	Low risk	"students were divided into two random groups... tablets were marked with codes understood only by staff members in the Department of Applied Biochemistry of the University of Concepcion." (see translation)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"students were divided into two random groups... tablets were marked with codes understood only by staff members in the Department of Applied Biochemistry of the University of Concepcion." (see translation)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Like the children, those who collected the data did not know who was taking vitamin C and who was taking the placebo (i.e., it was a double-blind study)" (see translation)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"None of the schoolchildren in the two grades analyzed were excluded from testing" (see translation)
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"vitamin C tablets and the placebo tablets were identical in colour, taste, size and consistency" (see translation)

Bancalari 1984 (*Continued*)

Contamination	Low risk	There was substantial difference in the plasma vitamin C levels between placebo and vitamin C groups (10 mg/L versus 25 mg/L) after 50 days of treatment (Figure 5, p. 94)

Briggs 1984

Methods	Double-blind RCT. Regular supplementation trial. Over 8 winters (1974 to 1981) for 3 or 6 months of commitment by each volunteer
Participants	Australian adults in full-time employment (aged 18+), male and female. 265 vitamin C (31% male); 263 placebo (29% male)
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) (Tables 20 and 21, pp. 64-5)
Notes	SD for duration was not published and it was imputed, see Methods. Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomize carefully screened volunteers" (p 59). "Volunteers were assigned to product A or B by the use of random number tables and neither the physician nor the volunteer was aware of the composition of the capsules prescribed." (p 59-60)
Allocation concealment (selection bias)	Low risk	"neither the physician nor the volunteer was aware of the composition of the capsules prescribed." (p 59-60)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"neither the physician nor the volunteer was aware of the composition of the capsules prescribed." (p 59-60)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"neither the physician nor the volunteer was aware of the composition of the capsules prescribed." (p 59-60)

Briggs 1984 (*Continued*)

		"Code broken only after subject dropped from study" (p 60)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of randomised participants is not reported, but the sizes of the groups 263 versus 265 is equal and inconsistent with substantial difference in drop out rates (p 63)
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
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 (950 mg to each 50 mg AA capsule) "
Contamination	High risk	Placebo group received 50 mg/d plus 200 mg/d when ill

Brown 1945

Methods	Placebo-controlled trial. Therapeutic trial
Participants	US college students. All girls. A total of 298 colds were studied - 179 vitamin C, 119 placebo (206 nose colds and 92 throat colds)
Interventions	1 g vitamin C at first examination at the start of the cold and then 1 g at 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 2)
Notes	Alternate allocation is not consistent with the distribution of participants in the vitamin C and placebo groups Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The ascorbic acid and placebo were given alternately insofar as was practicable and without knowledge on the subjects' part that placebos were being given" (p 173)
Allocation concealment (selection bias)	Unclear risk	There was insufficient reporting to enable assessment

Brown 1945 (*Continued*)

Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Apparently single-blind, see above
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient reporting to enable assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"On the following morning... A small percentage, greater for the citric acid group than for the ascorbic acid group, failed to report for second dosage and reexamination" (p 173), but no description of drop-outs thereafter
Selective reporting (reporting bias)	Unclear risk	Reported poorly, no unambiguous outcome. Included in Table 1
Vitamin C and placebo indistinguishable?	Low risk	"either one gram of that substance [ascorbic acid], by mouth, in water, or an equivalent amount of citric acid as a placebo" (p 173)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Carillo 2008a

Methods	Double-blind RCT. Regular supplementation trial
Participants	12 healthy participants. Males 8; Females 4. Age mean 23 y. Vit C group 6; placebo group 6
Interventions	1.5 g/d vitamin C (0.5 g 3 times per day) for 7 days
Outcomes	Incidence (Analysis 1.1)
Notes	HH contacted Drs. Carrillo and Cheung for more details of the trial Funding: supported by Dalhousie University Faculty of Graduate Studies

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Each participant was randomly assigned.." (p 518)

Carillo 2008a (*Continued*)

Allocation concealment (selection bias)	Low risk	"double-blind" (p 518)
Baseline balance	Low risk	Table 1 shows that age, height, body weight, and a set of dietary variables were balanced
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 518)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded "participants recorded daily infection logs" (p 520)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Incidence of colds reported
Vitamin C and placebo indistinguishable?	Unclear risk	"Placebo consisted of microcrystalline cellulose" (p 520)
Contamination	Unclear risk	Estimated vitamin C intake in the placebo group was 164 mg/day (Table 1, p 522)

Carillo 2008b

Methods	See Carillo 2008
Participants	Same participants
Interventions	Similar exercise test a second time
Outcomes	Incidence (Analysis 1.1)
Notes	HH contacted Drs. Carrillo and Cheung for more details of the trial Funding: supported by Dalhousie University Faculty of Graduate Studies

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Each participant was randomly assigned..." (p 518)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 518)

Carillo 2008b (*Continued*)

Baseline balance	Low risk	Table 1 shows that age, height, body weight, and a set of dietary variables were balanced
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 518)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded "participants recorded daily infection logs" (p 520)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Incidence of colds reported
Vitamin C and placebo indistinguishable?	Unclear risk	"Placebo consisted of microcrystalline cellulose" (p 520)
Contamination	Unclear risk	Estimated vitamin C intake in the placebo group was 164 mg/day (Table 1, p 522)

Carr 1981a

Methods	Double-blind RCT. Regular supplementation trial. Duration 100 days Identical twins: 1 group living together and the other living apart This includes those living together
Participants	Australian males and females age range 14 to 64 years (mean 25 years). Data were analysed for 38 male and 57 female pairs of twins in total (36 pairs under 18 years, 34 pairs aged 18 to 30, 25 pairs aged 30+). This arm is for 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 "Among the twins living together, those taking vitamin C had a significantly higher incidence, total duration, and total severity of colds ... Among the pairs living apart there were 9 significant treatment differences ... all of these favoured the vitamin C group." (p 252) Funding: Roche Products, supplied the tablets and gave financial support to cover postage costs

Risk of bias

Bias	Authors' judgement	Support for judgement

Carr 1981a (*Continued*)

Random sequence generation (selection bias)	Low risk	"One twin of a pair was assigned at random" (p 250)
Allocation concealment (selection bias)	Low risk	"The experiment was "double-blind" in that neither the subjects nor the experimenters involved with the subjects or with the analysis of the results knew which group was which until the experiment and the analysis were completed." (p 250)
Baseline balance	Low risk	Twins
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The experiment was "double-blind" in that neither the subjects nor the experimenters involved with the subjects or with the analysis of the results knew which group was which until the experiment and the analysis were completed." (p 250)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The experiment was "double-blind" in that neither the subjects nor the experimenters involved with the subjects or with the analysis of the results knew which group was which until the experiment and the analysis were completed." (p 250)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the 125 pairs of twins who began the trial, we have analyzed cold data for 95 pairs" (p 250)
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"matching of the active and placebo tablets was checked for both appearance and taste" (p 250)
Contamination	High risk	Placebo group received a multi-vitamin tablet containing 70 mg/d vitamin C. In addition, no effect of vitamin C was seen among twins who lived together, whereas a significant benefit of vitamin C was seen among twins living apart (Carr 1981b), which most probably is explained by swapping of tablets among twins living together

Carr 1981b

Methods	See Carr 1981a. This includes 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	SD for duration was not published and it was imputed, see Methods Funding: Roche Products, supplied the tablets and gave financial support to cover postage costs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"One twin of a pair was assigned at random" (p 250)
Allocation concealment (selection bias)	Low risk	"The experiment was "double-blind" in that neither the subjects nor the experimenters involved with the subjects or with the analysis of the results knew which group was which until the experiment and the analysis were completed." (p 250)
Baseline balance	Low risk	Twins
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The experiment was "double-blind" in that neither the subjects nor the experimenters involved with the subjects or with the analysis of the results knew which group was which until the experiment and the analysis were completed." (p 250)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The experiment was "double-blind" in that neither the subjects nor the experimenters involved with the subjects or with the analysis of the results knew which group was which until the experiment and the analysis were completed." (p 250)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the 125 pairs of twins who began the trial, we have analyzed cold data for 95 pairs" (p 250)
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported

Carr 1981b (*Continued*)

Vitamin C and placebo indistinguishable?	Low risk	"matching of the active and placebo tablets was checked for both appearance and taste" (p 250)
Contamination	High risk	Placebo group received a multi-vitamin tablet containing 70 mg/d vitamin C

Carson 1975

Methods	Double-blind RCT. Regular supplementation trial. Duration 40 days
Participants	Healthy, working adults in the UK (62% males). 121 vitamin C; 123 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) (Table III, p 101)
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"tablets or matching lactose dummies ... according to a random sequence code" (p 99)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 99)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 99)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 99)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rates were 21% (32/153) in the vitamin C group and 13% (19/142) in the placebo group (P = 0.1)
Selective reporting (reporting bias)	Low risk	Incidence of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"tablets or matching lactose dummies" (p 99)

Carson 1975 (*Continued*)

Contamination	Unclear risk	There was insufficient reporting to enable assessment

Charleston 1972

Methods	Single-blind trial. 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) (Table, p 1401)
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	There was insufficient reporting to enable assessment
Allocation concealment (selection bias)	Unclear risk	There was insufficient reporting to enable assessment
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Every week any symptoms of cold, and their duration, were recorded; only the operator of the survey (S. S. C.) knew the identity of the subjects in the two groups" (p 1401)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient reporting to enable assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rates were 6% (3/50) in the vitamin C group and 4% (2/45) in the placebo group
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"placebo similar in appearance but containing lactose and 5% citric acid" (p 1401)

Charleston 1972 (*Continued*)

Contamination	Low risk	Several surveys in the UK in the 1970s found that the dietary vitamin C intake was 30 to 60 mg/day (Hemilä 1997b) and the same author gave an estimate of 44 mg/day in a subsequent study (Clegg 1975)

Clegg 1975

Methods	Double-blind RCT. Regular supplementation trial. Duration 15 weeks
Participants	Healthy Scottish students. 67 vitamin C (63% male); 70 placebo (67% male)
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1) (Table 1, p 974)
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Allocation method not described
Allocation concealment (selection bias)	Low risk	"double-blind" (p 973); "The coding ... was not broken until the data had been assembled for statistical analysis" (p 973)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 973); "The coding ... was not broken until the data had been assembled for statistical analysis" (p 973)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 973); "The coding ... was not broken until the data had been assembled for statistical analysis" (p 973)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rates were 21% (18/85) in the vitamin C group and 18% (15/85) in the placebo group
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported

Clegg 1975 (*Continued*)

Vitamin C and placebo indistinguishable?	Low risk	"The placebo and ascorbic acid tablets were organoleptically indistinguishable" (p 973)
Contamination	Low risk	"The average British diet provides a comparatively low daily level (44 mg) of L-ascorbic acid during the winter months so that the dietary contribution would be minor in comparison to the test dose" (p 975)

Constantini 2011a

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 winter months Male swimmers
Participants	Male competitive swimmers in Israel. 12 vitamin C; 10 placebo. Mean age over both sexes 13.8 years, range 12 to 17 years
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) (Table 3, p 62)
Notes	Trial is divided into males and females since there was significant heterogeneity in vitamin C effect (P = 0.003) The tablets for the study were provided by Teva Pharmaceutical Industries Ltd., Israel

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...plastic bottles (identical number of vitamin C and placebo bottles) and, before their distribution to the swimmers, were numbered by a person unrelated to the study. Study participants were given a randomly selected plastic bottle, and its number was listed alongside the participant's name" (p 60)
Allocation concealment (selection bias)	Low risk	"...plastic bottles (identical number of vitamin C and placebo bottles) and, before their distribution to the swimmers, were numbered by a person unrelated to the study. Study participants were given a randomly selected plastic bottle, and its number was listed alongside the participant's name" (p 60)

Constantini 2011a (*Continued*)

Baseline balance	Low risk	Table 1 shows balance for age, sex, swimming duration (h/week)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...plastic bottles (identical number of vitamin C and placebo bottles) and, before their distribution to the swimmers, were numbered by a person unrelated to the study. Study participants were given a randomly selected plastic bottle, and its number was listed alongside the participant's name" (p 60)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...plastic bottles (identical number of vitamin C and placebo bottles) and, before their distribution to the swimmers, were numbered by a person unrelated to the study. Study participants were given a randomly selected plastic bottle, and its number was listed alongside the participant's name" (p 60)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the 42 participants initially recruited to the trial, three dropped out, all from the placebo group. One ... immediately after the study began, and two withdrew from competitive swimming ..." (across both males and females)
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"identical in appearance" (p 60)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Constantini 2011b

Methods	See Constantini 2011 Female swimmers
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) (Table 3, p 62)

Constantini 2011b (*Continued*)

Notes	Trial is divided into males and females since there was significant heterogeneity in vitamin C effect (P = 0.003) The tablets for the study were provided by Teva Pharmaceutical Industries Ltd., Israel

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...plastic bottles (identical number of vitamin C and placebo bottles) and, before their distribution to the swimmers, were numbered by a person unrelated to the study. Study participants were given a randomly selected plastic bottle, and its number was listed alongside the participant's name" (p 60)
Allocation concealment (selection bias)	Low risk	"...plastic bottles (identical number of vitamin C and placebo bottles) and, before their distribution to the swimmers, were numbered by a person unrelated to the study. Study participants were given a randomly selected plastic bottle, and its number was listed alongside the participant's name" (p 60)
Baseline balance	Low risk	Table 1 shows balance for age, sex, swimming duration (h/week)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...plastic bottles (identical number of vitamin C and placebo bottles) and, before their distribution to the swimmers, were numbered by a person unrelated to the study. Study participants were given a randomly selected plastic bottle, and its number was listed alongside the participant's name" (p 60)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...plastic bottles (identical number of vitamin C and placebo bottles) and, before their distribution to the swimmers, were numbered by a person unrelated to the study. Study participants were given a randomly selected plastic bottle, and its number was listed alongside the participant's name" (p 60)

Constantini 2011b (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the 42 participants initially recruited to the trial, three dropped out, all from the placebo group. One ... immediately after the study began, and two withdrew from competitive swimming ..." (across both males and females)
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"identical in appearance" (p 60)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Coulehan 1974a

Methods	Double-blind trial. Regular supplementation trial. Duration 14 weeks
Participants	USA. Students of both sexes at a Navajo Indian boarding school. This comparison includes older residential students aged 10 to 15 (grades 5 to 8). 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 imputed, see Methods 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." "Older children of both sexes had significantly higher blood ascorbic acid levels in March than in January, suggesting that some ... children may have been switching tablets..." (p 9) Funding: tablets were supplied by H offmann-LaRoche Inc., Nutley, NJ

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocation was "alternatively, from an alphabetical listing by classroom to one of two study groups. A pharmacist, not otherwise involved in this investigation, then allocated one group vitamin C and the other placebo. Tablets were distributed to school

		teachers in containers labeled only by code number. The only master list was maintained by the pharmacist.“ (p 7)
Allocation concealment (selection bias)	Low risk	”double-blind“ (p 6); Tablets were distributed to school teachers in containers labeled only by code number. The only master list was maintained by the pharmacist. ” (p 7)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“double-blind” (p 6); Tablets were distributed to school teachers in containers labeled only by code number. The only master list was maintained by the pharmacist. “ (p 7)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	”double-blind“ (p 6); Tablets were distributed to school teachers in containers labeled only by code number. The only master list was maintained by the pharmacist. ” (p 7)
Incomplete outcome data (attrition bias) All outcomes	Low risk	641 of the 666 children (96%) completed the entire 14-week study period The drop out rates were 4% (13/334) in the vitamin C group and 4% (12/332) in the placebo group. The 25 who were eliminated from the study dropped out of school during its course. There were no dropouts due to adverse effects. (p 7)
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
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” (p 7)
Contamination	Low risk	In boys, there was substantial difference in plasma vitamin C levels between placebo and vitamin C groups (20.6 versus 15.1 mg/l) and also in girls (20.8 versus 14.7 mg/l). Compared with baseline levels, there was a significant ($P < 0.05$) increase in the vitamin C level in the placebo groups of girls and boys suggesting that swapping tablets may have occurred, but this difference is

Coulehan 1974a (*Continued*)

		small compared with the vitamin C versus placebo group difference (Table 1, p 7) The authors also wrote "older P[lacebo] children of both sexes had significantly higher blood ascorbic acid levels in March than in January, suggesting that some P children may have been switching tablets at times with [vitamin] C children or getting excess ascorbic acid in some other way" (p 9)

Coulehan 1974b

Methods	See Coulehan 1974a
Participants	This comparison includes younger residential students aged 6 to 10 (grades 1 to 4). 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 imputed, see Methods 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." "Older children of both sexes had significantly higher blood ascorbic acid levels in March than in January, suggesting that some ... children may have been switching tablets..." (p 9) Funding: tablets were supplied by H offmann-LaRoche Inc., Nutley, NJ

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation was "alternatively, from an alphabetical listing by classroom to one of two study groups. A pharmacist, not otherwise involved in this investigation, then allocated one group vitamin C and the other placebo. Tablets were distributed to school teachers in containers labeled only by code number. The only master list was maintained by the pharmacist." (p 7)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 6); Tablets were distributed to school teachers in containers labeled only by code number. The only master list was maintained by the pharmacist." (p 7)
Baseline balance	Unclear risk	Baseline balance not demonstrated

Coulehan 1974b (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 6); Tablets were distributed to school teachers in containers labeled only by code number. The only master list was maintained by the pharmacist." (p 7)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 6); Tablets were distributed to school teachers in containers labeled only by code number. The only master list was maintained by the pharmacist." (p 7)
Incomplete outcome data (attrition bias) All outcomes	Low risk	641 of the 666 children (96%) completed the entire 14-week study period The drop out rates were 4% (13/334) in the vitamin C group and 4% (12/332) in the placebo group. The 25 who were eliminated from the study dropped out of school during its course. There were no dropouts due to adverse effects. (p 7)
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
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" (p 7)
Contamination	Low risk	In boys, there was substantial difference in plasma vitamin C levels between placebo and vitamin C groups (23.9 versus 15.5 mg/l) and also in girls (22.9 versus 15.6 mg/l)(Table 1, p 7)

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 imputed, see Methods Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Individual treatments were assigned randomly by computer within groups of 20 consequtive numbers" (p 973)

Coulehan 1976 (*Continued*)

Allocation concealment (selection bias)	Low risk	"double-blind" (p 973)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Each child received tablets from his or her own bottle, identified only by study number."; "People involved in data collection or tablet distribution had no access to treatment identification" (p 973)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the original 944 children participating, 76 (8%) dropped out during the investigation." (p 974)
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
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" (p 973)
Contamination	High risk	In boys aged ≤ 10 yr, there was no difference in plasma vitamin C levels between placebo and vitamin C groups (13.1 versus 12.5 mg/l) and the difference was small in older boys (12.4 versus 9.8 mg/l), in girls aged ≤10 yr (13.4 versus 10.4 mg/l) and older girls (12.6 versus 8.9 mg/l) (Table 3, p 975)

Cowan 1942

Methods	Placebo-controlled trial. Regular supplementation trial. Duration 28 weeks
Participants	US college students, males and females. 208 vitamin C; 155 placebo
Interventions	0.2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) (Table 1, p 1269)
Notes	SD for duration was not published and it was imputed, see Methods Funding: not reported

Cowan 1942 (*Continued*)

	Cowan 1942 also reported another vitamin C trial in the same study report. The second trial was excluded because of: Low dose with multiple vitamins. The vitamin C dose was 0.025 g/day for one group and 0.050 for another group, with the third group being given placebo Nevertheless the second trial was classified as a "vitamin C and common cold" trial in the influential review by Chalmers 1975

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" (p 1268) 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	There was insufficient reporting to enable assessment
Baseline balance	Unclear risk	There was insufficient reporting to enable assessment
Blinding of participants and personnel (performance bias) All outcomes	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." (p 1269) "The students in all groups were instructed to report to the Health Service whenever a cold developed so that a special report card could be filled in by a physician indicating the type of cold, the symptoms and the like. " (p 1268)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The [blinded] students in all groups were instructed to report to the Health Service whenever a cold developed so that a special report card could be filled in by a physician indicating the type of cold, the symptoms and the like." (p 1268)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The dropout rates were 11% (25/233) in the vitamin C group and 20% (39/194) in the placebo group, which gives P = 0.007
Selective reporting (reporting bias)	Low risk	Incidence of colds reported

Cowan 1942 (*Continued*)

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" (p 1269)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Cowan 1950a

Methods	Probably double-blind trial. Therapeutic trial
Participants	US college students who were especially susceptible to colds and colds constituted a real problem to them. 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 6.1) (Table 1, p 423)
Notes	SD for duration was not published and it was imputed, see Methods Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The medicaments were given out in strict rotation to the students as they enrolled" (p 423)
Allocation concealment (selection bias)	Unclear risk	There was insufficient reporting to enable assessment
Baseline balance	Low risk	Table 1 shows that the average number of colds in previous year and average duration of colds in previous year was similar
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"each subject was asked to fill out a questionnaire. Then, after a brief discussion, he was given a box of medicine with written instructions to take one dose at the first symptoms of a cold and to repeat the dose every four hours until the cold was definitely 'cured' or until the medicine (10

Cowan 1950a (*Continued*)

		doses) was used up" (p 423); see also below
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Each week the [blinded] subject received a report card for reporting the presence or absence of symptoms during the week of the report, the severity of symptoms and the effectiveness of the medication" (p 423)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 430 subjects enrolled in total at the beginning of the study (there were 3 other arms not relevant to this meta-analysis), the records of 367 were used in tabulating the final results. (p 423)
Selective reporting (reporting bias)	Low risk	Duration of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"Placebo (citric acid to simulate the taste of ascorbic acid, lactose, cornstarch, sugar, talc and stearic acid)" (p 423)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Cowan 1950b

Methods	Part of Cowan 1950a This is comparison in which phenindamine was administered to both groups
Participants	US college students who were especially susceptible to colds. 71 vitamin C + Phenindamine; 73 Phenindamine
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. 25 mg phenindamine with the same dosing for both groups
Outcomes	Duration (Analysis 6.1) (Table 1, p 423)
Notes	SD for duration was not published and it was imputed, see Methods Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The medicaments were given out in strict rotation to the students as they enrolled" (p 423)

Cowan 1950b (*Continued*)

Allocation concealment (selection bias)	Unclear risk	There was insufficient reporting to enable assessment
Baseline balance	Low risk	Table 1 shows that the average number of colds in previous year and average duration of colds in previous year was similar
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"each subject was asked to fill out a questionnaire. Then, after a brief discussion, he was given a box of medicine with written instructions to take one dose at the first symptoms of a cold and to repeat the dose every four hours until the cold was definitely 'cured' or until the medicine (10 doses) was used up" (p 423); see also below
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Each week the [blinded] subject received a report card for reporting the presence or absence of symptoms during the week of the report, the severity of symptoms and the effectiveness of the medication" (p 423)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 430 subjects enrolled in total at the beginning of the study (there were 3 other arms not relevant to this meta-analysis), the records of 367 were used in tabulating the final results. (p 423)
Selective reporting (reporting bias)	Low risk	Duration of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"Placebo (citric acid to simulate the taste of ascorbic acid, lactose, cornstarch, sugar, talc and stearic acid)" (p 423)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Craig 1976

Methods	Placebo-controlled therapeutic study. Reported briefly by Tyrrell 1977a, see Notes for a copy of the text
Participants	8 vit C; 11 placebo
Interventions	Vitamin C dose not reported, but Tyrrell 1977a administered 1 g vitamin C 4 times per day for 2½ days, and probably the intervention was similar in Craig et al

Craig 1976 (*Continued*)

Outcomes	We have imputed SD to reach the conventional level of statistical significance
Notes	Tyrrell 1977a reported this study as follows: "As a prelude to this study a small trial at Salisburywas carried out on 135 volunteers who between them had 66 colds. Eight of those on ascorbic acid were off work for an average of 1.6 days, and 11 on the placebo were off for 2.2 days; there was a similar finding for number of days in bed, and these two differences just reached a conventional level of statistical significance. There were no differences for the upper respiratory symptoms such as sneezing and sore throat (Craig et al., unpublished). However, the numbers studied were small, which was the main reason for proceeding to the larger trial now reported." We imputed the mean and SD values for the whole vitamin C and placebo groups (N = 66 colds) from the data reported above, see calculations at the web page of this review Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There was insufficient reporting to enable assessment
Allocation concealment (selection bias)	Unclear risk	There was insufficient reporting to enable assessment
Baseline balance	Unclear risk	There was insufficient reporting to enable assessment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Tyrrell was one of the major common cold researchers, and he described that this study was placebo-controlled, see Notes. We assume it was also double-blinded as the Tyrrell 1977a study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Tyrrell was one of the major common cold researchers, and he described that this study was placebo-controlled, see Notes. We assume it was also double-blinded as the Tyrrell 1977a study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient reporting to enable assessment
Selective reporting (reporting bias)	Unclear risk	Severity of colds reported, but duration of colds was not reported. Reporting very brief within Tyrrell 1977a

Craig 1976 (*Continued*)

Vitamin C and placebo indistinguishable?	Unclear risk	There was insufficient reporting to enable assessment
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Dahlberg 1944

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 months
Participants	Men in the Swedish army. 1259 vitamin C; 1266 placebo
Interventions	0.2 g/d vitamin C during the first 24 days; 50 mg/d thereafter, control group received a corresponding number of citric acid tablets. (p 545). Citric acid added to placebo to disguise any difference in taste (p 545)
Outcomes	Incidence Analysis 1.1. Capillary resistance tests (p 545)
Notes	"...we divided it up into two group: Group I, where, as far as we could ascertain from careful checking, the soldiers had taken the tablets regularly the whole time, and Group II, where most of the soldiers had in all probability taken the tablets for the greater part of the observation period, but only regularly during the time 3/3-6/4." (p 546) Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"All soldiers with odd identity numbers were given tablets containing ascorbic acid, and soldiers with even identity numbers were given control tablets" (p 545)
Allocation concealment (selection bias)	Low risk	Double-blind, "tablets ... composition was kept secret both from doctors and soldiers" (p 545)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, "tablets ... composition was kept secret both from doctors and soldiers" (p 545)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, "tablets ... composition was kept secret both from doctors and soldiers" (p 545)

Dahlberg 1944 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	The outcomes were unknown for 1% (8/1259) in the vitamin C group and 1% (14/1266) in the placebo group (p 548)
Selective reporting (reporting bias)	Low risk	Incidence of colds reported
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" (p 545)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Dick 1990

Methods	Double-blind, placebo-controlled trial. Experimentally induced colds
Participants	USA, adult male volunteers. 24 vitamin C; 24 placebo
Interventions	2 g/d vitamin C or placebo for 3-5 weeks prior to, during, and 2 weeks after the exposure period
Outcomes	See our Table 2. Mucus weights (study 3) and daily logs of signs and symptoms. Serum and leukocyte levels were measured at least weekly
Notes	3 abstracts, no full paper. Studies using exposure of participants to rhinovirus infected volunteers. EC attended seminar presented by Jennings at ARI conference in Canberra, Australia in July 1997 and obtained a 4th abstract Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Prophylactic study, random number table used for randomization (Notes from presentation by Jennings July 1997 ARI conference in Canberra)
Allocation concealment (selection bias)	Low risk	Double-blind
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Dick 1990 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Short-term laboratory study
Selective reporting (reporting bias)	Unclear risk	No unambiguous outcome. Included in Table 2
Vitamin C and placebo indistinguishable?	Unclear risk	There was no scope to test tastes of tablets as recipients were handed tablets (by a blinded monitor) and watched taking them. (Notes from presentation by Jennings July 1997 ARI conference in Canberra)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Elliot 1973

Methods	Double-blind RCT. Regular supplementation trial
Participants	Members of the crew of a Polaris submarine; 37 vitamin C, 33 placebo; similar with respect to age and smoking habits; probably all male
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	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"... were randomly placed in treatment or placebo groups."
Allocation concealment (selection bias)	Low risk	"double-blind"
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"

Elliot 1973 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Five dropouts occurred in the placebo group, and in the vitamin group two men did not take the capsules as directed for a short period of time. Data from the drop-outs and above two are included for the weeks they were fully participating in the study." The drop out rates were 5% (2/37) in the vitamin C group and 2% (5/33) in the placebo group
Selective reporting (reporting bias)	Unclear risk	No unambiguous outcome. Included in Table 1
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"
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Elwood 1976

Methods	Double-blind RCT. Regular supplementation trial for 100 days during the winter of 1973-74 (p 193)
Participants	Wales, young mothers who had had a confinement in the previous two years and were not again pregnant (p 193). 339 vitamin C; 349 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1) (Tables III, p 194, and Table V, p 195)
Notes	Funding: Roche Products Ltd supplied the tablets for the study The study was carried out within a longer trial published by Baker et al. (1980) We contacted Dr. Elwood to ask for the methods of the 1976 trial (email Sept 2016)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomised" (p 193)

Elwood 1976 (*Continued*)

Allocation concealment (selection bias)	Low risk	Neither patients nor researchers knew to which group the participants were allocated (Peter Elwood, email September 2016)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"matching placebo" (p 193); Neither patients nor researchers knew to which group the participants were allocated (Peter Elwood, email September 2016)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A record card was given, on which was to be recorded any respiratory symptom which was sufficiently severe to 'bother her' [blinded participant]" (p 193-4); The code was broken after the data had been collected (Peter Elwood, email September 2016)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 923 women who began the trial, 235 were omitted (mostly for poor cooperation) (p 194) The drop out rates were 24% (107/446) in the vitamin C group and 26% (121/470) in the placebo group
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"These contained either 1 g ascorbic acid in an effervescent base or a matching placebo" (p 193)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Elwood 1977

Methods	Double-blind RCT. Therapeutic trial (p 133)
Participants	Wales, young mothers and their husbands. 145 colds treated with vitamin C (71 males, 74 females) ; 119 with placebo (58 males, 61 females) (p 134-5)
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, they are pooled in our study (Tables II and III, p 134-5)

Elwood 1977 (*Continued*)

Notes	Funding: Roche Products Ltd supplied the tablets for the study The study was carried out within a longer trial published by Baker et al. (1980)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Allocation of households to vitamin C or placebo was random, but each husband received the same tablets as his wife" (p 133)
Allocation concealment (selection bias)	Low risk	"double-blind" (133)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (133)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (133)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No indication of unequal drop outs
Selective reporting (reporting bias)	Low risk	Duration of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"ten effervescent tablets of either vitamin C or an inert; placebo" (p 133)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Franz 1956

Methods	Double-blind trial. Regular supplementation trial. Duration 3 months from February to May 1956 (p 1224) 2 x 2 factorial: vitamin C and flavonoids
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) (Table 5, p 1226)

Franz 1956 (*Continued*)

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) Funding: drug preparations were provided by the Nepera Chemical Co., Inc

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Groups were assigned in rotation" (p 1225)
Allocation concealment (selection bias)	Low risk	"Every effort was made to disguise the contents of the capsules. All looked and tasted alike. Even the doctors conducting the study did not know the key to the code numbers used." (p 1225)
Baseline balance	Unclear risk	There was insufficient reporting to enable assessment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Every effort was made to disguise the contents of the capsules. All looked and tasted alike. Even the doctors conducting the study did not know the key to the code numbers used." (p 1225)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Every effort was made to disguise the contents of the capsules. All looked and tasted alike. Even the doctors conducting the study did not know the key to the code numbers used." (p 1225)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No indication that drop outs might be unequal
Selective reporting (reporting bias)	Low risk	Incidence of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"All looked and tasted alike" (p 1225) . "These substances were administered in capsules as nearly alike as possible". (p 1224)
Contamination	Unclear risk	?

Himmelstein 1998

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 months (July to October 1994) (p 2,4 1998)
Participants	US sedentary people (friends and coworkers of Duke City Marathon runners - Albuquerque) (p 2,4 1998). 23 vitamin C; 25 placebo. 65% male, age range 22 to 65 years (p 9 1998) The parallel trial with runners was excluded (Himmelstein 1998b)
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1) (Table 8, p 76, Thesis 1996)
Notes	A parallel trial with marathon runners was caried out, but it was excluded from our analysis, because the drop-out rate was very high and divergent in the trial arms. 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) Funding: Hoffman-LaRoche provided the study supplements,

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Each subject was assigned a number upon entry into the study and was randomly assigned ... by a computer generated randomization of the assigned numbers." (p 60; 1996)
Allocation concealment (selection bias)	Low risk	"The study was conducted as a double-blind ... " (p 60; 1996)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study was conducted as a double-blind ... " (p 60; 1996)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded "subjects were also instructed to complete a respiratory symptom report sheet on each day that they had a runny nose, cough, or sore throat." (p 60; 1996)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rates were 45% (19/42) in the vitamin C group and 44% (20/45) in the placebo group (p 59, 1996; p 4, 1998)

Himmelstein 1998 (*Continued*)

Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Unclear risk	"Placebo (similar looking and tasting tablets containing lactose)" (Methods 1998) "Subjects were queried regarding which treatment they believed they were taking .. . In the sedentary group no significant differences were found between actual and believed treatment ..." (p 10 1998)
Contamination	Low risk	Estimated vitamin C intake in the placebo groups was 149 mg/day (Table 2, p 8, 1998)

Johnston 2014

Methods	Double-blind RCT, prophylaxis study. 8 weeks - January through April 2011 (p 2574)
Participants	Healthy, non-smoking men recruited from a large college campus in the Southwestern United States (p 2574), N = 30, age 18 to 35 y, mean 23 y Vitamin C 15, placebo 13. (p 2572)
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1) (Table 3, p 2578)
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly assigned by a coin toss"; "The randomization was conducted by the lead investigator who did not have contact with participants or conduct data entry or blood analyses" (p 2574)
Allocation concealment (selection bias)	Low risk	"double-blind"; "The randomization was conducted by the lead investigator who did not have contact with participants or conduct data entry or blood analyses" (p 2574)

Johnston 2014 (*Continued*)

Baseline balance	Low risk	Table 1 shows baseline balance for age, weight, BMI, dietary vitamin C, diet quality score
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"; "The randomization was conducted by the lead investigator who did not have contact with participants or conduct data entry or blood analyses" (p 2574)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"data were unblinded once blood analyses and data entry were complete" (p 2574)
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 placebo participant was excluded from analysis because of non-compliancy and 1 placebo participant was excluded because of a severe cold lasting 24 days at the start of the study (p 2576) The dropout rates were 0% in the vitamin C group and 13% (2/15) in the placebo group
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
Vitamin C and placebo indistinguishable?	Unclear risk	"Vitamin C capsules were identical in appearance to the placebo capsules that contained white flour" (p 2574)
Contamination	Low risk	Estimated vitamin C intake in the placebo groups was 113 mg/day (Table 2, p 44)

Karlowski 1975a

Methods	Double-blind RCT. Regular supplementation and therapeutic 2x2 trial. Duration 9 months We compared 3 different arms with the placebo arm, and regular supplementation + therapeutic with regular supplementation This is the regular supplementation arm
Participants	USA, employees of the National Institutes of Health. 44 vitamin C; 46 placebo
Interventions	3 g/d vitamin C
Outcomes	Duration (Analysis 2.1) (Table 6, p 1040 in Karlowski et al 1975 and Table 1, p 505 in Lewis 1975)

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 Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"An unrestricted randomization was used" (p 1038)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 1040)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 1040) and see Notes above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 1040) and see Notes above
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rate over the whole study (n = 311) was 34% in the vitamin C group and 44% in the placebo group (p 1038)
Selective reporting (reporting bias)	Low risk	Duration of colds reported and included. Incidence of colds was reported as number of colds per person and cannot be included in our analysis, but findings are consistent with our Analysis 1.1
Vitamin C and placebo indistinguishable?	Unclear risk	"There was no time to design, test, and have manufactured a placebo that would be indistinguishable from ascorbic acid..." (p 1041) See Notes
Contamination	Unclear risk	There was insufficient reporting to enable assessment

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	Duration (Analysis 2.1) (Table 6, p 1040 in Karlowski et al 1975 and Table 1, p 505 in Lewis 1975)
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 Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"An unrestricted randomization was used" (p 1038)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 1040)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 1040) and see Notes above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 1040) and see Notes above
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rate over the whole study (n = 311) was 34% in the vitamin C group and 44% in the placebo group (p 1038)
Selective reporting (reporting bias)	Low risk	Duration of colds reported
Vitamin C and placebo indistinguishable?	Unclear risk	"There was no time to design, test, and have manufactured a placebo that would be indistinguishable from ascorbic acid..." (p 1041) See Notes

Karlowski 1975b (*Continued*)

Contamination	Unclear risk	There was insufficient reporting to enable assessment

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 5.1) (Table 6, p 1040 in Karlowski et al 1975 and Table 1, p 505 in Lewis 1975)
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 Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"An unrestricted randomization was used" (p 1038)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 1040)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 1040) and see Notes above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 1040) and see Notes above
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rate over the whole study (n = 311) was 34% in the vitamin C group and 44% in the placebo group (p 1038)
Selective reporting (reporting bias)	Low risk	Duration of colds reported

Karlowski 1975c (*Continued*)

Vitamin C and placebo indistinguishable?	Unclear risk	"There was no time to design, test, and have manufactured a placebo that would be indistinguishable from ascorbic acid..." (p 1041) See Notes
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Karlowski 1975d

Methods	See Karlowski 1975a This is regular plus therapeutic arm compared with regular supplementation arm to measure therapeutic effect above the regular supplementation in the 2 x 2 design
Participants	57 therapeutic vitamin C with 44 control
Interventions	3 g/d therapeutic vitamin C from the onset of cold for 5 days; and all participants 3 g/day over the whole study
Outcomes	Duration (Analysis 6.1) (Table 6, p 1040 in Karlowski et al 1975 and Table 1, p 505 in Lewis 1975)
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 Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"An unrestricted randomization was used" (p 1038)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 1040)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 1040) and see Notes above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 1040) and see Notes above

Karlowski 1975d (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rate over the whole study (n = 311) was 34% in the vitamin C group and 44% in the placebo group (p 1038)
Selective reporting (reporting bias)	Low risk	Duration of colds reported
Vitamin C and placebo indistinguishable?	Unclear risk	"There was no time to design, test, and have manufactured a placebo that would be indistinguishable from ascorbic acid..." (p 1041) See Notes
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Karlowski 1975e

Methods	See Karlowski 1975a. This is regular plus therapeutic arm compared with therapeutic supplementation arm to measure the regular supplementation effect above the therapeutic supplementation in the 2 x 2 design
Participants	57 therapeutic vitamin C with 43 control
Interventions	3 g/d therapeutic vitamin C from the onset of cold for 5 days; and all participants 3 g/day over the whole study
Outcomes	Duration (Analysis 2.1) (Table 6, p 1040 in Karlowski et al 1975 and Table 1, p 505 in Lewis 1975)
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 Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"An unrestricted randomization was used" (p 1038)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 1040)
Baseline balance	Unclear risk	Baseline balance not demonstrated

Karlowski 1975e (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 1040) and see Notes above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 1040) and see Notes above
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rate over the whole study (n = 311) was 34% in the vitamin C group and 44% in the placebo group (p 1038)
Selective reporting (reporting bias)	Low risk	Duration of colds reported and included. Incidence of colds was reported as number of colds per person and cannot be included in our analysis, but findings are consistent with our Analysis 1.1
Vitamin C and placebo indistinguishable?	Unclear risk	"There was no time to design, test, and have manufactured a placebo that would be indistinguishable from ascorbic acid..." (p 1041) See Notes
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Liljefors 1972

Methods	Double-blind RCT. Cross-over regular supplementation trial. Duration 2 + 2 weeks, during Autumn 1971 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	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Liljefors 1972 (*Continued*)

Random sequence generation (selection bias)	Low risk	"slumpvis" (p 3304), meaning "by random"
Allocation concealment (selection bias)	Low risk	"double-blind cross-over trial" (p 3304).
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind cross-over trial" (p 3304).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind cross-over trial" (p 3304).
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts during Period I of the trial. During Period II there were 3 dropouts. The dropout rate was 5% (1/19) in the vitamin C group, compared with 20% (2/10) in the placebo group
Selective reporting (reporting bias)	Low risk	Incidence of colds reported
Vitamin C and placebo indistinguishable?	Unclear risk	There was insufficient reporting to enable assessment
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Ludvigsson 1977a

Methods	Double-blind RCT. Regular supplementation trial. Duration 7 weeks in the spring of 1973. Pilot study to Ludvigsson 1977b
Participants	Swedish school children. 80 vitamin C (41 male, 39 female, average age at start 9.61 years); 78 placebo (42 male, 36 female, average age at start 9.55 years)
Interventions	1 g/d vitamin C. Placebo contained 30 mg/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1) (Table V, p 95)
Notes	Pilot study to Ludvigsson 1977b Funding: not reported
Risk of bias	

Ludvigsson 1977a (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Every class was divided at random into two groups" (p 91)
Allocation concealment (selection bias)	Low risk	"carried out totally double blind" (p 92). At the end of the study "the code used [was] decoded" (p 92)
Baseline balance	Low risk	Table I shows balance for age and sex
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"carried out totally double blind" (p 92). At the end of the study "the code used [was] decoded" (p 92)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"carried out totally double blind" (p 92). At the end of the study "the code used [was] decoded" (p 92)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 172 children who started in the pilot study 14 dropped out (p 93). The dropout rate due to suspected side effects was 1% (1/80) in the vitamin C group compared with 3% (2/78) in the placebo group
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
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"
Contamination	High risk	Placebo contained 30 mg/d vitamin C

Ludvigsson 1977b

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 months in the Spring of 1973
Participants	Swedish school children. 304 vitamin C (161 male, 143 female, average age at start 9.31 years); 311 placebo (155 male, 156 female, average age at start 9.31 years)
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) (Table V, p 95)

Ludvigsson 1977b (*Continued*)

Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Every class was divided at random into two groups" (p 91)
Allocation concealment (selection bias)	Low risk	"carried out totally double blind" (p 92). At the end of the study "the code used [was] decoded" (p 92)
Baseline balance	Low risk	Table I shows balance for age and sex
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"carried out totally double blind" (p 92). At the end of the study "the code used [was] decoded" (p 92)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"carried out totally double blind" (p 92). At the end of the study "the code used [was] decoded" (p 92)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 642 children who started in the main study 27 dropped out (p 93). The dropout rate due to suspected side effects was 0.3% (1/304) in the vitamin C group compared with 0.3% (1/311) in the placebo group
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
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"
Contamination	High risk	Placebo contained 10 mg/d vitamin C. There was no difference in the leucocyte ascorbic acid levels between placebo and vitamin C groups (17.0 versus 17.4) (p 94)

Miller 1977a

Methods	Double-blind RCT. Regular supplementation trial. Duration 5 months beginning in November 1974 Identical twins This includes "high body weight" twins administered 1 g/day vitamin C The twin pairs were separated by body weight into three dosage groups receiving 0.5 g, 0.75 g or 1 g ascorbic acid daily (p 248), see Miller 1977b and Miller 1977c
Participants	US school children, ranging in age from 6 to 15 years. 12 twin pairs (5 boy pairs, 7 girl 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) (Table 3, p 259)
Notes	SD for duration was not published and it was calculated from the SE for the paired difference "...four mothers acknowledged tasting the contents of the capsules. We cannot exclude the possibility that ... recognized the vitamin C by taste and ...may have influenced their subjective symptom ratings" (p 251) Funding: The tablets were supplied by Eli Lilly and Co., Indianapolis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Within a twin pair, the assignment to the treatment group was random" (p 248)
Allocation concealment (selection bias)	Low risk	"double-blind"; "The code was not broken until after the analysis of symptom data had been completed" (p 248)
Baseline balance	Low risk	Twins
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"; "The code was not broken until after the analysis of symptom data had been completed" (p 248)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind"; "The code was not broken until after the analysis of symptom data had been completed" (p 248)
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 pair of boy twins was omitted from the analysis because of incomplete data (p 249)
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported

Miller 1977a (*Continued*)

Vitamin C and placebo indistinguishable?	Unclear risk	"The capsules contained 250 mg vitamin C or starch" (p 248) "Four mothers acknowledged tasting the contents of the capsules ... cannot exclude the possibility ... that they recognized the vitamin C by taste." (p 251)
Contamination	High risk	Before the trial the placebo group excreted on average 314 mg/day vitamin C in urine and the daily intake must have been much higher In addition, urinary vitamin C level of placebo group boys increased from baseline level of 319 mg/d to the trial level of 430 mg/d suggesting that some twins may have swapped their tablets. (Table 2, p 249)

Miller 1977b

Methods	See Miller 1977a This includes "medium body weight" twins administered 0.75 g/day vitamin C
Participants	12 twin pairs (6 boy pairs, 6 girl 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) (Table 3, p 259)
Notes	SD for duration was not published and it was calculated from the SE for the paired difference "...four mothers acknowledged tasting the contents of the capsules. We cannot exclude the possibility that ... recognized the vitamin C by taste and ...may have influenced their subjective symptom ratings" (p 251) Funding: The tablets were supplied by Eli Lilly and Co., Indianapolis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Within a twin pair, the assignment to the treatment group was random" (p 248)
Allocation concealment (selection bias)	Low risk	"double-blind"; "The code was not broken until after the analysis of symptom data had been completed" (p 248)

Miller 1977b (*Continued*)

Baseline balance	Low risk	Twins
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"; "The code was not broken until after the analysis of symptom data had been completed" (p 248)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind"; "The code was not broken until after the analysis of symptom data had been completed" (p 248)
Incomplete outcome data (attrition bias) All outcomes	Low risk	One pair of boy twins was omitted from the analysis because of incomplete data (p 249)
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Unclear risk	"The capsules contained 250 mg vitamin C or starch" (p 248) "Four mothers acknowledged tasting the contents of the capsules ... cannot exclude the possibility ... that they recognized the vitamin C by taste." (p 251)
Contamination	High risk	Before the trial the placebo group excreted on average 198 mg/day vitamin C in urine and the daily intake must have been much higher. In addition, urinary vitamin C level of placebo group boys increased from baseline level of 153 mg/d to the trial level of 309 mg/d suggesting that some twins may have swapped their tablets (Table 2, p 249)

Miller 1977c

Methods	See Miller 1977a This is "low body weight" twins administered 0.5 g/day vitamin C
Participants	20 twin pairs (7 boy pairs, 13 girl 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) (Table 3, p 259)
Notes	SD for duration was not published and it was calculated from the SE for the paired difference

	"...four mothers acknowledged tasting the contents of the capsules. We cannot exclude the possibility that ... recognized the vitamin C by taste and ...may have influenced their subjective symptom ratings" (p 251) Funding: The tablets were supplied by Eli Lilly and Co., Indianapolis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Within a twin pair, the assignment to the treatment group was random" (p 248)
Allocation concealment (selection bias)	Low risk	"double-blind"; "The code was not broken until after the analysis of symptom data had been completed" (p 248)
Baseline balance	Low risk	Twins
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"; "The code was not broken until after the analysis of symptom data had been completed" (p 248)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind"; "The code was not broken until after the analysis of symptom data had been completed" (p 248)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Unclear risk	"The capsules contained 250 mg vitamin C or starch" (p 248) "Four mothers acknowledged tasting the contents of the capsules ... cannot exclude the possibility ... that they recognized the vitamin C by taste." (p 251)
Contamination	High risk	Before the trial the placebo group excreted on average 188 mg/day vitamin C in urine and the daily intake must have been much higher. In addition, urinary vitamin C level of placebo group boys increased from the baseline level of 187 mg/d to the trial level of 299 mg/d in the placebo group suggesting that some twins may have swapped their tablets (Table 2, p 249)

Moolla 1996a

Methods	Double-blind RCT. Regular supplementation trial. Duration 6 weeks before and 2 weeks after the 90 km Comrades marathon of 1993
Participants	South Africa. Ultra marathon runners (age 36.0 +/- 7.4 years). 13 vitamin C; 19 placebo
Interventions	0.25 g/d vitamin C for 6 weeks before and 2 weeks after the race
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) Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The runners were randomly assigned" (p 14)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 14)
Baseline balance	Unclear risk	Table 4.2 (p 14) shows that age, total mileage, running years, stress, alcohol and tobacco use were balanced
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 14)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 14)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The drop out rates were 13% (2/15) in the vitamin C group compared with 37% (11/30) in the placebo group (p 16)
Selective reporting (reporting bias)	Low risk	Incidence of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"placebo was identical in form to the ascorbic acid" (p 14)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Moolla 1996b

Methods	See Moolla 1996a
Participants	Sedentary controls for marathon runners (age 36.5 +/- 6.3 years). 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) Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The runners were randomly assigned ... The non-running control with which the runner was paired received the identical supplement" (p 14)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 14)
Baseline balance	Low risk	Table 4.3 (p 15) shows that age, stress, alcohol and tobacco use were balanced
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 14)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 14)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The drop out rates were 27% (4/15) in the vitamin C group compared with 37% (11/30) in the placebo group (p 16)
Selective reporting (reporting bias)	Low risk	Incidence of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"placebo was identical in form to the ascorbic acid" (p 14)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Peters 1993a

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 weeks before the 90 km Comrades Marathon 1990
Participants	South Africa. 84 ultramarathon runners (82 male, 2 female). 43 vitamin C; 41 placebo. Five were <25 years old, 57 were between 25 and 40, and 22 were > 40 (p 172)
Interventions	0.6 g/d vitamin C for 3 weeks before the race, but not after the race
Outcomes	Outcome assessment continued for 2 weeks after the race Incidence (Analysis 1.1) and duration (Analysis 2.1) (Table 3, p 173)
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"were randomly divided into" (p 170)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 170)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 170)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 170)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"8 runners failed to comply with all requirements of the protocol and were excluded" (p 171)
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"identical looking and tasting placebo containing citric acid" (p 170)
Contamination	High risk	The average dietary vitamin C intake in the placebo group was 494 mg/day (Table 1, p 171)

Peters 1993b

Methods	See Peters 1993a.
Participants	Sedentary controls for marathon runners. 34 vitamin C; 39 placebo
Interventions	0.6 g/d vitamin C for 3 weeks before the race, but not after the race
Outcomes	Outcome assessment continued for 2 weeks after the race Incidence (Analysis 1.1) and duration (Analysis 2.1) (Table 3, p 173)
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"were randomly divided into" (p 170)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 170)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 170)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 170)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"19 control [ie non-runners] failed to comply with all requirements of the protocol and were excluded" (p 171)
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"identical looking and tasting placebo containing citric acid" (p 170)
Contamination	High risk	The average dietary vitamin C intake in the placebo group was 280 mg/day (Table 1, p 171)

Peters 1996a

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 weeks before the 1993 Comrades Marathon (90 km)
Participants	South Africa. Ultramarathon runners. 44 vitamin C (36 males, 8 females, mean age 34.3); 47 placebo (42 males, 5 females, mean age 39.2)
Interventions	0.5 g/d vitamin C for 3 weeks before the race, but not after the race
Outcomes	Outcome assessment continued for 2 weeks after the race Incidence (Analysis 1.1) and duration (Analysis 2.1) (Table 4, p 26)
Notes	SD for duration was not published and it was imputed, see Methods Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"runners ... were randomly divided" (p 23)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 23)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 23)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 23)
Incomplete outcome data (attrition bias) All outcomes	Low risk	14% (8/55) of placebo participants and 20% (11/55) of vitamin C participants dropped out
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
Vitamin C and placebo indistinguishable?	Unclear risk	"lactose as placebo" (p 24)
Contamination	High risk	The average dietary vitamin C intake in the placebo group was 585 mg/day (Table 2, p 24)

Peters 1996b

Methods	Double-blind RCT. Regular supplementation trial. Duration 3 weeks before the 1993 Comrades Marathon (90 km)
Participants	South Africa. Family controls for marathon runners. 41 vitamin C (11 males, 30 females, mean age 33.1); 45 placebo (16 males, 29 females, mean age 32.8)
Interventions	0.5 g/d vitamin C for 3 weeks before the race, but not after the race
Outcomes	Outcome assessment continued for 2 weeks after the race Incidence (Analysis 1.1) and duration (Analysis 2.1) (Table 4, p 26)
Notes	SD for duration was not published and it was imputed, see Methods Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"... non-running controls, were randomly divided .." (p 23)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 23)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 23)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 23)
Incomplete outcome data (attrition bias) All outcomes	Low risk	18% (10/55) of placebo participants and 25% (14/55) of vitamin C participants dropped out
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
Vitamin C and placebo indistinguishable?	Unclear risk	"lactose as placebo" (p 24)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Pitt 1979

Methods	Double-blind RCT. Regular supplementation trial. Duration 8 weeks
Participants	USA male marine recruits. 331 vitamin C (mean age 18.5); 343 placebo (mean age 18.5)
Interventions	2 g/d vitamin C
Outcomes	Incidence (Analysis 1.1), duration (Analysis 2.1) and severity (Analysis 3.1) (Table 2, p 910)
Notes	SD for duration was not published and it was imputed, see Methods The severity of colds was classified on a numerical rating from 1 to 4. Since the minimum of the scale was 1, the value 1 was subtracted from the mean severity scores in our calculation of the relative effect Funding: study was supported in part by US Navy and Hoffmann-LaRoche Inc supplied the tablets

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"assigned randomly ... from a list of consecutive numbers randomized in pairs. Randomization was carried out by individual recruits within each platoon." (p 908)
Allocation concealment (selection bias)	Low risk	"Neither the recruits or drill instructors nor the physicians and corpsmen who treated the recruits were aware of which pill any individual recruit was taking." (p 908)
Baseline balance	Low risk	Table 1 shows balance for age, race, previous medical history, previous cold history, work days lost per year (p 909)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the recruits or drill instructors nor the physicians and corpsmen who treated the recruits were aware of which pill any individual recruit was taking." (p 908)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Neither the recruits or drill instructors nor the physicians and corpsmen who treated the recruits were aware of which pill any individual recruit was taking." (p 908)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 862 recruits who began taking the pills, 64 (34 vitamin C, 30 placebo) were removed from their platoons. An additional 123 recruits (64 vitamin C, 59 placebo)

Pitt 1979 (*Continued*)

		were excluded from the final analysis because they did not continue to take their pills for the full study period (p909) The dropout rates were 22.8% (98/429) in the vitamin C group, compared with 20. 6% (89/432) in the placebo group
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
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" (p 908)
Contamination	Unclear risk	After 6 wk of pill taking, the difference between placebo and vitamin C groups was not substantial (9.1 versus 13.6 mg/l) (p 909)

Regnier 1968

Methods	Initiated as a double-blind trial, but changed to a single-blind. Subjects were were studied for between three and five years (p 950)
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 ... and the oldest was 73" (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, 0.600 or 0.625g of vitamin C was administered every 3 h from the beginning of a cold for 3 to 4 days and then reduced to 0.375 to 0.400g every 3 hours for 2 to 3 days. The dose is further reduced until day 10 to 12 at which point it is ceased if there are no symptoms
Outcomes	See our Table 1
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Allocation method not described

Regnier 1968 (*Continued*)

Allocation concealment (selection bias)	Low risk	"I initiated a double-blind study" (p 949). Double-blind indicates that allocation was concealed
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"I initiated a double-blind study" (p 949)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"I initiated a double-blind study" (p 949)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Of the 160 "cold incidents" there were 23 which could not be included in the results, because for the particular cold the subjects did not correctly follow the particular treatment prescribed for them." (p 950)
Selective reporting (reporting bias)	Unclear risk	Reported poorly, no unambiguous outcome. Included in Table 1
Vitamin C and placebo indistinguishable?	Unclear risk	"lactose placebo" "All medications were issued in the orange duo-CVP capsules, except that during the later studies white tablets of ascorbic acid were sometimes used. ... capsules identical ..." (p 952)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Ritzel 1961

Methods	Double-blind RCT. Regular supplementation trial. Duration 2 weeks
Participants	Children attending two 5 to 7 day long ski camps in Swiss Alps. 139 vitamin C; 140 placebo
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1) (Tabelle 1, p 65, and p 66)
Notes	SD for duration was not published and the SD was calculated from the P value Funding: tablets were supplied by Hoffmann-LaRoche, Basel.

Risk of bias

Ritzel 1961 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The children were randomly separated into two groups" (p 1108; 1976)
Allocation concealment (selection bias)	Low risk	"Neither test subjects nor investigators knew whether the children got placebo or vitamin C" (p 1108; 1976)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above and "The study was double-blinded, neither the study participants nor the camp doctors were aware of the set up of the study" (p 3 of the English translation)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above and "Professionals who had absolutely no connection with personnel involved in the study decoded and statistically evaluated the study results" (p 3 of the English translation)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Short study in camp
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"The placebo was indistinguishable from the 1-gm ascorbic acid tablet" (p 1108; 1976)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

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 (mean age 25.3, range 17 to 40); 56 placebo (mean age 25.4, range 17 to 47)
Interventions	1 g/d vitamin C
Outcomes	Incidence (Analysis 1.1) and duration (Analysis 2.1) and severity (Analysis 3.1) (Table 4, p 5, and Table 6, p 6)

Sabiston 1974 (*Continued*)

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." Funding: Canadian Army

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Men in each tent were assigned randomly" (p 4) "we did assign people randomly. We had the names of people beforehand but we assigned them randomly and we provided their names on the pill vials. The Tent Group Commander was responsible for distributing the pills and recording the distribution. He did NOT know what was in the vials. ... While we pre-assigned Vit C and Placebo randomly, we did not break the code until after the trial. Two labelled vials were provided to the Tent Group Commanders but the Tent Group Commanders did NOT know what was in the vials" (email Radomski 12 September 2009)
Allocation concealment (selection bias)	Low risk	"we did assign people randomly. We had the names of people beforehand but we assigned them randomly and we provided their names on the pill vials. The Tent Group Commander was responsible for distributing the pills and recording the distribution. He did NOT know what was in the vials. ... While we pre-assigned Vit C and Placebo randomly, we did not break the code until after the trial. Two labelled vials were provided to the Tent Group Commanders but the Tent Group Commanders did NOT know what was in the vials" (email Radomski 12 September 2009)
Baseline balance	Low risk	Table 2 shows that age and common cold history were balanced
Blinding of participants and personnel (performance bias)	Low risk	"The Tent Group Commander was responsible for distributing the pills and record-

Sabiston 1974 (*Continued*)

All outcomes		ing the distribution. He did NOT know what was in the vials. ... While we pre-assigned Vit C and Placebo randomly, we did not break the code until after the trial. Two labelled vials were provided to the Tent Group Commanders but the Tent Group Commanders did NOT know what was in the vials" (email Radomski 12 September 2009)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The Tent Group Commander was responsible for distributing the pills and recording the distribution. He did NOT know what was in the vials. ... While we pre-assigned Vit C and Placebo randomly, we did not break the code until after the trial. Two labelled vials were provided to the Tent Group Commanders but the Tent Group Commanders did NOT know what was in the vials" (email Radomski 12 September 2009)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Short study in military conditions
Selective reporting (reporting bias)	Low risk	Incidence of colds, duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"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." (email Radomski 12 September 2009)
Contamination	Low risk	" it was determined that the RP-4 rations (1970-71) on which the men were living, apparently provided a maximum of 37-41 mg Vitamin C per day in a single fruit-drink mix." (p 4) "The whole-blood ascorbate levels of individuals receiving a Vitamin C supplement were increased well above normal (100-150%)" (p 8)

Sasazuki 2006

Methods	Double-blind RCT. Regular supplementation trial. Duration 3.5 years
Participants	Japanese male and female participants in annual screening programs for circulatory diseases and diagnosed as having atrophic gastritis, mean age 57 years, range 40 to 69 140 vitamin C (45 male, 79 female); 133 placebo (41 male, 79 female)
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 Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The assignment was based on simple randomization by using a table of random sampling numbers" (p 10)
Allocation concealment (selection bias)	Low risk	"randomized in a double-blind manner" (p 10)
Baseline balance	Low risk	Table 1 shows balance for age, sex, smoking, alcohol, BMI, dietary intake of vitamin C, and fruit
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"randomized in a double-blind manner" (p 10)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"randomized in a double-blind manner" (p 10)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"144 and 161 were assigned to receive 50 or 500 mg of vitamin C respectively ... 61 dropped out and 244 completed the trial" (p 9) The dropout rates were 23% (37/161) in the vitamin C group compared with 17% (24/144) in the placebo group
Selective reporting (reporting bias)	Low risk	Incidence of colds reported

Sasazuki 2006 (*Continued*)

Vitamin C and placebo indistinguishable?	Unclear risk	There was insufficient reporting to enable assessment
Contamination	High risk	Placebo contained 50 mg/d vitamin C

Scheunert 1949

Methods	Placebo controlled trial. Regular supplementation 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	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	There was insufficient reporting to enable assessment
Allocation concealment (selection bias)	Unclear risk	There was insufficient reporting to enable assessment
Baseline balance	Unclear risk	There was insufficient reporting to enable assessment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There was insufficient reporting to enable assessment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient reporting to enable assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient reporting to enable assessment
Selective reporting (reporting bias)	Unclear risk	Reported poorly, no unambiguous outcome. Included in Table 1

Scheunert 1949 (*Continued*)

Vitamin C and placebo indistinguishable?	Unclear risk	There was insufficient reporting to enable assessment
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Schwartz 1973

Methods	Double-blind trial. Experimentally induced colds
Participants	Male US prison volunteers, average age 28 years (range 22 to 51). 11 vitamin C; 10 placebo
Interventions	3 g/d vitamin C 2 weeks before nasal instillation of rhinovirus
Outcomes	See our Table 2
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of allocation not described
Allocation concealment (selection bias)	Low risk	"double-blind" (Abstract, p 500)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; "each man received two tablets from an individually coded bottle" (p 501)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Short study in a prison
Selective reporting (reporting bias)	Unclear risk	No unambiguous outcome. Included in Table 2
Vitamin C and placebo indistinguishable?	Unclear risk	There was insufficient reporting to enable assessment

Schwartz 1973 (*Continued*)

Contamination	Unclear risk	There was insufficient reporting to enable assessment

Tebrock 1956

Methods	Double-blinded trial. Therapeutic trial between January and May 1956
Participants	Adults from US 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	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"in order to reduce the possibility of the clinical judgments being influenced by continued association of better results with one of the preparations, each of them was supplied under two numbers, making eight test groups in all to which the patients were assigned in rotation" (p 1228)
Allocation concealment (selection bias)	Low risk	"Medicaments supplied to these physicians were identified only by number, so that neither they nor the patients were aware of what was being given" (p 1228); see also above
Baseline balance	Unclear risk	There was insufficient reporting to enable assessment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Medicaments supplied to these physicians were identified only by number, so that neither they nor the patients were aware of what was being given" (p 1228); see also above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Medicaments supplied to these physicians were identified only by number, so that neither they nor the patients were aware of what was being given" (p 1228); see also

Tebrock 1956 (*Continued*)

		above
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Almost 2000 individuals ... were used in the study. A small number were dropped for failure to report back on the third day, and a few study forms were not completely filled out, but over 1900 observations [were] reported under all headings ..." (p 1229)
Selective reporting (reporting bias)	Unclear risk	No unambiguous outcome. Included in Table 1
Vitamin C and placebo indistinguishable?	Unclear risk	There was insufficient reporting to enable assessment
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Tyrrell 1977a

Methods	Double-blind RCT. Therapeutic trial, males
Participants	Participants were recruited from retail stores, an engineering plant, headquarters and production sites of a large industrial group, a government office, and the staff of a hospital in the UK, from December 1975 to April 1976. This comparison is males (1977b is females). 124 males were administered vitamin C and 141 males were administered placebo
Interventions	4 g/d vitamin C for the first 2.5 days of illness
Outcomes	Duration (Analysis 6.1) and severity (Analysis 5.1) (Table 2, p 190)
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Allocation to ... treatment was made at random" (p 189)
Allocation concealment (selection bias)	Low risk	"neither the volunteer nor the trial organiser was aware which was the active and which was the placebo code until after the study" (p 189)
Baseline balance	Unclear risk	Baseline balance not demonstrated

Tyrrell 1977a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"neither the volunteer nor the trial organiser was aware which was the active and which was the placebo code until after the study" (p 189)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"neither the volunteer nor the trial organiser was aware which was the active and which was the placebo code until after the study" (p 189)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Records for 23 volunteers were excluded (10 vitamin C, 13 placebo) (p 190). The drop out rates were 4.3% (10/235) in the vitamin C group compared with 4.8% (13/270) in the placebo group
Selective reporting (reporting bias)	Low risk	Duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"the tubes with 'placebo treatment', contained inert substances of identical appearance and taste" "A small subsidiary trial confirmed that volunteers could not detect the difference between the two preparations by taste. "(p 189)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Tyrrell 1977b

Methods	Double-blind RCT. Therapeutic trial, females
Participants	Participants were recruited from retail stores, an engineering plant, headquarters and production sites of a large industrial group, a government office, and the staff of a hospital in the UK, from December 1975 to April 1976. This comparison is females (1977a is females) 101 females were administered vitamin C and 116 females were administered placebo
Interventions	4 g/d vitamin C for the first 2.5 days of illness
Outcomes	Duration (Analysis 6.1) and severity (Analysis 5.1) (Table 2, p 190)
Notes	Funding: not reported
Risk of bias	

Tyrrell 1977b (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Allocation to ... treatment was made at random" (p 189)
Allocation concealment (selection bias)	Low risk	"neither the volunteer nor the trial organiser was aware which was the active and which was the placebo code until after the study" (p 189)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"neither the volunteer nor the trial organiser was aware which was the active and which was the placebo code until after the study" (p 189)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"neither the volunteer nor the trial organiser was aware which was the active and which was the placebo code until after the study" (p 189)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Records for 23 volunteers were excluded (10 vitamin C, 13 placebo) (p 190). The drop out rates were 4.3% (10/235) in the vitamin C group compared with 4.8% (13/270) in the placebo group
Selective reporting (reporting bias)	Low risk	Duration of colds and severity of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"the tubes with 'placebo treatment', contained inert substances of identical appearance and taste" "A small subsidiary trial confirmed that volunteers could not detect the difference between the two preparations by taste." (p 189)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Van Straten 2002

Methods	Double-blind RCT. Regular supplementation trial. Duration 60 days between November and February
Participants	UK, both sexes. 84 vitamin C (15 males, 69 females, mean age 47.7); 84 placebo (12 males, 72 females, mean age 48.5)
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	Funding: tablets were provided by the Inter-Cal Corporation, Prescott, Arizona, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A simple random number generator assigned volunteers" (p 152)
Allocation concealment (selection bias)	Low risk	"double-blind" (p 153); "Randomization codes were kept secure and were not broken until all the survey data had been returned" (p 152)
Baseline balance	Unclear risk	Baseline balance not demonstrated, only sex distribution shown in Table 3
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" (p 153); "Randomization codes were kept secure and were not broken until all the survey data had been returned" (p 152)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" (p 153); "Randomization codes were kept secure and were not broken until all the survey data had been returned" (p 152)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Two participants withdrew from the study for personal reasons" (p 154)
Selective reporting (reporting bias)	Low risk	Incidence of colds and duration of colds reported
Vitamin C and placebo indistinguishable?	Low risk	"ascorbate 500 mg or a matched placebo" (p 152). "matched placebo control that looked and tasted exactly the same as the active material" (p 153)

Van Straten 2002 (*Continued*)

Contamination	Unclear risk	There was insufficient reporting to enable assessment

Walker 1967

Methods	Placebo-controlled trial. Experimentally induced colds.
Participants	UK adults both sexes, mean age 30.2 years, range 18 to 50. 47 vitamin C; 44 placebo
Interventions	3 g/d vitamin C for 3 days before and 6 days after nasal instillation of rhinovirus
Outcomes	See our Table 2.
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of allocation not described
Allocation concealment (selection bias)	Unclear risk	There was insufficient reporting to enable assessment
Baseline balance	Unclear risk	Baseline balance not demonstrated,
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There was insufficient reporting to enable assessment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient reporting to enable assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Laboratory study
Selective reporting (reporting bias)	Unclear risk	No unambiguous outcome. Included in Table 2
Vitamin C and placebo indistinguishable?	Low risk	"placebo tablets which were indistinguishable from the ascorbic acid tablets except by chemical analysis" (p 604)
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Wilson 1973a

Methods	Double-blind RCT. Regular supplementation trial. Duration 9 months from September 1967 to May 1968
Participants	UK boarding school girls aged 12 to 18 years. 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) (Table 1, p 28, 1973)
Notes	Complicated classification system makes comparison with other trials difficult. Kinlen and Peto pointed out that Wilson calculated 48 different P-values in the report without considering the multiple-comparison problem Funding: the authors thanked "the pharmaceutical industry for supplies of Vitamin C and Placebo tablets, and for financial assistance" but the name of the company was not mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"children ... randomly divided ... random number tables" (p 197)
Allocation concealment (selection bias)	Low risk	"Double-blind"; "The number codes for identification of the medication were kept in sealed envelopes in the university. None of the envelopes was opened by the investigators during the course of the trial" (p 198)
Baseline balance	Unclear risk	Baseline balance not demonstrated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"; "The number codes for identification of the medication were kept in sealed envelopes in the university. None of the envelopes was opened by the investigators during the course of the trial" (p 198)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind"; "The number codes for identification of the medication were kept in sealed envelopes in the university. None of the envelopes was opened by the investigators during the course of the trial" (p 198)

Wilson 1973a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient reporting to enable assessment
Selective reporting (reporting bias)	Unclear risk	There was insufficient reporting to enable assessment
Vitamin C and placebo indistinguishable?	Unclear risk	There was insufficient reporting to enable assessment
Contamination	Unclear risk	There was insufficient reporting to enable assessment

Wilson 1973b

Methods	Double-blind RCT. Regular supplementation trial. Duration 9 months from September 1967 to May 1968
Participants	UK boarding school boys aged 12 to 18 years. 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) (Table 1, p 28, 1973)
Notes	Complicated classification system makes comparison with other trials difficult. Kinlen and Peto pointed out that Wilson calculated 48 different P-values in the report without considering the multiple-comparison problem Funding: the authors thanked "the pharmaceutical industry for supplies of Vitamin C and Placebo tablets, and for financial assistance" but the name of the company was not mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"children ... randomly divided ... random number tables" (p 197)
Allocation concealment (selection bias)	Low risk	"Double-blind"; "The number codes for identification of the medication were kept in sealed envelopes in the university. None of the envelopes was opened by the investigators during the course of the trial" (p 198)
Baseline balance	Unclear risk	There was insufficient reporting to enable assessment

Wilson 1973b (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"; "The number codes for identification of the medication were kept in sealed envelopes in the university. None of the envelopes was opened by the investigators during the course of the trial" (p 198)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind"; "The number codes for identification of the medication were kept in sealed envelopes in the university. None of the envelopes was opened by the investigators during the course of the trial" (p 198)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient reporting to enable assessment
Selective reporting (reporting bias)	Unclear risk	There was insufficient reporting to enable assessment
Vitamin C and placebo indistinguishable?	Unclear risk	There was insufficient reporting to enable assessment
Contamination	Unclear risk	There was insufficient reporting to enable assessment

g/d: grams per day
h: hours
mg/d: milligrams per day
SD: standard deviation
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
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 1997b and Hemilä 2006a). The heterogeneity between sexes was highly significant (Hemilä 2008). The benefit of low-dose vitamin C supplementation for males may be explained by low dietary vitamin C intake in the UK (Hemilä 1997b)

(*Continued*)

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 not a parallel comparison. 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. Vitamin C was argued to be beneficial
Bergquist 1943	Low dose. A Swedish trial involving supplementation with only 0.03 g/d vitamin C
Bessel-Lorck 1959	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 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 people with poliomyelitis
Chavance 1993	Low dose. Double-blind RCT of 0.09 g/d vitamin C in elderly participants. No benefit was demonstrated
Cuendet 1949	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

(*Continued*)

	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 = 0.034, Hemilä 2004)
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 not a parallel comparison. 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)
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 with acute bronchitis or pneumonia who were admitted to hospital for treatment were administered 0.2 g/d of vitamin C (see Hemilä 2013b)
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 2013b)
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 of rhinorrhoea
Masek 1974	Low dose. 2 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
Miegl 1957	No placebo comparison. Case series reporting benefit of vitamin C
Miegl 1958	No placebo comparison. Case series reporting benefit of vitamin C
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

(*Continued*)

Pico Sirvent 2013	Not a parallel comparison. Vitamin C was administered together with beta-glucan to 166 children from 1 to 10 years old. "Number of respiratory infections... registered during four visits and compared with the same 6 months period from previous year"
Renker 1954	No placebo comparison. Participants worked at a shipyard and those administered vitamin C had lower incidence of colds and flu-like symptoms
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

DATA AND ANALYSES

Comparison 1. Incidence of colds when on regular vitamin C

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	35	11941	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.93, 0.99]
1.1 General community trials with ≥1 g/day vitamin C	20	7308	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.95, 1.01]
1.2 General community trials with <1 g/day vitamin C	8	4011	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.90, 1.03]
1.3 Short-term exposure to severe physical stress and/or cold	7	622	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.37, 0.64]

Comparison 2. Duration of colds occurring when on regular vitamin C

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ≥ 0.2 g/day vitamin C (effect in %)	36	9832	Mean Difference (IV, Fixed, 95% CI)	-9.61 [-12.94, -6.29]
1.1 Adults	22	7300	Mean Difference (IV, Fixed, 95% CI)	-8.09 [-11.89, -4.29]
1.2 Children	14	2532	Mean Difference (IV, Fixed, 95% CI)	-14.54 [-21.37, -7.70]
2 ≥ 1 g/day vitamin C (effect in %)	27	8206	Mean Difference (IV, Fixed, 95% CI)	-9.92 [-13.48, -6.35]
2.1 Adults	17	6672	Mean Difference (IV, Fixed, 95% CI)	-8.14 [-12.08, -4.19]
2.2 Children	10	1534	Mean Difference (IV, Fixed, 95% CI)	-17.82 [-26.14, -9.50]
3 ≥ 1 g/day vitamin C (effect in days)	28	8836	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-0.63, -0.28]
3.1 Adults	18	7302	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.58, -0.20]
3.2 Children	10	1534	Mean Difference (IV, Fixed, 95% CI)	-0.97 [-1.48, -0.47]

Comparison 3. Severity of colds occurring when on regular vitamin C (effect in %)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severity of the common cold (effect in %)	15	6118	Mean Difference (IV, Fixed, 95% CI)	-13.25 [-18.28, -8.22]
1.1 Days indoors or off work or school	8	4388	Mean Difference (IV, Fixed, 95% CI)	-13.55 [-20.01, -7.09]
1.2 Symptom severity score	7	1730	Mean Difference (IV, Fixed, 95% CI)	-12.79 [-20.81, -4.77]

Comparison 4. Duration of colds with therapeutic vitamin C (effect in %)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of the common cold (effect in %)	13	4017	Mean Difference (IV, Fixed, 95% CI)	-4.21 [-8.65, 0.23]
1.1 vitamin C dose 1.5-4 g/day	12	3299	Mean Difference (IV, Fixed, 95% CI)	-2.39 [-7.10, 2.31]
1.2 vitamin C dose 8 g/day	1	718	Mean Difference (IV, Fixed, 95% CI)	-18.90 [-32.28, -5.52]
2 1-day colds: Anderson (1974) therapeutic 8 g/day comparisons	1		Risk Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 8 g/day vs. Placebo group #4	1	920	Risk Difference (IV, Fixed, 95% CI)	0.13 [0.07, 0.19]
2.2 8 g/day vs. 4 g/day vitamin C	1	900	Risk Difference (IV, Fixed, 95% CI)	0.07 [0.00, 0.13]
2.3 8 g/day vs. regular vitamin C groups	1	2307	Risk Difference (IV, Fixed, 95% CI)	0.08 [0.03, 0.13]

Comparison 5. Severity of colds with therapeutic vitamin C (effect in %)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severity of common cold (effect, %)	9	2780	Mean Difference (IV, Fixed, 95% CI)	-6.26 [-17.35, 4.82]
1.1 Days indoors or off work or school	7	2641	Mean Difference (IV, Fixed, 95% CI)	-11.91 [-24.61, 0.79]
1.2 Symptom severity score	2	139	Mean Difference (IV, Fixed, 95% CI)	11.78 [-10.92, 34.47]

Comparison 6. Within-trial subgroup comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anderson (1972): Contact with children	1	818	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.90, -0.23]
1.1 Contact young children	1	288	Mean Difference (IV, Fixed, 95% CI)	-1.12 [-1.68, -0.56]
1.2 No contact young children	1	530	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.68, 0.16]
2 Anderson (1972): Usual frequency of colds	1	818	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-0.91, -0.24]
2.1 Usually 0-1 colds per winter	1	415	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.67, 0.27]
2.2 Usually ≥ 2 colds per winter	1	403	Mean Difference (IV, Fixed, 95% CI)	-0.98 [-1.46, -0.50]
3 Carr (1981): Twins living together and apart	2	292	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-2.49, -0.41]
3.1 Apart	1	165	Mean Difference (IV, Fixed, 95% CI)	-2.64 [-4.04, -1.24]
3.2 Together	1	127	Mean Difference (IV, Fixed, 95% CI)	0.04 [-1.52, 1.60]
4 Constantini (2011): Boys and girls	1	98	Mean Difference (IV, Fixed, 95% CI)	-2.27 [-4.93, 0.39]
4.1 Boys	1	51	Mean Difference (IV, Fixed, 95% CI)	-4.9 [-8.42, -1.38]
4.2 Girls	1	47	Mean Difference (IV, Fixed, 95% CI)	1.20 [-2.85, 5.25]

Comparison 7. Adverse effects in large trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects	3	3219	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.86, 1.37]

Comparison 8. Karlowski and Anderson 95% confidence interval calculations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Karlowski 1975	3	379	Mean Difference (IV, Fixed, 95% CI)	-11.30 [-21.34, -1.25]
2 Anderson 1974 therapy	2	1774	Mean Difference (IV, Fixed, 95% CI)	-14.66 [-22.56, -6.76]

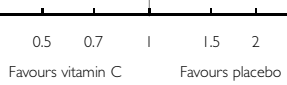
Analysis 1.1. Comparison 1 Incidence of colds when on regular vitamin C, Outcome 1 Proportion of participants developing ≥ 1 cold episodes during the trial.

Review: Vitamin C for preventing and treating the common cold

Comparison: 1 Incidence of colds when on regular vitamin C

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 General community trials with ≥ 1 g/day vitamin C					
Anderson 1972	302/407	335/411		11.0 %	0.91 [0.85, 0.98]
Anderson 1974a	212/277	157/202		6.0 %	0.98 [0.89, 1.09]
Anderson 1974b	210/275	156/200		5.9 %	0.98 [0.89, 1.08]
Anderson 1974c	243/308	175/225		6.7 %	1.01 [0.93, 1.11]
Bancalari 1984	21/32	21/30		0.7 %	0.94 [0.67, 1.32]
Briggs 1984	125/265	121/263		4.0 %	1.03 [0.85, 1.23]
Carson 1975	85/121	84/123		2.7 %	1.03 [0.87, 1.22]
Charleston 1972	31/47	37/43		1.3 %	0.77 [0.60, 0.97]
Clegg 1975	48/67	50/70		1.6 %	1.00 [0.81, 1.24]
Coulehan 1974a	19/190	23/192		0.8 %	0.83 [0.47, 1.48]
Coulehan 1974b	16/131	17/128		0.6 %	0.92 [0.49, 1.74]
Coulehan 1976	98/428	98/428		3.2 %	1.00 [0.78, 1.28]
Elwood 1976	296/339	298/349		9.7 %	1.02 [0.96, 1.09]
Himmelstein 1998	10/23	8/25		0.3 %	1.36 [0.65, 2.84]
Johnston 2014	7/15	11/13		0.4 %	0.55 [0.31, 0.99]
Liljefors 1972	10/33	9/33		0.3 %	1.11 [0.52, 2.38]
Ludvigsson 1977a	49/80	44/78		1.5 %	1.09 [0.84, 1.41]
Ludvigsson 1977b	230/304	240/311		7.8 %	0.98 [0.90, 1.07]
Pitt 1979	298/331	309/343		10.0 %	1.00 [0.95, 1.05]
Van Straten 2002	35/84	34/84		1.1 %	1.03 [0.72, 1.48]
Subtotal (95% CI)	**3757**	**3551**		**75.3 %**	**0.98 [0.95, 1.01]**
Total events: 2345 (Vitamin C), 2227 (Placebo)					
Heterogeneity: Chi^2 = 17.09, df = 19 (P = 0.58); I^2 =0.0%					
Test for overall effect: Z = 1.10 (P = 0.27)					
2 General community trials with <1 g/day vitamin C					
Anderson 1974d	257/331	188/241		7.2 %	1.00 [0.91, 1.09]



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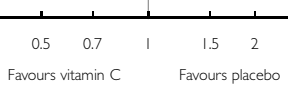
Study or subgroup	Vitamin C n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cowan 1942	184/208	142/155		5.4 %	0.97 [0.90, 1.03]
Dahlberg 1944	131/1259	140/1266		4.6 %	0.94 [0.75, 1.18]
Franz 1956	14/44	15/45		0.5 %	0.95 [0.52, 1.74]
Moolla 1996b	5/11	12/19		0.3 %	0.72 [0.35, 1.50]
Peters 1993b	18/34	18/39		0.6 %	1.15 [0.72, 1.82]
Peters 1996b	5/41	11/45		0.3 %	0.50 [0.19, 1.31]
Sasazuki 2006	68/140	67/133		2.3 %	0.96 [0.76, 1.23]
Subtotal (95% CI)	**2068**	**1943**		**21.0 %**	**0.96 [0.90, 1.03]**
Total events: 682 (Vitamin C), 593 (Placebo)					
Heterogeneity: Chi^2 = 3.49, df = 7 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 1.04 (P = 0.30)					
3 Short-term exposure to severe physical stress and/or cold					
Carillo 2008a	3/6	4/6		0.1 %	0.75 [0.28, 2.00]
Carillo 2008b	2/6	4/6		0.1 %	0.50 [0.14, 1.77]
Moolla 1996a	4/13	13/19		0.3 %	0.45 [0.19, 1.07]
Peters 1993a	14/43	28/41		0.9 %	0.48 [0.30, 0.77]
Peters 1996a	7/44	19/47		0.6 %	0.39 [0.18, 0.84]
Ritzel 1961	17/139	31/140		1.0 %	0.55 [0.32, 0.95]
Sabiston 1974	6/56	14/56		0.5 %	0.43 [0.18, 1.04]
Subtotal (95% CI)	**307**	**315**		**3.6 %**	**0.49 [0.37, 0.64]**
Total events: 53 (Vitamin C), 113 (Placebo)					
Heterogeneity: Chi^2 = 1.38, df = 6 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 5.13 (P < 0.00001)					
Total (95% CI)	**6132**	**5809**		**100.0 %**	**0.96 [0.93, 0.99]**
Total events: 3080 (Vitamin C), 2933 (Placebo)					
Heterogeneity: Chi^2 = 49.54, df = 34 (P = 0.04); I^2 =31%					
Test for overall effect: Z = 2.77 (P = 0.0056)					
Test for subgroup differences: Chi^2 = 24.94, df = 2 (P = 0.00), I^2 =92%					



Analysis 2.1. Comparison 2 Duration of colds occurring when on regular vitamin C, Outcome 1 ≥ 0.2 g/day vitamin C (effect in %).

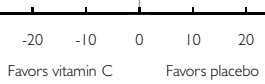
Review: Vitamin C for preventing and treating the common cold

Comparison: 2 Duration of colds occurring when on regular vitamin C

Outcome: 1 ≥ 0.2 g/day vitamin C (effect in %)

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 Adults							
Johnston 2014	12	40.7 (26)	17	100 (83)		0.6 %	-59.30 [-101.41, -17.19]
Van Straten 2002	37	58.1 (96)	50	100 (150)		0.4 %	-41.90 [-93.72, 9.92]
Himmelstein 1998	14	59.5 (26)	12	100 (83)		0.5 %	-40.50 [-89.40, 8.40]
Carr 1981b	57	64.8 (60)	71	100 (60)		2.5 %	-35.20 [-56.11, -14.29]
Sabiston 1974	6	71.7 (50)	14	100 (50)		0.5 %	-28.30 [-76.12, 19.52]
Peters 1993b	18	75 (38)	18	100 (57)		1.1 %	-25.00 [-56.65, 6.65]
Charleston 1972	44	84.2 (46)	80	100 (20)		5.4 %	-15.80 [-30.08, -1.52]
Peters 1996a	7	85.3 (78)	19	100 (91)		0.2 %	-14.70 [-85.50, 56.10]
Anderson 1974d	508	88.3 (80)	122	100 (91)		3.6 %	-11.70 [-29.28, 5.88]
Karlowski 1975e	76	91.6 (54)	56	100 (45)		3.9 %	-8.40 [-25.32, 8.52]
Anderson 1974c	465	91.7 (83)	111	100 (91)		3.2 %	-8.30 [-26.83, 10.23]
Elwood 1976	627	93.6 (90)	690	100 (99)		10.6 %	-6.40 [-16.61, 3.81]
Briggs 1984	125	93.9 (85)	121	100 (91)		2.3 %	-6.10 [-28.12, 15.92]
Karlowski 1975a	52	94 (54)	65	100 (52)		2.9 %	-6.00 [-25.37, 13.37]
Clegg 1975	68	94.7 (41)	73	100 (39)		6.3 %	-5.30 [-18.53, 7.93]
Anderson 1972	561	94.7 (92)	609	100 (82)		11.0 %	-5.30 [-15.32, 4.72]
Anderson 1974b	414	95.1 (87)	99	100 (91)		2.8 %	-4.90 [-24.69, 14.89]
Anderson 1974a	436	97 (88)	105	100 (91)		3.0 %	-3.00 [-22.27, 16.27]
Pitt 1979	600	97.4 (89)	619	100 (91)		10.8 %	-2.60 [-12.70, 7.50]
Carr 1981a	94	100.7 (92)	70	100 (91)		1.4 %	0.70 [-27.59, 28.99]
Peters 1993a	14	103.4 (17)	28	100 (42)		3.4 %	3.40 [-14.53, 21.33]
Peters 1996b	5	136.2 (124)	11	100 (91)		0.1 %	36.20 [-85.06, 157.46]
Subtotal (95% CI)	**4240**		**3060**			**76.4 %**	**-8.09 [-11.89, -4.29]**

Heterogeneity: Chi² = 23.17, df = 21 (P = 0.33); I² =9%



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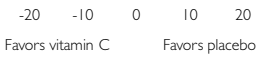
Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Test for overall effect: Z = 4.18 (P = 0.000030)							
2 Children							
Constantini 2011a	30	52.9 (48)	21	100 (68)		1.0 %	-47.10 [-80.88, -13.32]
Ludvigsson 1977a	62	61.3 (41)	55	100 (67)		2.6 %	-38.70 [-59.14, -18.26]
Ritzel 1961	17	69.2 (50)	31	100 (50)		1.3 %	-30.80 [-60.38, -1.22]
Coulehan 1974b	16	70.6 (64)	17	100 (82)		0.4 %	-29.40 [-79.43, 20.63]
Bancalari 1984	38	75.6 (62)	46	100 (65)		1.5 %	-24.40 [-51.63, 2.83]
Wilson 1973a	160	84.5 (118)	126	100 (134)		1.3 %	-15.50 [-45.19, 14.19]
Miller 1977c	116	87.3 (73)	122	100 (73)		3.2 %	-12.70 [-31.25, 5.85]
Coulehan 1974a	19	87.6 (80)	23	100 (82)		0.5 %	-12.40 [-61.56, 36.76]
Miller 1977a	53	92.8 (111)	42	100 (111)		0.5 %	-7.20 [-52.14, 37.74]
Ludvigsson 1977b	423	94.1 (85)	398	100 (114)		5.8 %	-5.90 [-19.72, 7.92]
Coulehan 1976	98	94.8 (86)	98	100 (82)		2.0 %	-5.20 [-28.73, 18.33]
Miller 1977b	42	96.7 (51)	40	100 (51)		2.3 %	-3.30 [-25.38, 18.78]
Wilson 1973b	205	108.1 (202)	187	100 (133)		1.0 %	8.10 [-25.49, 41.69]
Constantini 2011b	25	116.2 (74)	22	100 (111)		0.4 %	16.20 [-38.51, 70.91]
Subtotal (95% CI)	**1304**		**1228**			**23.6 %**	**-14.54 [-21.37, -7.70]**
Heterogeneity: Chi^2 = 17.15, df = 13 (P = 0.19); I^2 =24%							
Test for overall effect: Z = 4.17 (P = 0.000030)							
Total (95% CI)	**5544**		**4288**			**100.0 %**	**-9.61 [-12.94, -6.29]**
Heterogeneity: Chi^2 = 42.94, df = 35 (P = 0.17); I^2 =18%							
Test for overall effect: Z = 5.68 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 2.61, df = 1 (P = 0.11), I^2 =62%							



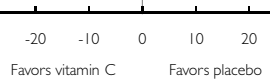
Analysis 2.2. Comparison 2 Duration of colds occurring when on regular vitamin C, Outcome 2 ≥ 1 g/day vitamin C (effect in %).

Review: Vitamin C for preventing and treating the common cold

Comparison: 2 Duration of colds occurring when on regular vitamin C

Outcome: 2 ≥ 1 g/day vitamin C (effect in %)

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 Adults							
Johnston 2014	12	40.7 (26)	17	100 (83)		0.7 %	-59.30 [-101.41, -17.19]
Van Straten 2002	37	58.1 (96)	50	100 (150)		0.5 %	-41.90 [-93.72, 9.92]
Himmelstein 1998	14	59.5 (26)	12	100 (83)		0.5 %	-40.50 [-89.40, 8.40]
Carr 1981b	57	64.8 (60)	71	100 (60)		2.9 %	-35.20 [-56.11, -14.29]
Sabiston 1974	6	71.7 (50)	14	100 (50)		0.6 %	-28.30 [-76.12, 19.52]
Charleston 1972	44	84.2 (46)	80	100 (20)		6.2 %	-15.80 [-30.08, -1.52]
Karlowski 1975e	76	91.6 (54)	56	100 (45)		4.4 %	-8.40 [-25.32, 8.52]
Anderson 1974c	465	91.7 (83)	155	100 (91)		4.9 %	-8.30 [-24.49, 7.89]
Elwood 1976	627	93.6 (90)	690	100 (99)		12.2 %	-6.40 [-16.61, 3.81]
Briggs 1984	125	93.9 (85)	121	100 (91)		2.6 %	-6.10 [-28.12, 15.92]
Karlowski 1975a	52	94 (54)	65	100 (52)		3.4 %	-6.00 [-25.37, 13.37]
Anderson 1972	561	94.7 (92)	609	100 (82)		12.7 %	-5.30 [-15.32, 4.72]
Clegg 1975	68	94.7 (41)	73	100 (39)		7.3 %	-5.30 [-18.53, 7.93]
Anderson 1974b	414	95.1 (87)	137	100 (91)		4.2 %	-4.90 [-22.29, 12.49]
Anderson 1974a	436	97 (88)	145	100 (91)		4.4 %	-3.00 [-19.96, 13.96]
Pitt 1979	600	97.4 (89)	619	100 (91)		12.5 %	-2.60 [-12.70, 7.50]
Carr 1981a	94	100.7 (92)	70	100 (91)		1.6 %	0.70 [-27.59, 28.99]
Subtotal (95% CI)	**3688**		**2984**			**81.6 %**	**-8.14 [-12.08, -4.19]**
Heterogeneity: Chi^2 = 19.90, df = 16 (P = 0.22); I^2 =20%							
Test for overall effect: Z = 4.04 (P = 0.000054)							
2 Children							
Constantini 2011a	30	52.9 (48)	21	100 (68)		1.1 %	-47.10 [-80.88, -13.32]
Ludvigsson 1977a	62	61.3 (41)	55	100 (67)		3.0 %	-38.70 [-59.14, -18.26]
Ritzel 1961	17	69.2 (50)	31	100 (50)		1.5 %	-30.80 [-60.38, -1.22]
Coulehan 1974b	16	70.6 (64)	17	100 (82)		0.5 %	-29.40 [-79.43, 20.63]



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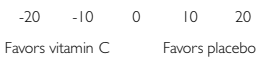
Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bancalari 1984	38	75.6 (62)	46	100 (65)		1.7 %	-24.40 [-51.63, 2.83]
Coulehan 1974a	19	87.6 (80)	23	100 (82)		0.5 %	-12.40 [-61.56, 36.76]
Miller 1977a	53	92.8 (111)	42	100 (111)		0.6 %	-7.20 [-52.14, 37.74]
Ludvigsson 1977b	423	94.1 (85)	398	100 (114)		6.7 %	-5.90 [-19.72, 7.92]
Coulehan 1976	98	94.8 (86)	98	100 (82)		2.3 %	-5.20 [-28.73, 18.33]
Constantini 2011b	25	116.2 (74)	22	100 (111)		0.4 %	16.20 [-38.51, 70.91]
Subtotal (95% CI)	**781**		**753**			**18.4 %**	**-17.82 [-26.14, -9.50]**
Heterogeneity: Chi^2 = 13.78, df = 9 (P = 0.13); I^2 =35%							
Test for overall effect: Z = 4.20 (P = 0.000027)							
Total (95% CI)	**4469**		**3737**			**100.0 %**	**-9.92 [-13.48, -6.35]**
Heterogeneity: Chi^2 = 37.92, df = 26 (P = 0.06); I^2 =31%							
Test for overall effect: Z = 5.45 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 4.24, df = 1 (P = 0.04), I^2 =76%							



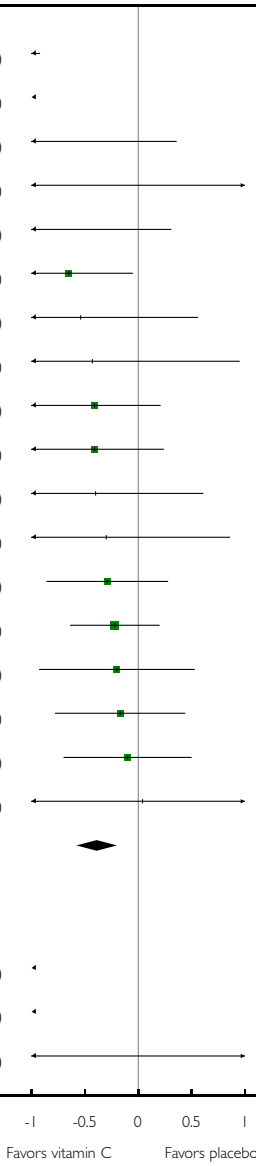
Analysis 2.3. Comparison 2 Duration of colds occurring when on regular vitamin C, Outcome 3 ≥ 1 g/day vitamin C (effect in days).

Review: Vitamin C for preventing and treating the common cold

Comparison: 2 Duration of colds occurring when on regular vitamin C

Outcome: 3 ≥ 1 g/day vitamin C (effect in days)

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 Adults							
Johnston 2014	12	2.2 (1.4)	17	5.4 (4.5)		0.6 %	-3.20 [-5.48, -0.92]
Carr 1981b	57	4.86 (4.53)	71	7.5 (4.53)		1.2 %	-2.64 [-4.22, -1.06]
Himmelstein 1998	14	2.5 (1.1)	12	4.2 (3.5)		0.7 %	-1.70 [-3.76, 0.36]
Sabiston 1974	6	4.3 (3)	14	6 (3)		0.4 %	-1.70 [-4.57, 1.17]
Van Straten 2002	37	1.8 (2.98)	50	3.1 (4.65)		1.2 %	-1.30 [-2.91, 0.31]
Charleston 1972	44	3.55 (1.93)	80	4.2 (0.82)		8.6 %	-0.65 [-1.25, -0.05]
Karlowski 1975e	76	5.92 (3.49)	56	6.46 (2.92)		2.6 %	-0.54 [-1.64, 0.56]
Karlowski 1975a	52	6.71 (3.82)	65	7.14 (3.71)		1.6 %	-0.43 [-1.81, 0.95]
Anderson 1974d	508	3.11 (2.83)	122	3.52 (3.2)		8.0 %	-0.41 [-1.03, 0.21]
Elwood 1976	627	5.97 (5.73)	690	6.38 (6.33)		7.2 %	-0.41 [-1.06, 0.24]
Clegg 1975	68	7.2 (3.1)	73	7.6 (3)		3.0 %	-0.40 [-1.41, 0.61]
Pitt 1979	600	11.2 (10.19)	619	11.5 (10.47)		2.3 %	-0.30 [-1.46, 0.86]
Anderson 1974c	465	3.23 (2.94)	155	3.52 (3.2)		9.4 %	-0.29 [-0.86, 0.28]
Anderson 1972	561	3.96 (3.84)	609	4.18 (3.43)		17.5 %	-0.22 [-0.64, 0.20]
Briggs 1984	125	3.12 (2.84)	121	3.32 (3.02)		5.7 %	-0.20 [-0.93, 0.53]
Anderson 1974b	414	3.35 (3.05)	137	3.52 (3.2)		8.2 %	-0.17 [-0.78, 0.44]
Anderson 1974a	436	3.42 (3.11)	145	3.52 (3.2)		8.6 %	-0.10 [-0.70, 0.50]
Carr 1981a	94	5.46 (4.97)	70	5.42 (4.93)		1.3 %	0.04 [-1.49, 1.57]
Subtotal (95% CI)	**4196**		**3106**			**88.0 %**	**-0.39 [-0.58, -0.20]**
Heterogeneity: Chi^2 = 20.76, df = 17 (P = 0.24); I^2 =18%							
Test for overall effect: Z = 4.08 (P = 0.000044)							
2 Children							
Ludvigsson 1977a	62	8.9 (5.96)	55	14.53 (9.75)		0.3 %	-5.63 [-8.60, -2.66]
Constantini 2011a	30	5.5 (5)	21	10.4 (7.1)		0.2 %	-4.90 [-8.42, -1.38]
Coulehan 1974b	16	4.44 (4.04)	17	6.29 (5.72)		0.3 %	-1.85 [-5.21, 1.51]



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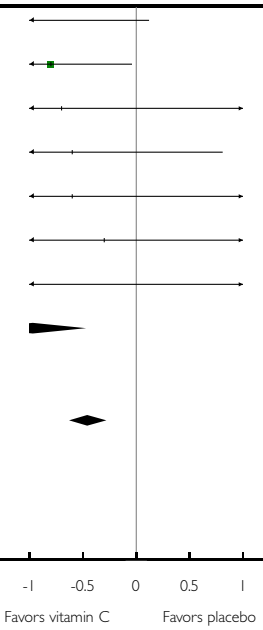
Study or subgroup	Vitamin C N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bancalari 1984	38	3.4 (2.77)	46	4.5 (2.92)		2.1 %	-1.10 [-2.32, 0.12]
Ritzel 1961	17	1.8 (1.29)	31	2.6 (1.29)		5.3 %	-0.80 [-1.56, -0.04]
Coulehan 1974a	19	4.95 (4.5)	23	5.65 (5.14)		0.4 %	-0.70 [-3.62, 2.22]
Ludvigsson 1977b	423	9.54 (8.65)	398	10.14 (11.6)		1.5 %	-0.60 [-2.01, 0.81]
Miller 1977a	53	7.7 (9.2)	42	8.3 (9.2)		0.2 %	-0.60 [-4.33, 3.13]
Coulehan 1976	98	5.5 (5.01)	98	5.8 (5.28)		1.5 %	-0.30 [-1.74, 1.14]
Constantini 2011b	25	8.6 (5.5)	22	7.4 (8.2)		0.2 %	1.20 [-2.85, 5.25]
Subtotal (95% CI)	**781**		**753**			**12.0 %**	**-0.97 [-1.48, -0.47]**
Heterogeneity: Chi^2 = 16.98, df = 9 (P = 0.05); I^2 =47%							
Test for overall effect: Z = 3.78 (P = 0.00016)							
Total (95% CI)	**4977**		**3859**			**100.0 %**	**-0.46 [-0.63, -0.28]**
Heterogeneity: Chi^2 = 42.27, df = 27 (P = 0.03); I^2 =36%							
Test for overall effect: Z = 5.14 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 4.53, df = 1 (P = 0.03), I^2 =78%							

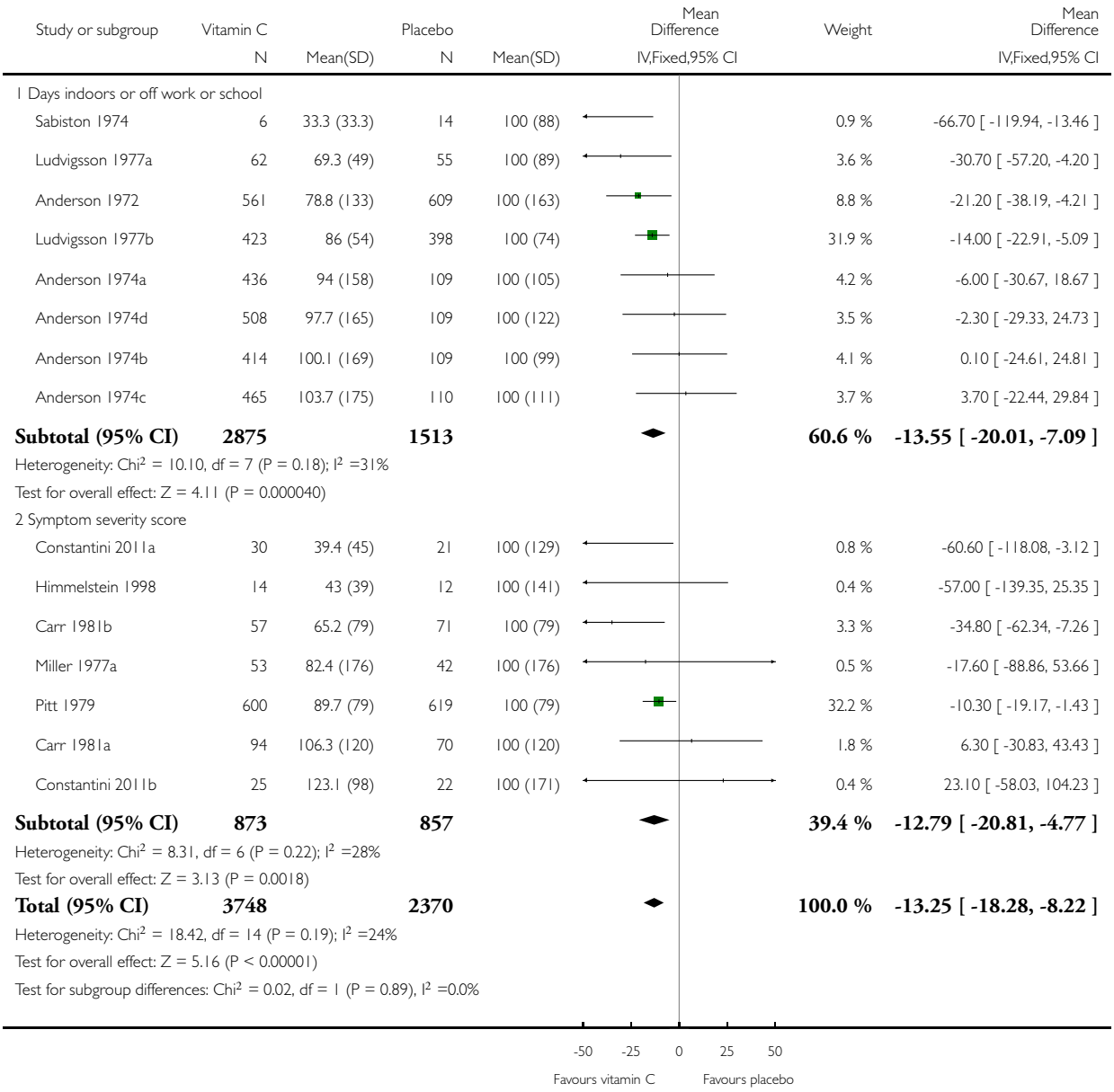


Analysis 3.1. Comparison 3 Severity of colds occurring when on regular vitamin C (effect in %), Outcome 1 Severity of the common cold (effect in %).

Review: Vitamin C for preventing and treating the common cold

Comparison: 3 Severity of colds occurring when on regular vitamin C (effect in %)

Outcome: 1 Severity of the common cold (effect in %)



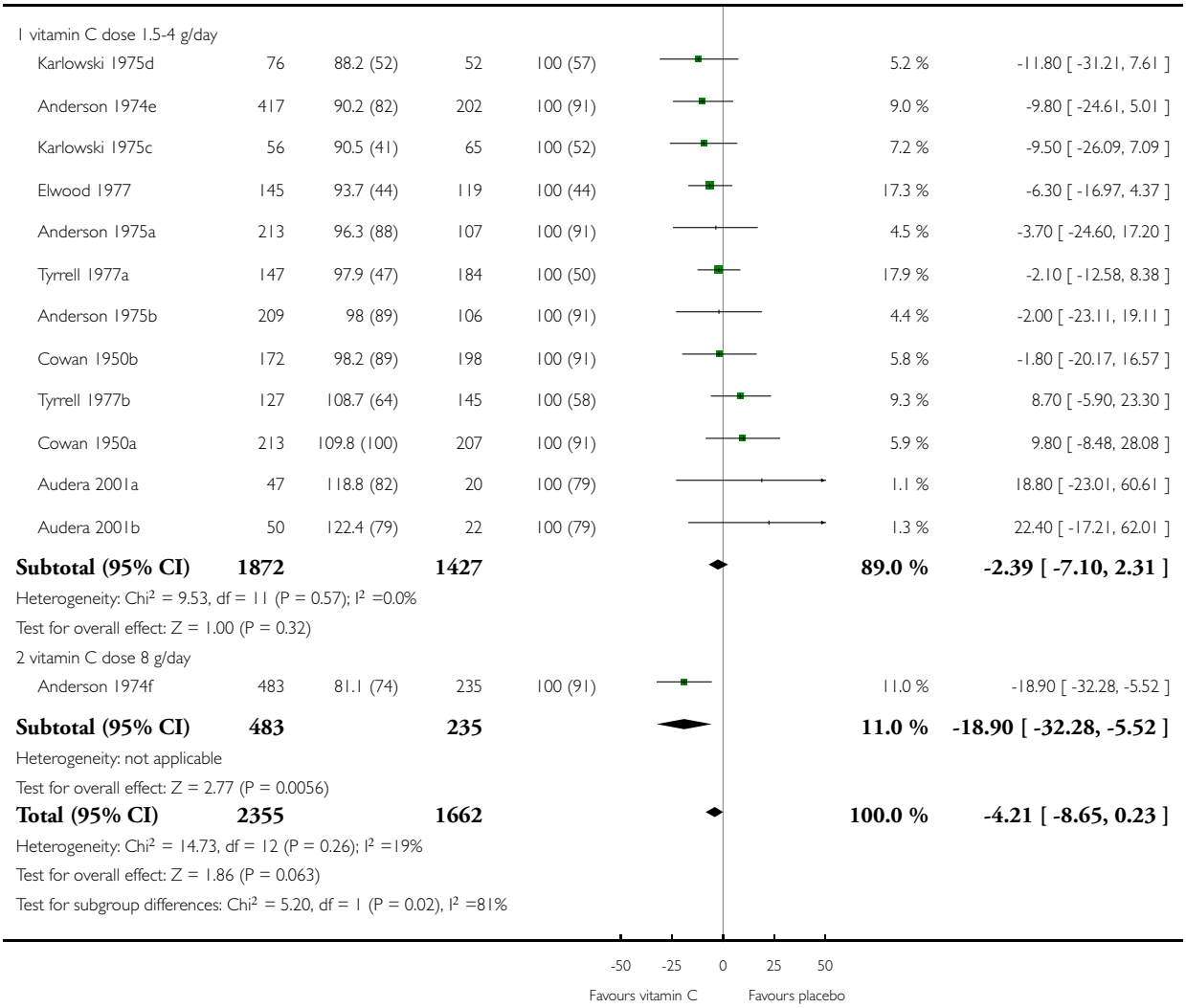
Analysis 4.1. Comparison 4 Duration of colds with therapeutic vitamin C (effect in %), Outcome 1 Duration of the common cold (effect in %).

Review: Vitamin C for preventing and treating the common cold

Comparison: 4 Duration of colds with therapeutic vitamin C (effect in %)

Outcome: 1 Duration of the common cold (effect in %)

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 vitamin C dose 1.5-4 g/day							
Karlowski 1975d	76	88.2 (52)	52	100 (57)		5.2 %	-11.80 [-31.21, 7.61]
Anderson 1974e	417	90.2 (82)	202	100 (91)		9.0 %	-9.80 [-24.61, 5.01]
Karlowski 1975c	56	90.5 (41)	65	100 (52)		7.2 %	-9.50 [-26.09, 7.09]
Elwood 1977	145	93.7 (44)	119	100 (44)		17.3 %	-6.30 [-16.97, 4.37]
Anderson 1975a	213	96.3 (88)	107	100 (91)		4.5 %	-3.70 [-24.60, 17.20]
Tyrrell 1977a	147	97.9 (47)	184	100 (50)		17.9 %	-2.10 [-12.58, 8.38]
Anderson 1975b	209	98 (89)	106	100 (91)		4.4 %	-2.00 [-23.11, 19.11]
Cowan 1950b	172	98.2 (89)	198	100 (91)		5.8 %	-1.80 [-20.17, 16.57]
Tyrrell 1977b	127	108.7 (64)	145	100 (58)		9.3 %	8.70 [-5.90, 23.30]
Cowan 1950a	213	109.8 (100)	207	100 (91)		5.9 %	9.80 [-8.48, 28.08]
Audera 2001a	47	118.8 (82)	20	100 (79)		1.1 %	18.80 [-23.01, 60.61]
Audera 2001b	50	122.4 (79)	22	100 (79)		1.3 %	22.40 [-17.21, 62.01]
Subtotal (95% CI)	**1872**		**1427**			**89.0 %**	**-2.39 [-7.10, 2.31]**
Heterogeneity: Chi² = 9.53, df = 11 (P = 0.57); I² =0.0%							
Test for overall effect: Z = 1.00 (P = 0.32)							
2 vitamin C dose 8 g/day							
Anderson 1974f	483	81.1 (74)	235	100 (91)		11.0 %	-18.90 [-32.28, -5.52]
Subtotal (95% CI)	**483**		**235**			**11.0 %**	**-18.90 [-32.28, -5.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.77 (P = 0.0056)							
Total (95% CI)	**2355**		**1662**			**100.0 %**	**-4.21 [-8.65, 0.23]**
Heterogeneity: Chi² = 14.73, df = 12 (P = 0.26); I² =19%							
Test for overall effect: Z = 1.86 (P = 0.063)							
Test for subgroup differences: Chi² = 5.20, df = 1 (P = 0.02), I² =81%							



Analysis 4.2. Comparison 4 Duration of colds with therapeutic vitamin C (effect in %), Outcome 2 1-day colds: Anderson (1974) therapeutic 8 g/day comparisons.

Review: Vitamin C for preventing and treating the common cold

Comparison: 4 Duration of colds with therapeutic vitamin C (effect in %)

Outcome: 2 1-day colds: Anderson (1974) therapeutic 8 g/day comparisons

Study or subgroup	Vitamin C 4 g n/N	Vitamin C 8 g n/N	Risk Difference(Non-event) IV,Fixed,95% CI	Weight	Risk Difference(Non-event) IV,Fixed,95% CI
1 8 g/day vs. Placebo group #4					
Anderson 1974e	143/437	222/483		100.0 %	0.13 [0.07, 0.19]
Subtotal (95% CI)	**437**	**483**		**100.0 %**	**0.13 [0.07, 0.19]**
Total events: 143 (Vitamin C 4 g), 222 (Vitamin C 8 g)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.15 (P = 0.000033)					
2 8 g/day vs. 4 g/day vitamin C					
Anderson 1974e	164/417	222/483		100.0 %	0.07 [0.00, 0.13]
Subtotal (95% CI)	**417**	**483**		**100.0 %**	**0.07 [0.00, 0.13]**
Total events: 164 (Vitamin C 4 g), 222 (Vitamin C 8 g)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.01 (P = 0.044)					
3 8 g/day vs. regular vitamin C groups					
Anderson 1974e	699/1824	222/483		100.0 %	0.08 [0.03, 0.13]
Subtotal (95% CI)	**1824**	**483**		**100.0 %**	**0.08 [0.03, 0.13]**
Total events: 699 (Vitamin C 4 g), 222 (Vitamin C 8 g)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.01 (P = 0.0026)					

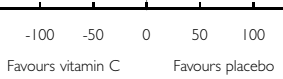
Analysis 5.1. Comparison 5 Severity of colds with therapeutic vitamin C (effect in %), Outcome 1 Severity of common cold (effect, %).

Review: Vitamin C for preventing and treating the common cold

Comparison: 5 Severity of colds with therapeutic vitamin C (effect in %)

Outcome: 1 Severity of common cold (effect, %)

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 Days indoors or off work or school							
Craig 1976	30	63 (115)	36	100 (160)		2.8 %	-37.00 [-103.52, 29.52]
Anderson 1975a	213	75.8 (111)	107	100 (153)		11.6 %	-24.20 [-56.80, 8.40]
Anderson 1975b	209	80.2 (120)	106	100 (153)		11.0 %	-19.80 [-53.16, 13.56]
Anderson 1974f	483	91.2 (137)	235	100 (152)		23.3 %	-8.80 [-31.76, 14.16]
Anderson 1974e	417	95.6 (143)	202	100 (152)		19.6 %	-4.40 [-29.45, 20.65]
Tyrrell 1977b	127	96.3 (205)	145	100 (254)		4.1 %	-3.70 [-58.29, 50.89]
Tyrrell 1977a	147	100 (265)	184	100 (259)		3.8 %	0.0 [-56.88, 56.88]
Subtotal (95% CI)	**1626**		**1015**			**76.2 %**	**-11.91 [-24.61, 0.79]**
Heterogeneity: Chi² = 1.98, df = 6 (P = 0.92); I² =0.0%							
Test for overall effect: Z = 1.84 (P = 0.066)							
2 Symptom severity score							
Audera 2001a	47	109.4 (68)	20	100 (61)		11.2 %	9.40 [-23.66, 42.46]
Audera 2001b	50	113.9 (65)	22	100 (61)		12.6 %	13.90 [-17.31, 45.11]
Subtotal (95% CI)	**97**		**42**			**23.8 %**	**11.78 [-10.92, 34.47]**
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² =0.0%							
Test for overall effect: Z = 1.02 (P = 0.31)							
Total (95% CI)	**1723**		**1057**			**100.0 %**	**-6.26 [-17.35, 4.82]**
Heterogeneity: Chi² = 5.20, df = 8 (P = 0.74); I² =0.0%							
Test for overall effect: Z = 1.11 (P = 0.27)							
Test for subgroup differences: Chi² = 3.19, df = 1 (P = 0.07), I² =69%							



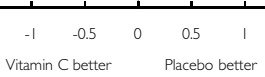
Analysis 6.1. Comparison 6 Within-trial subgroup comparisons, Outcome 1 Anderson (1972): Contact with children.

Review: Vitamin C for preventing and treating the common cold

Comparison: 6 Within-trial subgroup comparisons

Outcome: 1 Anderson (1972): Contact with children

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 Contact young children							
Anderson 1972	140	1.31 (2.04)	148	2.43 (2.8)		35.4 %	-1.12 [-1.68, -0.56]
Subtotal (95% CI)	**140**		**148**			**35.4 %**	**-1.12 [-1.68, -0.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.89 (P = 0.000098)							
2 No contact young children							
Anderson 1972	267	1.3 (2.04)	263	1.56 (2.8)		64.6 %	-0.26 [-0.68, 0.16]
Subtotal (95% CI)	**267**		**263**			**64.6 %**	**-0.26 [-0.68, 0.16]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.22 (P = 0.22)							
Total (95% CI)	**407**		**411**			**100.0 %**	**-0.56 [-0.90, -0.23]**
Heterogeneity: Chi^2 = 5.77, df = 1 (P = 0.02); I^2 =83%							
Test for overall effect: Z = 3.30 (P = 0.00097)							
Test for subgroup differences: Chi^2 = 5.77, df = 1 (P = 0.02), I^2 =83%							

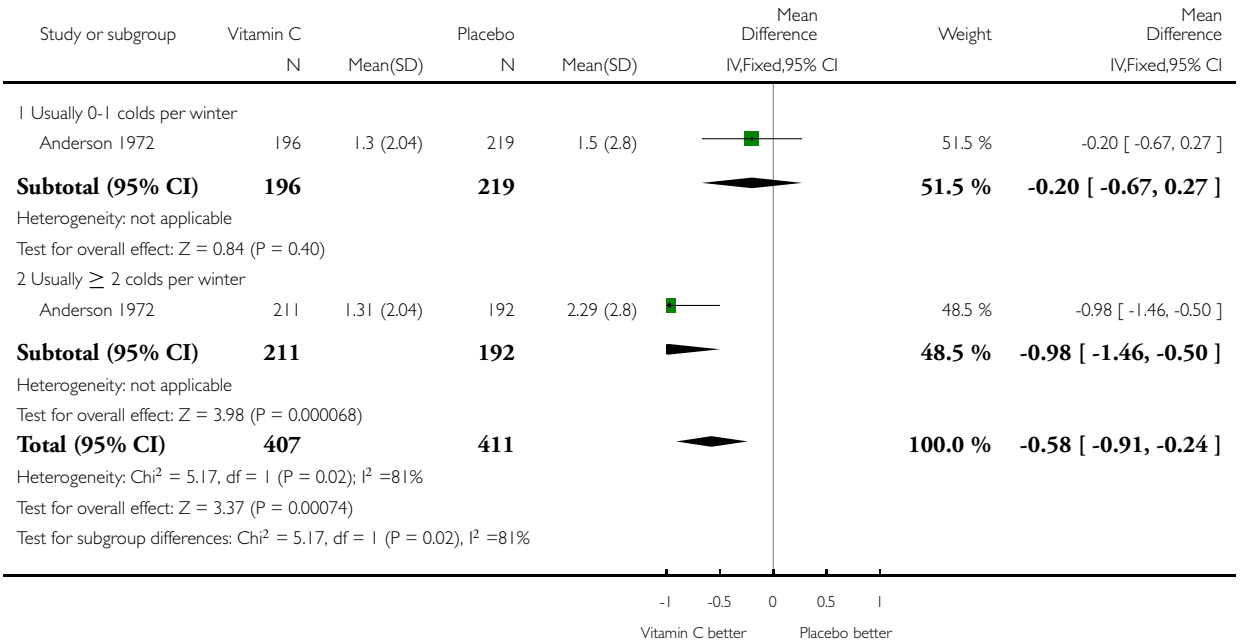


Analysis 6.2. Comparison 6 Within-trial subgroup comparisons, Outcome 2 Anderson (1972): Usual frequency of colds.

Review: Vitamin C for preventing and treating the common cold

Comparison: 6 Within-trial subgroup comparisons

Outcome: 2 Anderson (1972): Usual frequency of colds

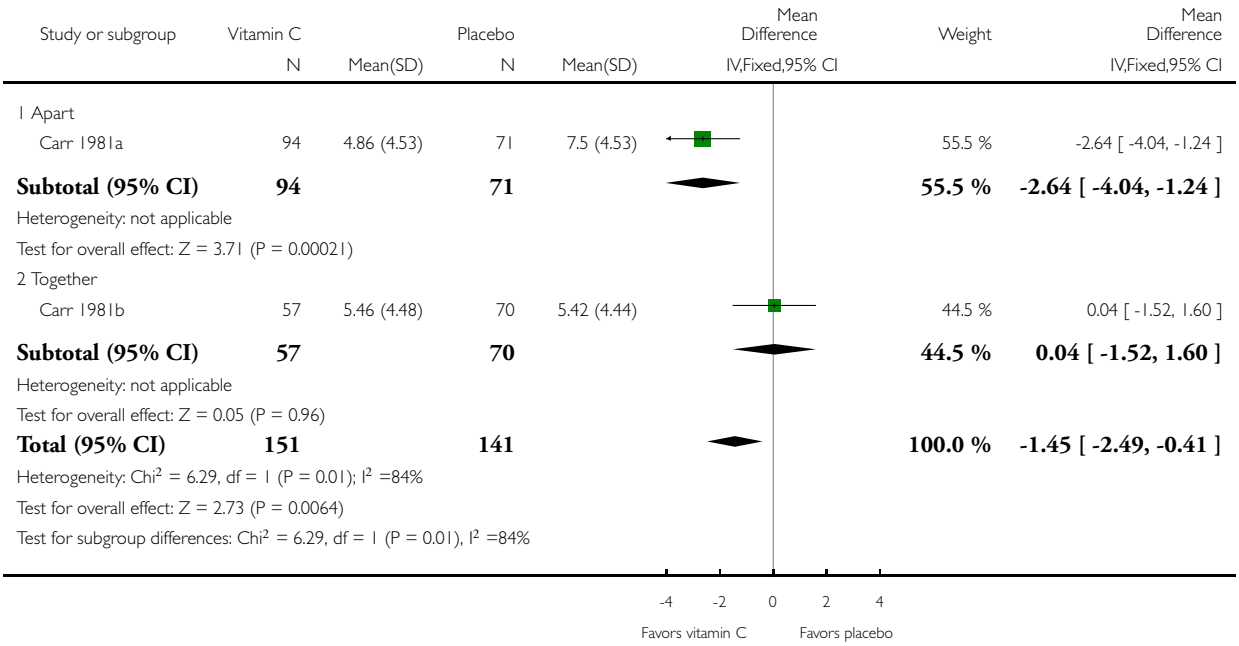


Analysis 6.3. Comparison 6 Within-trial subgroup comparisons, Outcome 3 Carr (1981): Twins living together and apart.

Review: Vitamin C for preventing and treating the common cold

Comparison: 6 Within-trial subgroup comparisons

Outcome: 3 Carr (1981): Twins living together and apart



Analysis 7.1. Comparison 7 Adverse effects in large trials, Outcome 1 Adverse effects.

Review: Vitamin C for preventing and treating the common cold

Comparison: 7 Adverse effects in large trials

Outcome: 1 Adverse effects

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
Pitt 1979	50/331	51/342		41.9 %	1.01 [0.71, 1.45]
Anderson 1972	49/407	45/411		37.4 %	1.10 [0.75, 1.61]
Anderson 1974a	30/860	25/868		20.8 %	1.21 [0.72, 2.04]
Total (95% CI)	**1598**	**1621**		**100.0 %**	**1.09 [0.86, 1.37]**

Total events: 129 (Vitamin C), 121 (Placebo)

Heterogeneity: $Chi^2 = 0.32$, df = 2 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable

Analysis 8.1. Comparison 8 Karlowski and Anderson 95% confidence interval calculations, Outcome 1 Karlowski 1975.

Review: Vitamin C for preventing and treating the common cold

Comparison: 8 Karlowski and Anderson 95% confidence interval calculations

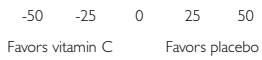
Outcome: 1 Karlowski 1975

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
Karlowski 1975c	76	82.91 (48.84)	65	100 (51.94)		36.0 %	-17.09 [-33.82, -0.36]
Karlowski 1975a	56	90.48 (40.88)	65	100 (51.94)		36.8 %	-9.52 [-26.08, 7.04]
Karlowski 1975b	52	93.98 (53.53)	65	100 (51.94)		27.2 %	-6.02 [-25.28, 13.24]
Total (95% CI)	**184**		**195**			**100.0 %**	**-11.30 [-21.34, -1.25]**

Heterogeneity: $Chi^2 = 0.79$, df = 2 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 2.20 (P = 0.027)

Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8 Karlowski and Anderson 95% confidence interval calculations, Outcome 2 Anderson 1974 therapy.

Review: Vitamin C for preventing and treating the common cold

Comparison: 8 Karlowski and Anderson 95% confidence interval calculations

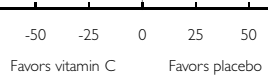
Outcome: 2 Anderson 1974 therapy

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 1974f	483	81.13 (73.83)	437	100 (91)		53.7 %	-18.87 [-29.65, -8.09]
Anderson 1974e	417	90.22 (82.1)	437	100 (91)		46.3 %	-9.78 [-21.39, 1.83]
Total (95% CI)	**900**		**874**			**100.0 %**	**-14.66 [-22.56, -6.76]**

Heterogeneity: $Chi^2 = 1.26$, df = 1 (P = 0.26); $I^2 = 21\%$

Test for overall effect: Z = 3.64 (P = 0.00027)

Test for subgroup differences: Not applicable



ADDITIONAL TABLES

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

Trial	Findings
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 = 0.001). There was no difference in the curing of 92 "throat colds" (35/56 [63%] versus 22/36 [61%], respectively). The great difference in the distribution of participants is not consistent with the reported alternate allocation
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
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
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]
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

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

	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 0.0155 and 0.0327) but not for hoarseness or non-productive coughs" [p 12] (Hemilä 2004)
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

Table 2. Trials with experimentally-induced rhinovirus 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	3 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)

Table 2. Trials with experimentally-induced rhinovirus colds (*Continued*)

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

Table 3. NNTB in studies with short-term physical stress (Analysis 1.1.2)

Study	Incidence of colds		Difference	NNTB	NNTB
	Vitamin C	Placebo		from Results	from RR = 0.49
Peters 1996b	16%	40%	25%	4.1	5.0
Sabiston 1974	11%	25%	14%	7.0	8.2
Moolla 1996b	31%	68%	38%	2.7	3.0
Peters 1993b	33%	68%	36%	2.8	3.0
Ritzel 1961	12%	22%	10%	10.1	9.2

Carillo 2008a and Carillo 2008b were not included because numbers of participants was low (six participants per group)
NNTB: number-needed-to-treat-to-benefit
NNTB (from results) is calculated as an inverse of the observed difference
NNTB (from RR) is calculated from the inverse of the (1-RR)*Placebo group incidence

Table 4. Variation in vitamin C intake in diet and supplement doses

Trial, country, participants	Dietary vitamin C (g/day)	Supplement vitamin C to placebo group (g/day)	Supplement vitamin C to vitamin C group (g/day)
Cowan 1942b USA, school children	?	0	0.025 to 0.050
Bartley 1953 UK, adults	0	0	0.01 to 0.06
Glazebrook 1942 UK, school boys	0.010 to 0.015	0	0.05 to 0.3
Baird 1979 UK, students	0.05	0	0.08

Table 4. Variation in vitamin C intake in diet and supplement doses *(Continued)*

Miller 1977a USA, school children	> 0.25	0.05	0.5 to 1.0
Peters 1993a South Africa, marathon runners	0.5	0	0.6
Sabiston 1974 Canada, military recruits	0.04	0	1.0
Carr 1981a Australia, twin children	?	0.07	1.0
Karlowski 1975a USA, NIH employees	Probably quite high	0	3.0 to 6.0

This is a selection of studies to show the great variation in vitamin C doses in diet and in supplements. There is an up to 240-fold range in vitamin C intakes in the vitamin C groups of Cowan 1942b to Karlowski 1975a, yet both of them were presented side by side in the influential Chalmers 1975 review, ignoring the doses.

In some studies the dietary vitamin C intake and the supplementation of placebo group have been much higher than the supplementation of vitamin C group in some other trials. The Karlowski 1975a trial was carried with employees of NIH and therefore the dietary vitamin C intake probably was higher than the average of the US population. An earlier version of this table was published on p. 34 of Hemilä 2006a.

APPENDICES

Appendix 1. History and search strategies prior to 2012

The 1998 review (Douglas 1998) presented an analysis of 30 published trials selected by 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). The 2004 update (Douglas 2004) included all known publications on the topic in the past 64 years. 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 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). One new trial was identified for the 2007 update (Sasazuki 2006).

MEDLINE search (2007)

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).

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: 1 January 2006 to 3 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. MEDLINE (Ovid) search strategy

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

Appendix 3. Embase.com search strategy

#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 4. CINAHL (EBSCOhost) search strategy

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
S1 (MH "Common Cold") 1400

Appendix 5. LILACS (BIREME) search strategy

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 6. Web of Science (Thomson Reuters) search strategy

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 7. Trials Registers search strategy

"vitamin C" AND "common cold"
"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.
David Wooff

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

Contributors

Reply supplied by the Authors of the review
Comment and reply posted 28 August 2004

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.
Julian Higgins

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, even 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.

Contributors

Reply supplied by the Authors of the review
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
Reuven Gilmore

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.

Contributors

Reply supplied by the Authors of the review
Comment and reply posted 28 August 2004

Vitamin C for preventing and treating the colds, 10 July 2005

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.

Steve Hickey PhD. Manchester Metropolitan University
Hilary Roberts PhD

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.

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.

Contributors

Harri Hemilä and Robert M Douglas
Comment and reply posted 16 November, 2005

Vitamin C doses in trial, 24 July 2007

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.

Sean Emerson

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 2001c). 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.

Contributors

Hemilä, Douglas and Liz Chalker
22 August, 2007

Vitamin C and the common cold, 2 April 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.

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, 274-8.
[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),125-32.
[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, 1359-76.
[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.
Steve Hickey PhD and Hilary Roberts PhD

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 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 of Systematic Reviews 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

Harri Hemilä, Robert M Douglas, Elizabeth Chalker, Barbara Treacy
23 May 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.

Roger Mann M.D.

Occupation Family Physician

Reply

We have previously replied to overlapping feedback on the dose-response issue (see 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 1996; 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.

Contributors

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

Vitamin C for preventing and treating the common cold, 11 February 2013

Summary

Re review of studies about Vit C and prevention of urti. Linus Pauling recommended up to 16 g/day. Were any of the studies using these doses?
I agree with the conflict of interest statement below:
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.
Dr Robert McKillop
General Practitioner

Reply

As a short answer to the question, none of the studies in the review used doses as high as 16 g/day, but we will briefly summarise the question of doses.
In our review we acknowledge Linus Pauling's role in the 1970s in promoting publicity about the possible role of vitamin C against the common cold and in leading to the conduct of dozens of placebo-controlled trials on the topic. However, conclusions about reasonable vitamin C doses should not be based on what Pauling said or wrote, but should be based on empirical evidence.
Doses of 3 g/day vitamin C have not prevented natural colds in ordinary people (Karlowski 1975) or laboratory colds (Walker 1967; Schwartz 1973). We do not see any basis to speculate that higher regular doses such as 16 g/day may have a different preventive effect for ordinary people. In our review we found a subgroup of five trials in which vitamin C halved the incidence of colds. However, the benefit was not explained by particularly high vitamin C dosage but by the special conditions of the participants: heavy acute physical stress.
The case for treating colds is different. The Karlowski 1975 study found significant dose dependency so that 6 g/day of vitamin C shortened colds in adults by twice as much as 3 g/day and Coulehan 1974 found that 2 g/day of vitamin C shortened colds of children twice as much as 1 g/day (Hemilä 1999a Table 2 and Figure 2). Anderson 1974 found that a single dose of 8 grams of vitamin C was significantly more beneficial than a single dose of 4 grams at the beginning of the cold (Hemilä 2006a Table 39). Asfora 1977 found that 6 g/day caused such obvious clinical progress that it further led to the breakage of the double-blind code (this review Table 3).
We do not see any basis to assume that 6 or 8 g/day would lead to the maximal effect of vitamin C. Instead, linear extrapolation of the results of the Karlowski 1975 study, and of all adult trials, suggested that 18 g/day and 10 g/day, respectively, might decrease the duration of common cold episodes by half (Hemilä 1999a Figs. 1 and 2). Even though we must be cautious about simple linear extrapolation, if there is curvature in the dose dependency so that higher doses cause less than the assumed linear benefit, then the doses that halve the duration of colds would be even greater than those suggested by linear extrapolations.
Some clinicians have proposed 10 to 30 g/day vitamin C for treating colds on the basis of their personal empirical evidence with their patients (Bee 1980; Cathcart 1981). We do not know what the maximal therapeutic benefits are and the vitamin C doses leading to them. Nevertheless, as described in our review vitamin C is safe in high doses and we conclude that it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them. Therapeutic trials explicitly testing dose dependency are needed.

Contributors

Harri Hemilä and Elizabeth Chalker
15 April 2013

WHAT'S NEW

Last assessed as up-to-date: 3 May 2016.

Date	Event	Description
3 May 2016	New search has been performed	We included three new studies (Carillo 2008a; Craig 1976; Johnston 2014). Carillo 2008a reported two comparisons. We undertook extensive rewriting and made several changes in the Methods, see section Differences between protocol and review.
3 May 2016	New citation required but conclusions have not changed	Searches updated. Our conclusions remain unchanged.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 1998

Date	Event	Description
17 April 2013	Feedback has been incorporated	Feedback comment and reply added to the review
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).
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

(*Continued*)

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

Harri Hemilä: None known.

Elizabeth Chalker: None known.

SOURCES OF SUPPORT

Internal sources

- Australian National University (until 2004), Australia.

External sources

- Commonwealth Department of Health and Ageing, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for this review was written in the mid-1990s and is now outdated. The first version was published in 1998 as Douglas 1998. The review was extensively rewritten in 2004 by Harri Hemilä and Robert M Douglas and was published as Douglas 2004, *see* Appendix 1. Therefore the description of differences between the protocol and the review is not relevant.

In this section we describe the major, primarily methodological, changes that have been done since the 2004 version.

1. In 2013, seven placebo-controlled trials which were previously excluded because there were no data suitable for our meta-analyses were included (Table 1). Their exclusion was inconsistent with our Methods section. Although their inclusion did not result in changes to our conclusions, they were included for consistency and transparency.

2. In 2004, "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 2013 version, we changed to the term "regular supplementation" to indicate trials in which vitamin C was administered every day. This reduces confusion when we consider the effect of vitamin C on the duration and severity of colds that occur during supplementation.

3. The standard format of the RevMan reviews has been extensively changed since 2004. The description of studies and the risk of bias table in the included studies has more space. In 2016 we reread all the included studies to fill the "support for judgement" boxes for the items. This rereading led to some changes in the evaluation of risk domains

4. In 2016, we added a new risk item "baseline balance" since this is fundamentally important, and the primary goal of randomizations and allocation concealment is to reach baseline balance. The importance of looking directly at baseline balance was encouraged by Corbett 2013. They commented that "if randomisation methods are unclear, then the risk of selection bias in the included studies will be unclear, with consequent reticence to draw firm conclusions from the review. But if baseline data demonstrate that all important prognostic factors were balanced across arms, then that reticence may be misplaced. Alternatively, randomisation methods may appear robust, but important group baseline imbalance not noticed, leading to unwarranted confidence in the findings of the study and hence in the broader findings of the review; selection bias is low as formally defined, but chance differences may need to be considered." (p. 80) ... "Use of suboptimal randomisation methods may be due to clinical practicalities or resource limitations. ... Suboptimal methods do not necessarily imply that the allocations were manipulated. Examination of a study characteristics table may be able to clarify whether such bias is present. In some trials, adequate similarity across baseline will be achieved. The results of such studies could therefore be considered as being at a low risk of bias (p. 83)." Therefore we added descriptions of the available information on baseline balances of the included studies.

5. In 2016, we added "contamination" as a risk of bias domain. This enabled assessment of whether the vitamin C level in the placebo group was higher than recommended vitamin C doses.

6. We have not used data collection forms for collecting the data. Instead we have compared the entered data against the published data. In 2016 we constructed a spreadsheet in which we collected the original published data and carried out the calculations to transform the data to a version suitable for our meta-analyses. This makes the process transparent and helps us to check the collected data and the transformation processes. The spreadsheet is available on the web page of this review.

7. Several trials reported the mean duration of colds in the vitamin C and placebo groups, without SDs. To include those studies in the meta-analysis, we need to impute SDs. In 2004 we calculated that on average the ratio between the SD and the mean common

cold duration was 0.7 and, to be conservative, we used a ratio of 1.0 for imputing SD values for those common cold durations that did not report the actual SD. In 2016 we considered that the ratio 1.0 was not based on any direct analysis. In 2016 we reanalyzed the ratios between the SD and the mean duration of colds for studies that we had available. We decided to use the 80th percentile of the ratio distribution as the value for imputing the SDs. This means that on average 80% of the imputed SDs are too conservative and 20% are too liberal. This level of conservatism in the imputation seemed appropriate to us.

8. In the 2004 version, 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. To make the review more consistent and transparent, in 2016 we imputed the SD for the common cold duration by the ratio method, see the previous item. This change did not materially affect the SD estimates of those studies.

9. In 2004 Robert M Douglas collected adverse effects data and the statements in the review were based on his data. We do not have that data available in 2016 and we revised the analysis of adverse effects so that we focus only on the large studies with high vitamin C doses, which are the most informative. Furthermore, there are other vitamin C studies that are much more informative about the adverse effects as described in the Background.

10. In 2016, we revised the calculation of the effect of vitamin C on common cold severity. In the 2004 version we used the SMD method for pooling the severity results. In the Methods section we had written "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." The SMD scale is very poor for communication since few people have a personal understanding of whether one SD unit is a large or small effect. Friedrich 2011 also pointed out the problems of the SMD scale when communicating the results of meta-analysis to researchers and patients. The percentage effect had been used previously in our analyses of common cold duration. Therefore in 2016 we decided to analyse the effect of vitamin C on the severity of colds also as percentages. Many trials provide relevant data on the severity of colds as "days indoors, days off work or school". For such outcomes, the percentage effect of vitamin C is much more informative than the vitamin C effects in SD-units (the unit in the SMD method).

11. A few studies had several vitamin C arms which were compared against a single placebo arm. In 2004 we pooled the vitamin C arms to a single vitamin C arm which we compared with the single placebo arm. However, such pooling decreases transparency. In addition, such pooling is based on an assumption that the true effect in the pooled arms is equal, so that the differences between the arms are caused just by random variation. This assumption need not be correct. Therefore in 2016 we show all vitamin C arms separately and we divide the placebo arms evenly between the vitamin C arms.

12. As a consequence of the change described in the previous item, we observed that the therapeutic 4 g/day and 8 g/day arms of the 1974 trial by Anderson were significantly inconsistent indicating that the arms should be analysed separately. The difference between the 4 and 8 g/day arms indicates dose response (Figure 6). Therefore, we stratified the analysis of therapeutic studies by dose in Analysis 4.1, and in 2016 we revised our analysis of the Anderson 1974e and Anderson 1974f studies.

13. In previous versions we discussed the possible dose response relation between the benefit of vitamin C and the administered dose, but in the 2016 we constructed linear regression models to explicitly investigate the issue (Analysis 4.1).

14. In previous versions we discussed the evidence that the effects of vitamin C on the common cold seem to be heterogeneous. In 2016 we added a new analysis, in which we collected the within-trial subgroup variations that have been reported (Analysis 6).

15. We used 0.2 g/day of vitamin C as an inclusion criterion. However, that does not mean that all included studies with different doses are similarly informative about the effects of vitamin C. In 2016 we divided the general community studies in Analysis 1.1 to studies that used < 1 g/day and those that used ≥ 1 g/day vitamin C. The latter are much more informative to the question whether high doses of vitamin C might have effects. We did not remove the low dose studies from the table, but show them as a separate subgroup. Similarly, we show the effect of vitamin C on common cold duration in all trials in Analysis 2.1, but present a separate forest plot of trials with ≥ 1 g/day vitamin C as Analysis 2.2, because the high dose studies are much more informative when considering possible effects of high vitamin C doses on the duration of colds. In the case of common cold severity in the regular supplementation studies, we present only the ≥ 1 g/day vitamin C studies in Analysis 3.1.

16. Our primary analysis of common cold duration is focused on the relative effect (percentages), since the relative scale adjusts for baseline variations between the trials (Hemilä 2016b). In 2016 we reasoned that it is useful to present the effect of vitamin C also on the absolute scale, i.e.., on the number of days the common cold shortened (Analysis 2.3). The absolute effects does have its own merits, but this also allowed us to compare the two methods.

17. In 2016, we calculated NNTB estimates for vitamin C effect on people with heavy short-term physical activity (Table 3)

18. In 2016, we added a new section to Results "Other effects of regular vitamin C in subgroup 1 of Analysis 1.1" in which we present other effects reported in the regular vitamin C trials. This covers issues that are directly relevant to the topic of our review, but not exactly as the outcomes formulated in the Methods section.

19. In 2016, we constructed Summary of findings for the main comparison.

20. In 2016, we added a PRISMA flow chart depicting study selection for this update (Figure 2). The flow chart shows the number of identified "studies" which indicates the primary study reports. Some of the study reports describe more than one trial and some describe more than one vitamin C arm. Some study reports contain trials or trial arms that are excluded from our analyses (Audera 2001a; Cowan 1942; Himmelstein 1998). In the previous versions of our review, these excluded comparisons were listed in the Characteristics of excluded studies table. However, with the revision to show the search findings as the main study reports, listing such studies in the excluded studies list would lead to double counting of those studies. Therefore we removed those studies from the excluded list and descibe the reason for the exclusion of particular trials or trial arms of the included studies in the Notes section of the Characteristics of included studies table. Revision to count the identified records by the studies (primary study reports) instead of vitamin C comparisons also changed the number of search results described in the Abstract and the Plain Language Summary.

NOTES

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