

Vitamin C Supplementation and Common Cold Symptoms: Problems with Inaccurate Reviews

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ABSTRACT

In 1971, Linus Pauling carried out a meta-analysis of four placebo-controlled trials and concluded that it was highly unlikely that the decrease in the "integrated morbidity of the common cold" in vitamin C groups was caused by chance alone ($P < 0.00003$). Studies carried out since then have consistently found that vitamin C (≥ 1 g/d) alleviates common cold symptoms, indicating that the vitamin does indeed have physiologic effects on colds. However, widespread conviction that the vitamin has no proven effects on the common cold still remains. Three of the most influential reviews drawing this conclusion are considered in the present article. Two of them are cited in the current edition of the RDA nutritional recommendations as evidence that vitamin C is ineffective against colds. In this article, these three reviews are shown to contain serious inaccuracies and shortcomings, making them unreliable sources on the topic. The second purpose is to suggest possible conceptual reasons for the persistent resistance to the notion that vitamin C might have effects on colds. Although placebo-controlled trials have shown that vitamin C does alleviate common cold symptoms, important questions still remain. ©Elsevier Science Inc. 1996 *Nutrition* 1996; 12:804-809

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INTRODUCTION

In the early 1970s, Linus Pauling^{1,2} suggested that vitamin C (≥ 1 g/d) may substantially decrease the incidence and severity of common cold episodes. Pauling did not carry out his own experimental work on the topic but derived his conclusions from earlier studies. Since Pauling's analyses a large number of trials have been carried out to examine whether the vitamin really does have an effect on colds.^{3,4} These reports have shown that vitamin C supplementation has no marked effect on common cold incidence in the general population. However, the symptoms of the common cold have consistently been alleviated. Table I shows the results of all placebo-controlled trials in which ≥ 2 g/d of vitamin C was regularly administered to the subjects. All eight studies found a statistically significant benefit in at least one of the outcome parameters. The combined P value is extremely small for the five studies published up to 1975, indicating that in 1975 or earlier an unequivocal conclusion could have been drawn that vitamin C alleviates the symptoms of the common cold. Six of the eight studies found that the duration or severity of colds was

decreased by more than 20% in the vitamin group, suggesting that the effect may be of practical importance. Nevertheless, there has been great quantitative variation in the results, hampering the evaluation of the clinical significance of vitamin C in treating colds (Table I^{3,4}).

Although placebo-controlled trials have consistently found benefit from vitamin C on common cold symptoms, a widespread belief that the vitamin has no real effects on the common cold still remains.²⁰⁻²² In this paper we shall briefly analyze three of the most influential reviews which have concluded that vitamin C has no proven effects on the common cold,²³⁻²⁵ in order to expose their major shortcomings. The second purpose of the present work is to suggest possible conceptual reasons why there has been such persistent resistance to the notion that vitamin C has effects on common cold symptoms.

ANALYSIS OF THE THREE MAJOR REVIEWS

Chalmers' 1975 Review

In 1975 Thomas Chalmers analyzed the results of seven placebo-controlled vitamin C-common cold studies which he

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TABLE I.

VITAMIN C SUPPLEMENTATION AND COMMON COLD SYMPTOMS

Study (Ref.)	Subjects, Country	Dose (g/d)	No. of episodes in vitamin C group	Effect on duration or severity ^a	P (one-tail)	-2 × ln(P)
<i>Studies up to 1975</i>						
Anderson et al. 1972 (5, 6)	Adults, Canada	1 + 3 ^b	561	-21 ^c	0.008	9.66*
Elliott 1973 (7)	Military recruits, USA	2	37 ^d	-5 -72 ^e	0.016	8.27*
Schwartz et al. 1973 (8)	Adults, USA	3	11 ^f	-30 ^g	0.005	10.60*
Coulehan et al. 1974 (9)	School children, USA	2	16	-29	0.006 ^h	10.23*
Karlowski et al. 1975 (10, 11)	Adults, USA	3 + 3 ^b	76	-17	0.025	7.38*
<i>Studies after 1975</i>						
Pitt & Costrini 1979 (12)	Military recruits, USA	2	600	-5 ⁱ -3	0.012	8.85
Bancalari et al. 1984 (13)	School children, Chile	2	38	-24	0.041	6.39
Mink et al. 1988 (14)	Adults, USA	2	4 ^f	-50 ⁱ	0.023	7.55
				Weighted mean: -15		
				Median: -26		
				Mean: -31		

* Five studies up to 1975: χ^2 (10 df) = 46.1 combined P (two-tail) = 0.000002.

All eight studies: χ^2 (16 df) = 68.9 combined P (two-tail) = 0.00000002.

NOTES: Studies in which ≥ 2 g/d of vitamin C was regularly administered were selected. The eight studies in the table were double-blind placebo-controlled studies and five were randomized.^{5,7,10,12,13} For short-term studies, supplementation was initiated before the symptoms started and continued after the symptoms ended. Anderson et al.'s⁵ 1972 study was included in the table as the dose during the episodes was 4 g/d although the regular dose was only 1 g/d. Anderson's 1974 study was excluded since there is bias in the distribution of subjects in the study groups.^{15,16} For the studies by Anderson et al.⁵ and Pitt and Costrini,¹² the days indoors and severity of symptoms, respectively, were selected as outcomes in the calculations. For a more comprehensive list of the original data see Table 1 in Ref. 3. The weighted mean was calculated using the number of episodes in the vitamin C group as the weight. The P values were recalculated when appropriate data were available. The combined P value was calculated by the Fisher method.¹⁷⁻¹⁹

^aThe outcome is the duration of cold symptoms except when otherwise indicated. ^bAt the onset of a cold episode an additional 3 g/d was given for 3-5 d. ^cDays confined to house per episode. ^dThe number of subjects; the number of episodes is not given in the report. ^eDays of morbidity for sore throats. ^fInduced rhinovirus infection. ^gTotal illness score at the 4th d after challenge. ^h P value for comparing the number of sickness days between the groups. ⁱSeverity of symptoms.

considered technically acceptable.²³ He calculated that the episodes were 0.11 ± 0.24 (SE) days shorter in the vitamin C groups compared to the placebo groups. Even if real, a 0.11 day decrease in the duration of a cold episode is without any clinical significance. Moreover, the great variation in the results, as indicated by the standard error, suggests that there probably was no real effect at all.

Recently, Chalmers' review was shown to contain serious errors.¹⁶ For example, in some cases the data presented were inconsistent with the originally published results. Neither did Chalmers consider the amount of vitamin C used in the studies, and he included in the meta-analysis a study in which only 0.025-0.050 g/d of the vitamin was used. The studies known to Chalmers that had used ≥ 1 g/d of vitamin C were recently reanalyzed and the common cold episodes were calculated to be 0.93 ± 0.22 (SE) days shorter in the vitamin groups.¹⁶ An estimate more than eight times Chalmers' estimate was thus obtained by employing correct values and considering only studies that used doses as high as Pauling^{1,2} had proposed. The problems of Chalmers' review have been discussed in more detail elsewhere.¹⁶

Dykes and Meier's 1975 Review

In 1975, the *Journal of the American Medical Association* published a review of vitamin C and the common cold by Michael Dykes and Paul Meier,²⁴ which contained several shortcomings worthy of note. For instance, while Dykes and Meier discussed the technical aspects of certain studies, in most cases they did not present the original results, thereby hampering the reader in drawing his or her own conclusions about the published results.

The primary results of Anderson et al.'s⁵ 1972 study were presented by Dykes and Meier, but certain important findings were neglected. For example, on biological grounds one would expect the benefit of supplementation to be greater for subjects with a low dietary vitamin C intake. Indeed, in Anderson's study vitamin C (1 g/d regularly, 3 g/d extra during a cold) decreased the total number of "days confined to house" per person by 48% in subjects with a low intake of fruit juices (< 0.12 L/d). The decrease was only 22% in those with a higher intake of fruit juices.⁵ Similar results were obtained in Anderson et al.'s²⁶ 1975 study, indicating that the subgroup difference was not just statistical fluctuation.

Dykes and Meier²⁴ commented on Coulehan's 1974 study⁹ of

schoolchildren: "Because the data required for an appropriate analysis are not presented, the statistical significance of the differences reported cannot be considered to have been established." However, Coulehan et al.⁹ explicitly reported that 32% (61 of 190) of lower grade children administered vitamin C were "never ill on active surveillance," while only 16% (30 of 192) of those administered placebo were never ill. It is highly unlikely that such a difference in favor of vitamin C would be caused purely by chance ($P = 0.0002$; 2-tailed Fisher's exact test). The data for children in the higher grades was also presented: 63% (82/131) of those administered vitamin C were "never ill on active surveillance," but only 49% (63/128) of those administered placebo were never ill ($P = 0.041$; 2-tailed Fisher's exact test). Thus, important elements of Coulehan's⁹ results were explicitly published and can be statistically re-analyzed, in contrast to Dykes and Meier's claims. Furthermore, Coulehan et al.⁹ found that the duration of colds was 12% and 29% shorter in children administered 1 and 2 g/d of vitamin C respectively suggesting dose dependency up to 2 g/d, but these data were not given by Dykes and Meier.²⁴

Karlowski et al.¹⁰ carried out a vitamin C-common cold study at the National Institutes of Health, which was published in the same issue of the *Journal of the American Medical Association* as the Dykes and Meier review. Karlowski used placebo capsules containing lactose, which can easily be distinguished from ascorbic acid by taste. The authors suggested that the apparent benefit due to vitamin C was caused by the placebo effect, as some of the subjects admitted having tasted their capsules. This interpretation was uncritically reiterated by Dykes and Meier.²⁴ The "placebo effect" explanation, however, is simply inconsistent with Karlowski's data.¹¹ Compared to the placebo group, 3 g/d of vitamin C decreased the duration of colds by 6–9%, whereas 6 g/d decreased it by 17%, suggesting dose dependency up to 6 g/d.^{10,11} Dykes and Meier did not reveal the results of Karlowski's study in their review, apparently due to their faith in the "placebo effect" explanation.

In the case of Ritzel's study of schoolchildren in a ski resort, Dykes and Meier did not mention that there was a 29% decrease in the mean duration of episodes, a 45% decrease in the incidence of colds, and a 61% decrease in the total number of days of illness per person in the group administered 1 g/d of vitamin C.^{1,2,27-29} Dykes and Meier²⁴ merely commented that the difference in cold incidence in the two groups was only marginally significant ($P = 0.04$; 2-tailed), which appears to be intentional camouflaging of the actual results.

Dykes and Meier also discussed a few more studies of lesser importance, but excluded some studies using large vitamin C doses (≥ 1 g/d), although these had been published prior to their review.²³

Truswell's 1986 Minireview

In 1986, the *New England Journal of Medicine* published a brief analysis of the vitamin C-common cold studies as a letter by A. Steward Truswell.²⁵ The main text was half a column long, and in this respect it was a highly superficial review. However, the forum, a journal with great prestige and a very wide circulation, makes the statements in this minireview influential and worthy of brief comments.

Truswell did not present any figures or P values from the original reports, offering only subjective conclusions about the studies. He made no efforts to rationalize the great variations in the published results. For example, on pharmacologic grounds it would seem obvious that the dose is an important variable affecting the results, yet Truswell made no distinction between studies using 6 g/d¹⁰ and 0.05 g/d³¹ of vitamin C.

Truswell,²⁵ referring to certain common cold studies, stated that, "there was no reduction in duration or severity with ascorbic acid as compared with placebo."^{15,31-37} Actually, Coulehan et al.,³² Clegg and Macdonald,³³ and Elwood et al.³⁴ found a 5–6% shorter duration of cold episodes in the vitamin C group (1 g/d). Miller et al.³⁵ found an 8% decrease in the "average duration of episodes" and a 12% decrease in "days in bed" among twins administered 0.5–1.0 g/d of the vitamin. A small but reproducible benefit suggests that there may be a real physiologic effect. The effect could be greater in some other groups of subjects and with larger doses, so that it is inaccurate to describe these four independent studies as if no reduction were observed at all. Cowan et al.³⁶ reported 31% less days lost from school per person in subjects given 0.1–0.2 g/d of vitamin C.^{1,2} Glazebrook and Thomson³⁷ found no effect on the duration of colds, but a 40% decrease in the average stay in the hospital due to tonsillitis in children administered 0.05–0.3 g/d of vitamin C.¹

At the end of his minireview, Truswell²⁵ further claims that "in another five combined trials there appeared to be slight amelioration of symptoms, which was not statistically significant."^{10,12,38-40} In fact, all of the six studies reported in the five papers cited had found a statistically significant benefit in one of the outcome parameters (Table II). Thus, Truswell's statement is gravely misleading, even though the five reports did contain some other outcomes in which the benefit was not significant statistically.

DISCUSSION

Conceptual Problems in the Interpretation of Common Cold Studies

In 1971 Pauling carried out a meta-analysis of four placebo-controlled vitamin C-common cold studies, calculating that there was very low probability ($P < 0.00003^2$) that all the reported benefits were purely due to chance. There were technical deficiencies in the studies on which Pauling based his hypothesis and consequently it was possible that the apparent effects were due to biases in the studies. Nevertheless, trials carried out since the early 1970s have consistently shown that vitamin C supplementation alleviates the symptoms of the common cold, indicating that the vitamin does indeed have physiologic effects (Tables I and II^{3,4,41}). With this experimental background it seems surprising that a widely held opinion that vitamin C has no proven effects on the common cold persists.²⁰⁻²⁵

Usually the evaluation of the potential effectiveness of a therapeutic method depends greatly on the possibility of biologically rationalizing the method. Goodwin and Goodwin^{42,43} reviewed several cases in which an effective method of treatment was erroneously rejected due to a lack of understanding of the physiologic mechanism of the effect. Thus, the question in evaluating a new method of therapy is not just whether a moderate effect is reproducible in controlled trials.

It seems quite clear that the great quantitative variation in the results is one of the factors hampering the conclusion that vitamin C has real effects on the severity of colds. However, it has been previously proposed that there also are conceptually much deeper problems in the interpretation of the results, at the paradigm level, to use Thomas Kuhn's terminology.⁴⁴⁻⁴⁶ Traditionally it has been assumed that vitamin C only prevents scurvy and apparently this notion has created strong prejudices against all other physiologic effects produced by this vitamin.^{11,44,45}

The view that vitamin C has some effects on the immune system and on the susceptibility to infections is an old one, long predating Pauling's analyses.⁴⁷⁻⁴⁹ Also, it has been known since the 1940s that the concentration of vitamin C in leuko-

TABLE II.

FIVE TRIALS IN WHICH THE AMELIORATION OF COMMON COLD SYMPTOMS BY VITAMIN C WAS NOT STATISTICALLY SIGNIFICANT ACCORDING TO TRUSWELL²⁵

Study (Ref.)	No. of subjects	Vitamin C dose (g/d)	Effect of vitamin C (%)	P (two-tailed)	Outcome
Karlowski et al. 1975 (10, 11)	103	6	-17	0.047	Duration of symptoms
Pitt & Costrini 1979 (12)	674	2	-5	0.023	Severity of symptoms
Ludvigsson et al. 1977 (38)*	158	1	-39	0.003	Duration of symptoms
Ludvigsson et al. 1977 (38)*	615	1	-14	0.016	Absence from school
Carr et al. 1981 (39)	190	1	-19	<0.05	Duration of symptoms
Wilson et al. 1973 (40)†	128	0.2	-45	0.035	Intensity of symptoms

In all listed studies placebo was administered to the control subjects, and the effect refers to the difference between the vitamin C and placebo groups. The exact *P* values were calculated when appropriate data were available.

* Ludvigsson reported the results of two separate studies in the same paper.

† "Whole colds" among girls administered 0.2 g/d of vitamin C; for details, see ref. 40.

cytes is tens of times higher than in blood plasma,^{50,51} and it was known even earlier that leukocytes participate in defense against infectious agents. It does not seem reasonable to assume that leukocytes would serve only as a storage compartment, and the high concentration of vitamin C thus suggests that it has functional roles in these immune system cells. Had the reviewers been more familiar with the previous work on vitamin C and the immune system, they might presumably have been more rigorous in their analyses of the common cold trials.²³⁻²⁵

The magnitude of the effect considered clinically significant may also be an issue confounding the analysis of the common cold studies. Many antibiotics have truly dramatic effects on certain bacterial infections and vitamin C has such an effect on scurvy. Possibly the reviewers had such truly dramatic effects in mind when considering whether vitamin C has clinically meaningful effects on colds. For example, Dykes and Meier²⁴ said of Anderson's 1972 study that "the estimated effect is considerably less than that predicted by Pauling for the dose level." Anderson had reported a 30% decrease ($P < 0.001$) in the total number of days confined to house per subject.⁵ Many people might consider that with an inexpensive nutrient that costs pennies per gram and that is safe in large doses^{41,52,53} even such moderate benefits are worthy of exploitation irrespective of how they compare to Pauling's predictions.

A further conceptual problem may be the high doses of vitamin C used in the studies. The doses that have consistently shown benefits (1-6 g/d) are some hundreds of times greater than the doses which prevent scurvy (0.01 g/d^{20,51}). Consequently, the doses used in the common cold studies may appear "pharmacologic" rather than "physiologic." However, it has been estimated that the diet of our ancestors contained 0.4-2.0 g/d of vitamin C,^{41,54,55} and the gorilla, a close biological relative of ours, obtains some grams of vitamin C per day in its diet.⁴⁹ Evidently there has been an evolutionary trend in our ancestors to manage with smaller vitamin C intakes, especially in the Northern regions where fruits were not available. No strong conclusions can therefore be drawn from the evolutionary data as regards the optimum dose for modern human beings. Nevertheless, the evolutionary data indicate that gram doses of the vitamin are not strictly unfamiliar to human physiology.

Finally, one problem in the analysis of the vitamin C supplementation studies may be the social implications. For example, if vitamin supplements are shown to be beneficial for certain pur-

poses, there may be a concern that some people would prefer to eat a poor quality diet and supplement it with vitamins rather than eat a higher quality diet containing lots of fruits and vegetables. It is also possible that any modest effects may be greatly exaggerated by commercial entrepreneurs. Nevertheless, such social concerns should not bias investigation of the actual scientific questions, although they should make a reviewer cautious in the exact formulation of his or her conclusions.

Pauling complained that many of his critics had not read either his texts or the original reports carefully, giving several examples to support his assertion.⁴¹ The diverse and numerous shortcomings in the three major reviews discussed here support Pauling's allegations. In fact, motivated by the numerous shortcomings in the Dykes and Meier review, Pauling submitted an analysis of the vitamin C-common cold studies to the *Journal of the American Medical Association*. It was rejected even though Pauling twice made revisions to meet the suggestions of the referees^{30,41} and it was finally published elsewhere.^{29,30} As a further example of careless reading or reporting by Pauling's critics, Chalmers claimed that "Pauling averaged *P* values from the different studies."²³ However, in his statistical analysis Pauling² explicitly used the well-established Fisher procedure of combining independent *P* values,¹⁷⁻¹⁹ which cannot be described as naive averaging of the *P* values.

Open Questions

Looking at the studies published to date, it seems clear that Pauling was too optimistic as regards the quantitative benefits of vitamin C supplementation, although he was correct in his general conclusion that the physiologic effects of vitamin C are not limited to the prevention of scurvy. Pauling^{1,2} suggested that large doses of the vitamin would substantially decrease the incidence of colds. It is possible that vitamin C supplementation decreases the common cold incidence in certain restricted groups of people,^{56,57} but there seems to be no worthwhile effect on cold incidence in the general population of Western countries.^{3,4,56} Pauling's other conclusion, that vitamin C ameliorates the symptoms of the common cold, has been corroborated in subsequent work, but the benefit has been smaller than he thought.¹⁻⁴

Although placebo-controlled trials have shown that vitamin C has physiologic effects on the common cold, there are scores of open questions awaiting answers. For example, in the case of treating the common cold, it may be asked what is the best method

of supplementation, what are the optimum doses, what is the maximum treatment effect, and how does the benefit vary among different groups of people? It also seems important to understand the biochemical mechanisms of the effect as this could eventually help in the identification of groups of people who would benefit most. Furthermore, it may be asked whether vitamin C supplementation has moderate effects on certain other diseases, as has been suggested in a few recent reviews.^{41,53,58-63}

Such questions are important, yet they are not often asked.

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