27

Vitamin C and Infectious Diseases

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INTRODUCTION

In the early part of this century it was thought that low vitamin C intake may decrease resistance to infections (1-6). Nevertheless, the precise role of vitamin C in infectious diseases is still poorly understood. The purpose of this chapter is to review the literature relating vitamin C intake to the susceptibility to and severity of infections. Two exhaustive searches of the old literature on studies about vitamin C and infections have been carried out, but the data of the original publications were not thoroughly analyzed in either of these reviews (7,8).

VITAMIN C AND THE COMMON COLD

In the early 1970s Linus Pauling suggested that vitamin C supplementation may decrease the incidence and severity of common cold infections (9,10). His conclusions were based on earlier studies in which groups supplemented with vitamin C showed some benefit. Since Pauling has made the issue popular, a large number of studies have been carried out to examine whether vitamin C supplementation has an effect on colds (8,11-15).

Severity of Common Cold Episodes

There are eight published studies that have examined the effect of high-dosage (≥ 2 g/day) regular vitamin C supplementation on the duration and severity of common cold episodes (Table 1) (16-25). Each of these studies found a statistically significant decrease in at least one outcome. If the p values found in the eight studies are combined by the Fisher method (28,29), a very small combined p value results. Thus it is unlikely that the published differences in favor of vitamin C are caused by chance alone. All of the eight studies were placebo-controlled, double-blind studies and five of them were randomized (16,20,21

Table 1 Vitamin C and Common Cold Symptoms[a]

Ref.	Subjects, country	No. of episodes in vitamin C group	Dose (g/day)	Effect on duration or severity[b]	p $(1 - t)$	$-2 \times \ln(p)$
16	Military recruits, USA	37[c]	2	−72[d]	0.016	8.27
17	Adults, USA	4[e]	2	−50[f]	0.023	7.55
18	Adults, USA	11[e]	3	−30[g]	0.005	10.60
19	Schoolchildren, USA	16	2	−29	0.006[h]	10.23
20	Schoolchildren, Chile	38	2	−24	0.041	6.39
21,22	Adults, Canada	561	1 + 3[i]	−21[j] −5	0.008	9.66
23,24	Adults, USA	76	3 + 3[i]	−17	0.025	7.38
25	Military recruits, USA	600	2	−5[f] −3	0.012	8.85
	Total:	1343	Median	−26	χ^2 (16 df) = 68.9	
			Mean	−31	combined $p(1 - t)$ =	
			Weighted mean	−15	0.00000001	

[a]Studies in which ≥2 g/day of vitamin C was regularly administered were selected. In the case of short-term studies supplementation was initiated before the symptoms started and continued after the symptoms ended. For a more comprehensive list of the original data see Table 1 in Ref. 14. Anderson's 1972 study (26) was included as the dose was 4 g/day during the episodes although the regular dose was 1 g/day. Anderson's 1974 study was excluded since there is bias in the distribution of subjects in the study groups (26,27). In the case of the studies by Anderson (21) and Pitt and Costrini (25) the days indoors and the severity of symptoms, respectively, were selected as outcomes in the calculations. The weighted mean was calculated using the number of episodes in the vitamin C groups as the weight. The p values were recalculated when appropriate data were available. The combined p value was calculated by the Fisher method (28,29).
[b]The outcome is the duration of cold symptoms except when otherwise indicated.
[c]The number of subjects; the number of episodes is not given in the report.
[d]Days of morbidity for sore throats.
[e]Induced rhinovirus infection.
[f]Severity of symptoms.
[g]Severity of symptoms at the fourth day after challenge.
[h]p Value for comparing the sickness days between the groups.
[i]At the onset of a cold episode an additional 3 g/day was given for 3–5 days.
[j]Days indoors due to a cold episode.

23,25). Consequently it is unlikely that biases between the study groups or the placebo effect would cause the consistent differences in favor of vitamin C.

From the published studies it is clear that vitamin C has physiological effects on common cold symptoms. Nevertheless, there have been great quantitative differences in the effects (Table 1; 14,15), and it is not clear what the practical significance of vitamin C supplementation in the treatment of colds is. Most of the controlled studies have administered vitamin C regularly, whereas in the treatment of symptoms it would appear more reasonable to start supplementation immediately after the first symptoms, but it is not clear whether the effects of therapeutic supplements are comparable to those found with regular supplements (Table 1).

Incidence of the Common Cold

If high vitamin C doses decreased common cold incidence substantially, the most convincing evidence should be seen in studies using large vitamin doses and recording large numbers of cold episodes. However, none of the four largest studies using ≥ 1 g/day of vitamin C found a significant decrease in cold incidence (Table 2; 21,25,30,31). Furthermore, the pooled estimate does not suggest any real difference between vitamin C and placebo groups. Consequently, high-dose vitamin C supplementation has no meaningful preventive effect on cold episodes in subjects comparable to those used in the four major studies.

Nonetheless, although the major studies show that a high vitamin C dose per se does not prevent colds to any meaningful extent in large segments of the general population, this should not be interpreted as definite evidence that vitamin C intake can have no effects on cold incidence in any conditions. A number of smaller studies have found a statistically significant decrease in cold incidence in subjects supplemented with vitamin C. It is possible that some of the positive results are caused by the use of different kinds of subjects or by other differences in the experimental conditions compared to the major studies in Table 2. In a recent metaanalysis of three studies using subjects under acute heavy physical stress it was calculated that the pooled risk ratio (RR) of cold episodes in vitamin C groups was 0.50 (90% confidence interval [CI]: 0.37, 0.66; $p(1 - t) = 0.00003$), suggesting that vitamin C intake can affect cold incidence in certain specific conditions (33).

Furthermore, it is possible that some of the positive results are not due to the high vitamin C dose used, but to the correction of marginal deficiency in the control group. In this respect the randomized double-blind study by Baird et al. (34) is particularly interesting as the dietary vitamin C intake was rather low, 50 mg/day, and the supplement dose was also small, 80 mg/day. This study is relevant to the question of whether marginally low intake in the control group (50 mg/day) increases susceptibility to colds compared to the

Table 2 Vitamin C and Common Cold Incidence[a]

Ref.	Subjects, country	Vitamin C dose (g/day)	Duration (months)	No. of episodes: Vitamin C	Placebo		RR	90% CI
21	Adults, Canada	1	3	561	609		0.93	0.84, 1.03
30	Women, UK	1	3	627	690		0.93	0.85, 1.03
25	Military recruits, USA	2	2	600	619		1.00	0.91, 1.10
31	Schoolchildren, Sweden	1	3	657	622		1.08	0.98, 1.19
			Totals:	2,445	2,540	RR_{Pool}:	0.99	0.94, 1.03

[a]Studies in which ≥1 g/day of vitamin C was regularly administered and >300 cold episodes were recorded were selected. The smaller studies using ≥1 g/day of vitamin C excluded from this table contain approximately 1500 episodes in all (cf. Table 1 in Ref. 14) and thus their weight is small compared to that of the studies included. Anderson's 1974 study is excluded since there is bias in the distribution of subjects in the study groups (26,27). The RR and CI values were calculated with the normal approximation of the Poisson distribution and the pooled values were calculated using the inverses of variances as weights (32). RR, relative risk; CI, confidence interval.

somewhat higher intake (130 mg/day). There were 184 and 135 cold episodes among the 133 and 61 male subjects administered vitamin C and placebo, respectively. Thus, among Baird's male subjects receiving higher vitamin C intake (130 mg/day) the RR of cold episodes was 0.63 (90% CI: 0.52, 0.75; $p(1 - t) = 0.00002$). A few other studies are also consistent with the suggestion that low vitamin C intake increases the susceptibility to colds (34a). Even if the association of vitamin C intake and common cold susceptibility were largely limited to the marginal deficiency region, this could be of great importance globally. For example, vitamin A supplementation has been shown to decrease the mortality rate of children in several developing countries in which dietary vitamin A intakes are low (35); in developed countries vitamin A supplementation has no comparable effects.

Subgroup Differences in the Effects of Vitamin C on Cold Severity

Some of the common cold studies have compared the effects of vitamin C supplementation on different subgroups (Table 3; 21,36,37). Anderson et al. (21,36) carried out two studies with adults, both of which compared various subgroups. However, the experimental protocols of his studies differed considerably. In the first, subjects were given 1 g/day of vitamin C regularly over the entire study period and 3 g/day extra for 3 days during cold episodes (21). In the other study 1.5 g was administered on the first day of the cold episode and 1 g/day on 4 consecutive days (36); these subjects were also administered a regular dose of 0.5 g per week (i.e., 0.07 g/day), which is such a small dose that it should not affect the results. Thus the former study (21) may be considered one with regular supplementation (1-4 g/day), whereas the latter (36) may be considered one with therapeutic supplementation (1-1.5 g/day), i.e., supplementation starting only after the onset of cold symptoms.

In both studies Anderson found that vitamin C supplementation was more beneficial for subjects who had a low intake of fruit juices, which are a major dietary source of vitamin C (Table 3). This finding is biologically reasonable as supplementation should be most beneficial for people with low dietary intake. The effect of vitamin C status on cold duration was also studied by Coulehan, who determined the plasma vitamin C level in selected subjects administered placebo or vitamin C and divided the subjects of both study groups into three subgroups on the basis of vitamin C plasma levels (Table 4). Coulehan found that the duration of colds gradually decreased while the vitamin C level in plasma increased; however, the subjects with the highest plasma levels had the longest colds (Table 4; 38). Thus it appears possible that 1 g/day of vitamin C supplementation produced plasma levels that were too high for a subgroup of subjects. Still, there are no other data indicating that excessive vitamin C intakes or plasma levels could increase the duration of colds. Two studies comparing two different vitamin C doses found a greater decrease in the duration of colds in the group given the higher vitamin dose (19,23,24). The significance of Coulehan's puzzling observation thus remains unclear.

Children are an important source of common cold infections in the community (39), and therefore Anderson's observation in both studies that vitamin C is more beneficial to adults having contact with children is noteworthy (Table 3). Anderson also found other subgroup differences, but these were not consistent between the studies. For example, regular supplementation was more beneficial to people frequently in crowds, but this subgroup difference was not found in the therapeutic study (Table 3). It is possible that some of the further subgroup differences are caused by chance; however, different protocols in the two

Table 3 Effect of Vitamin C Supplementation on Colds in Certain Subgroups

	Effect on the "total days indoors"	
	1972 Study (21) regular supplement	1975 Study (36) therapeutic supplement
Anderson et al. studies (21,36)		
Daily juice		
0–3 oz	−48%	−33%
4+ oz	−22%	−22%
Contact with young children		
Yes	−46%	−40%
No	−17%	−13%
Frequently in crowds		
Yes	−34%	−25%
No	−17%	−29%
Smoker		
Yes	−30%	−31%
No	−31%	−22%
Sex		
Male	−36%	−25%
Female	−26%	−27%
Age (years)		
<25	−30%	<30 −37%
≥25	−31%	≥30 −15%
Student		
No	−39%	—
Yes	−18%	—
Usual colds		
2+	−43%	—
0–1	−13%	—
	Effect on the symptom	
	"Duration"	"Severity"
Carr et al. study (37)		
Twins living		
Together	+1%	+6%
Apart	−35%	−35%

studies (regular/therapeutic) can also determine which groups show the greatest benefits from supplements.

Carr et al. found that vitamin C had a considerable effect on twins living apart, but no effect on twins living together (Table 3). An obvious explanation of the difference is that twins living together exchanged their tablets to great extent. Two other studies with children found an increase in plasma (19) and urine (40) vitamin C levels in the placebo [sic!] groups, a finding which even more directly shows that tablet exchange may take place among playful children under study conditions. It is also noteworthy that in Carr's study

Table 4 Plasma Vitamin C Level and the Duration of Colds

Vitamin C level in plasma	Episodes (no.)	Mean duration (days)	Difference from low-placebo
	Placebo group		
Low	20	5.6	0%
Middle	18	4.5	−20%
High	10	4.4	−21%
	Vitamin C group (1 g/day)		
Low	22	4.0	−29%
Middle	15	2.7	−52%
High	13	6.8	+21%

Source: Ref. 38.

(37) the average duration of colds in both groups of twins living together (5.4 days) was intermediate between that of the vitamin C (4.9 days) and placebo (7.5 days) groups of twins living apart, also consistent with the notion that tablets were exchanged by twins living together. Carr's subgroup analysis is important in suggesting that in some studies with children the mischief of the subjects may have confounded the results and the observed difference may underestimate the true physiological effect.

Some Problems in the Interpretation of the Common Cold Studies

Many people have drawn more or less inappropriate conclusions about the vitamin C-common cold studies. From the studies published so far it is clear that Pauling (9,10) was correct in his general conclusion that vitamin C has effects on colds, on both their severity and incidence. Nevertheless, quantitatively he was substantially overoptimistic. Pauling based his quantitative conclusions (10) on the study by Ritzel on schoolchildren in a skiing school in the Swiss Alps (41,42), but such children are not a good representative sample of the general population. Thus, when Pauling implicitly extrapolated the results to all people (i.e., children at school and adults), he took a bold step and went wrong. Furthermore, Pauling's conclusion (10) that the 45% decrease in cold incidence in the vitamin group in Ritzel's study was caused by the high vitamin C dose (1 g/day) per se was also hasty. It is possible that the effect was due to the correction of marginal vitamin C deficiency in the control group, in which case a much smaller dose could have produced a similar effect. This interpretation is supported, for example, by Baird's study (34), as noted. The lack of effect of high vitamin C doses in the major studies (Table 2) also suggests that if the vitamin affects cold incidence it is in the low-intake range rather than in the high-intake range.

Several reviewers have drawn quite different conclusions about the effects of vitamin C on colds than Pauling. However, there are profound problems in many reviews of the topic. In one major review (43) there were data inconsistent with the original publications and the data were analyzed improperly (27,44). In another major review (45) some data were misrepresented and some other relevant data were not presented at all (44,46,47). In a brief review of vitamin C and colds in a major medical journal (48) a few explicit statements were gravely inconsistent with the data in the original reports (44). Furthermore, the vitamin C-common cold trial carried out at the National Institutes of Health (NIH) in the middle of the 1970s (23), which appears to be the most influential study so far, was interpreted inappropriately (24). However, overtly negative conclusions from the original data are not a problem that appeared after Pauling made the issue popular, since in some earlier studies the authors' conclusions were much more negative than objective interpretation of the findings would have permitted (13).

It appears quite clear that the great quantitative variation in the results (Table 1; 14,15) has been an important factor hampering the conclusion that vitamin C has real effects on the severity of colds. However, it seems that there are also much deeper conceptual reasons for prejudice against vitamin C at the paradigm level, to use Thomas Kuhn's terminology (44,49-51).

There is a widespread belief that the sole physiological role of vitamin C is to prevent scurvy, and evidently this belief has generated strong prejudices against all other observed physiological effects of the vitamin (44,49,50). Nevertheless, vitamin C participates in the function of several enzymes that are unrelated to connective tissue metabolism (52-55), and as a major physiological antioxidant it can have numerous nonspecific biochemical effects. Consequently, there are no biochemical reasons to assume that the physiological effects of vitamin C are strictly limited to the prevention of overt scurvy. None of the three major reviews (43,45,48) discussed the possible effects of vitamin C on the immune system to provide a background to the examination of whether the effects of vitamin C on the common cold make any sense biologically. This is important as the evaluation of the effectiveness of a therapeutic method usually depends greatly on the possibility of rationalizing the method biologically, and not just on the interpretation of experimental results (56,57).

Furthermore, if a treatment bypasses the medical establishment and is marketed directly to the public there may be a temptation in the medical community to accept the first bad news that comes along uncritically without considering the entire body of relevant data (57). Vitamin C is of great interest among nonprofessionals and therefore such psychological effects may be pertinent. Finally, there are numerous obviously erroneous claims about the effects of vitamin C supplementation and a vast commercial exploitation of such claims. In the minds of critical people not engaged with vitamin C in particular, this kind of background may lead to a biased view of vitamin C in general.

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Vitamin C and Infectious Diseases

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INTRODUCTION

In the early part of this century it was thought that low vitamin C intake may decrease resistance to infections (1-6). Nevertheless, the precise role of vitamin C in infectious diseases is still poorly understood. The purpose of this chapter is to review the literature relating vitamin C intake to the susceptibility to and severity of infections. Two exhaustive searches of the old literature on studies about vitamin C and infections have been carried out, but the data of the original publications were not thoroughly analyzed in either of these reviews (7,8).