

Vitamin C Supplementation and Respiratory Infections: a Systematic Review

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In this review, the vitamin C trials with military personnel and with other subjects living under conditions comparable to those of military recruits are analyzed to find out whether vitamin C supplementation affects respiratory infections. For this systematic review, we identified seven trials with military personnel, three trials with students in crowded lodgings, and two trials with marathon runners. Eight of these trials were double blind and placebo controlled and seven were randomized. Five small trials found a statistically significant 45 to 91% reduction in common cold incidence in the vitamin C group. These trials were short and the participants were under heavy exertion during the trial. Furthermore, three other trials found a statistically significant 80 to 100% reduction in the incidence of pneumonia in the vitamin C group. The large number of positive findings seems to warrant further consideration of the role of vitamin C in respiratory infections, particularly in military recruits.

Introduction

A high incidence of pneumonia and other respiratory infections is a common problem among military recruits, possibly caused by the crowding together of young adults from widely dispersed geographic areas.^{1,4} Navy and Marine recruits were at 30 times higher risk of hospital admission for pneumonia than were nonrecruits,¹ and Navy and Marine personnel with less than 1 year of service were at five times higher risk of pneumonia than their peers with 4 or more years of service.⁴ Consequently, factors affecting susceptibility to respiratory infections in military recruits are of considerable practical importance.

The notion that vitamin C affects susceptibility to various infections—and respiratory infections in particular—is an old one,^{5,6} but the topic came to wider popularity only in the 1970s, when Pauling^{7,8} suggested that vitamin C supplementation would reduce the incidence and severity of colds. Trials carried out since then have consistently found that vitamin C alleviates common cold symptoms, but yields only modest benefit.⁹⁻¹² Vitamin C had no effect on the incidence of the common cold in the largest trials,^{6,12,13} but trials with British men¹³ and with subjects under heavy, acute physical stress¹⁴ found reduction in common cold incidence, suggesting that vitamin C affects susceptibility to respiratory infections in restricted groups of people. Although Pauling was considerably overoptimistic about the potential benefits of vitamin C,^{7,8,11-13} another problem in this area of interest has been the negative bias against vitamin C. Three influential reviews concluded that vitamin C is ineffective against colds; however, the reviews presented data inconsistent

with the original reports, overlooked several highly relevant findings, and analyzed data inappropriately.^{9,10}

The purpose of the present review was to analyze the findings of vitamin C trials with military personnel and of trials with participants under conditions similar to those of military recruits to find out whether vitamin C affects the incidence or severity of respiratory infections.

Methods

Selection of the Trials

I previously searched the literature on vitamin C and respiratory infections using various MEDLINE, EMBASE, and SCISEARCH database searches, and I inspected the reference lists of reviews and original reports.^{6,11,13} One other author independently searched for trials on vitamin C and the common cold and published the identified bibliography.¹⁵ For this systematic review, further MEDLINE searches covering the years 1999-2002 were carried out.

The present review covers only controlled trials in which vitamin C was administered to one study group; the control group may or may not have received a placebo. This analysis focused on trials reporting respiratory tract infection outcomes. Two groups of trials were selected on the basis of subjects used in the trials: military personnel (seven trials; Table I) and students accommodated in crowded lodgings and marathon runners (five trials; Table II). Except for one trial,¹⁸ the trials in the tables are prophylactic such that participants were healthy at the trial's outset and supplementation continued over the occurring respiratory infection episodes. Although one trial examined patients hospitalized for influenza A, it was nevertheless prophylactic with respect to the occurrence of pneumonia after the initiation of vitamin C supplementation.¹⁸

Statistical Methods

Tables I and II show the *p* values calculated by the current author for the differences in the outcome values between the two groups. For dichotomous data, the mid-*p* modification²⁸ of the Fisher's exact test²⁹ was used to calculate *p*. For continuous variables, the exact *p* value was calculated using the *t* test,²⁹ when mean and SD were reported in the original articles. The χ^2 test²⁹ was used to test whether the distribution of participants with correct and incorrect answers in the Pitt and Costrini trial¹⁶ is explained by random variation. Assuming pure guessing, the expected number of correct and wrong answers is equal; both are one-half of all of the answers. Consequently, with 316 answers in the Pitt and Costrini trial, the expected number of correct and wrong answers is 158.

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TABLE I
VITAMIN C AND RESPIRATORY INFECTIONS IN MILITARY PERSONNEL

Trial ^a	Variable	Treatment		Difference in Outcome (%)	<i>p</i> (one-tailed) ^b
		Vitamin C	Control		
Pitt and Costrini ¹⁶	Subjects	331	343		
United States	Common cold episodes	600	619	0	
2 g/day	Severity of colds ^b	1.87	1.97	-5	0.012 ^c
2 months	Duration of colds (days)	11.2	11.5	-3	
	Pneumonia cases	1	7	-85	0.022
Dahlberg et al. ¹⁷	Subjects	1,259	1,266		
Sweden	Subjects with the common cold	126	130	-2	
0.5 g/day	Subjects with more severe respiratory infections ^d	5	10	-50	0.11
3 months					
Kimbarowski and Mokrow ¹⁸	Patients with influenza A	114	112		
Soviet Union	Pneumonia cases	2	10	-80	0.009
0.3 g/day	Stay at hospital, all subjects (average, days)	9	12		
Therapeutic trial					
Sabiston and Radomski ¹⁹	Subjects	56	56		
Canada	Subjects with the common cold	6	14	-57	0.027
1 g/day	Constitutional symptoms (mean ± SD, days) ^e	0.8 ± 0.8	2.4 ± 2.1	-67	0.045
1-2 week	Throat /chest symptoms (mean ± SD, days)	4.3 ± 3.0	6.0 ± 3.0	-28	0.13
	Nasal symptoms (mean ± SD, days)	4.2 ± 3.8	5.6 ± 2.8	-25	0.2
Elliott ²⁰	Subjects	37	33		
United States	Number of common cold episodes	— ^a	—	0	
2 g/day	Sore throat (days/group)	—	107	-72	0.016 ^b
2.5 months	Hoarseness (days/group)	—	36	-63	
	Productive cough (days/group)	—	72	-69	0.033 ^b
	Nonproductive cough (days/group)	—	42	-60	
Liljefors ²¹	Subjects	33	33		
Sweden	Subjects with the common cold	10	9	+11	0.6
2 g/day					
2 weeks					
Niemi ²²	Subjects	147	152		
Finland	Subjects with the common cold	24	18	+33	0.8
0.1 g/day					
2-3 months					

^a Reflects country, dose of vitamin C, and duration, respectively.

^b The *p* values were calculated by this author, except for the Elliott data. Elliott used the Wilcoxon test to calculate *p*. —, Data not published.

^c Difference between the treatment groups: *p* was calculated from χ^2 (15 *df*) = 27.8 reported by Pitt and Costrini.¹⁶ Severity scale is from 1 to 4.

^d Pneumonia, bronchitis, sinusitis, tonsillitis, and otitis media.

^e General malaise, headache, chills and fever, and vomiting.

The one-tailed *p* values are used in the tables and text because the explicit question in the present analysis is whether vitamin C supplementation decreases the incidence and severity of respiratory infections. There is no experimental or theoretical reason to expect that vitamin C supplementation would increase morbidity from respiratory infections. Confidence intervals are not calculated because the primary purpose of this review was to test the hypothesis that vitamin C affects respiratory infections. Trial settings and outcome definitions vary substantially, which limits the possibility to generalize the point estimates; therefore, no pooled estimates were calculated.

Trials with Military Personnel

Seven trials examined the effect of vitamin C supplementation on respiratory infections in military personnel. Table I shows the number of participants, the duration of the trial,

the dosage of vitamin C, and the outcome values. There is substantial variation in the common cold incidence in the control groups. Pitt and Costrini¹⁶ observed 11 colds per person-year, whereas Dahlberg et al.¹⁷ observed only 0.4 colds per person-year, although both of these large trials examined military recruits.

Pitt and Costrini¹⁶ carried out a large-scale, randomized, double-blind, placebo-controlled trial with Marine recruits in a training camp in South Carolina in the wintertime. The participants were vaccinated against adenovirus and influenza, and they received penicillin or erythromycin as streptococcal prophylaxis. The study groups showed no difference in common cold incidence. Vitamin C caused a statistically significant, although clinically minor, reduction in common cold severity. Of the eight pneumonia cases observed, five were caused by pneumococcus but two of them had a coinfection with parainfluenza virus. The incidence of pneumonia was significantly lower in the vitamin C group.

TABLE II

VITAMIN C AND RESPIRATORY INFECTIONS IN STUDENTS ACCOMMODATED IN CLOSED QUARTERS AND IN MARATHON RUNNERS

Trial ^a	Variable	Treatment		Difference in Outcome (%)	<i>p</i> (one-tailed) ^b
		Vitamin C	Control		
Glazebrook and Thomson ²³	Subjects	335	1,100		
United Kingdom	Subjects with the common cold	72	286	-17	0.047
Boarding school	Admitted to hospital	59	253	-23	0.017
0.05-0.1 g/day	Stay at hospital (mean, days)	6.3	6.4	0	
6 months	Streptococcal infections ^c	29	94	0	
	Admitted to hospital	18	83	-29	0.09
	Stay at hospital (mean ± SD, days)	10.1 ± 7.0	16.7 ± 11.9	-40	0.012
	Pneumonia cases	0	17	-100	0.006
	Rheumatic fever cases	0	16	-100	0.007
	Stay at hospital, all subjects (mean, days)	2.5	5.0	-50	
Ritzel ^{11,24}	Subjects	139	140		
Switzerland	Subjects with the common cold	17	31	-45	0.015
Skiing camp	Duration of colds (days)	1.8	2.6	-31	<0.05 ^b
1 g/day	Constitutional symptoms ^d				
1 week	Cases	8	21	-62	0.006
	Days/group	9	48	-81	
Bessell-Lorck ²⁵	Subjects	26	20		
West Geramny	Subjects with the common cold	1	9	-91	0.001
Skiing camp					
1 g/day					
1 week					
Peters et al. ²⁶	Subjects	43	41		
South Africa	Subjects with the common cold	14	28	-52	0.0006
Marathon runners	Duration of colds (mean ± SD, days)	6.0 ± 1.0	5.8 ± 2.5	+3	
0.5 g/day					
2 weeks					
Peters et al. ²⁷	Subjects	44	47		
South Africa	Subjects with the common cold	7	19	-61	0.006
Marathon runners	Duration of colds (mean, days)	5.8	6.8	-15	
0.5 g/day					
2 weeks					

^a Reflects country, location/subjects, dose of vitamin C, and duration, respectively.

^b The *p* values were calculated by this author, except for the Ritzel data for the duration of colds, for which Ritzel used the *t* test.

^c Diseases caused by hemolytic streptococci: sore throat, pharyngitis, tonsillitis, cervical adenitis, and otitis media. Throat swabs were taken of large numbers of patients to determine that the causative agent was hemolytic streptococcus.

^d General malaise, headache, muscle ache, abdominal pain, vomiting, and diarrhea.

Interestingly, Pitt and Costrini¹⁶ also found that a considerable proportion of their participants correctly inferred their treatment from subjective observations (for a comparable case, see Ref. 10). When asked which pill they thought they were taking, 53% (358) of all participants (674) stated they did not know. Of those who replied vitamin C or placebo (316), 27% (89) and 26% (89) answered correctly, whereas 20% (66) and 21% (72) answered incorrectly in the vitamin C and placebo groups, respectively. Consequently, in all, 178 participants answered correctly and 138 incorrectly. Assuming pure guessing, the expected number of correct and incorrect answers is 158, which allows the calculation of observed and expected difference to yield $\chi^2(1 \text{ df}) = 5.0$ and $p[\text{one-tail}] = 0.013$. Consequently, 40 participants (178 - 138) correctly inferred their treatment in this double-blind trial. Formulated from citric acid, the placebo tablets were indistinguishable in appearance and taste from the ascorbic acid tablets. Therefore, it is worth noting that 6% (40 of 674) of all participants inferred their treatment by subjective perception alone.

Dahlberg et al.¹⁷ performed a large-scale, double-blind, placebo-controlled trial with infantry recruits in Northern Sweden in the wintertime. Allocation to the study groups was by odd and even identity numbers. Low doses of vitamin C had no effect on the number of participants who caught the common cold. However, the number of participants in the vitamin C group with more severe respiratory infections was only one-half that of the placebo group level, although the difference was not statistically significant.

Kimbarowski and Mokrow¹⁸ carried out a therapeutic trial in the former Soviet Union with military personnel hospitalized for influenza A infections. The method of allocation was not described and placebo was not used. Nevertheless, the distribution of influenza severity in the vitamin C and control groups was similar, indicating that the groups were comparable in this respect. The authors focused primarily on the usefulness of a laboratory test in evaluating the severity of uncomplicated influenza and excluded from further studies those participants who caught pneumonia during vitamin C supplementation. The

number of pneumonia cases was reported and it was significantly lower in the vitamin C group. The authors were uninterested in pneumonia per se, and therefore the placebo effect and information bias²⁸ seem unlikely explanations for the reported difference.

Kimbarowski and Mokrow¹⁸ also noted that most vitamin C patients were released on the 9th day of illness, whereas the control patients were released 2 to 3 days later, mostly on the 12th day of illness. However, the authors failed to publish the actual mean and SD, thus *p* cannot be calculated for the stay in hospital.

Sabiston and Radomski¹⁹ carried out a small randomized, double-blind, placebo-controlled trial with troops on a winter exercise in Northern Canada. The vitamin C group saw not only significantly fewer common cold episodes, but also a significantly shorter duration of constitutional symptoms as well. Moreover, it is worth noting the uneven distribution of colds in the 14 tents. There was at least one cold in nine tents: six tents had colds only in the placebo subjects, and three tents had colds in the placebo and vitamin C subjects, but no tents had colds only in the vitamin C subjects.¹⁹ Accordingly, vitamin C appeared to increase resistance against colds so that vitamin C subjects fell ill only if exposed to infected placebo subjects within the same tents but not if exposed to infected subjects outdoors.^{19,30}

Elliott²⁰ carried out a small randomized, double-blind, placebo-controlled trial in a Polaris submarine. Vitamin C had no effect on common cold incidence, but Elliott failed to report explicit data. Nevertheless, the vitamin C group saw fewer days of morbidity for productive and nonproductive cough, hoarseness, and sore throat. The effect on productive cough and sore throat was statistically significant.

Liljefors²¹ performed a small randomized, placebo-controlled, double-blind cross-over trial in Sweden in the autumn. The subjects participated in military repetition exercise and were considerably older than ordinary recruits (mean age 36 years in the Liljefors trial). Vitamin C had no effect on common cold incidence in this small and short trial.

Niemi²² failed to describe properly the technical aspects of his trial with military recruits in two garrisons in Southern Finland. The number of observed common cold episodes was small, leading to low statistical power to observe moderate treatment effects. The low dosage of vitamin C did not reduce the number of common cold episodes.

Trials with Students in Crowded Lodgings and with Marathon Runners

For this review, the most essential criteria among military recruits are their age and the crowded nature of their accommodations, which regularly subjects them to close contact with each other. Three vitamin C trials with students residing in closed and crowded lodgings share these same criteria (Table II). An additional criterion typical of military recruits is their frequent heavy physical exertion, which arises interest in trials with marathon runners as well (Table II).

Glazebrook and Thomson²³ carried out a large-scale trial with male students (15-20 years old) in a boarding school in Scotland. For practical reasons, the participants were not randomly allocated to the study groups, but certain administrative divi-

sions occupying the same tables in the dining room were served vitamin C-supplemented food, whereas others remained as controls. There was, however, a fair amount of mixing of the dining divisions in the sleeping quarters. The authors reported that a tonsillitis epidemic affected all of the dining divisions uniformly the year before, suggesting that the divisions should not be regarded as separate units. Because vitamin C was added to the food in the kitchen, the placebo effect does not seem a relevant concern, although no placebo powder was used. Vitamin C supplementation continued even when a student fell so ill that he was admitted to the hospital.

Glazebrook and Thomson²³ found a statistically significant, but clinically minor, reduction in common cold incidence by vitamin C, but they observed a greater effect in the number of youths hospitalized for severe colds. In the control group, 23.0% of participants were admitted to the hospital because of severe colds, whereas in the vitamin C group, only 17.6% of participants were hospitalized for colds. Accordingly, 5.4% of vitamin C subjects obtained benefit for this outcome. There was no difference in the incidence of streptococcal infections, but fewer vitamin C participants were hospitalized, and their stay at the hospital was on average significantly shorter than those in the control group. Finally, no cases of pneumonia or rheumatic fever occurred in the vitamin C group, whereas several cases occurred in the control group. Although this was not a double-blind, placebo-controlled trial, the placebo effect and information bias²⁸ fail to explain easily the findings for the hospital stay or the dramatic difference in the incidence of pneumonia and rheumatic fever. In particular, the duration of treatment in the hospital was completely beyond the authors' control.

Ritzel^{7,24} performed a short, randomized, double-blind, placebo-controlled trial with male high school students (15-17 years old) at a skiing camp in the Swiss Alps. Vitamin C significantly reduced the incidence and duration of colds. Furthermore, the vitamin C group saw substantially fewer days with constitutional symptoms.

Bessel-Lorck²⁵ carried out a small and short trial with high school students (14-16 years old) at a skiing camp in the Bavarian mountains. The control group received no placebo, and the allocation method was not described. The vitamin C group experienced a significantly lower incidence of colds.

Peters et al.^{26,27} carried out two randomized, double-blind, placebo-controlled trials in South Africa with marathon runners. The number of colds recorded during a 2-week period after the race indicated that vitamin C supplementation before the race significantly reduced the number of colds after the race, but had no effect on the duration of symptoms.

Effect of Vitamin C on the Common Cold and Pneumonia

Three of the trials involved a large number of participants.^{16,17,23} In two of these large-scale trials, vitamin C had no effect on common cold incidence.^{16,17} The third trial, carried out in the United Kingdom, found a statistically significant, but rather small, reduction in common cold incidence,^{13,23} but a somewhat greater effect on hospitalization for colds. These large-scale trials suggest that any potentially important effects of vitamin C supplementation on common cold incidence are restricted to specific groups of subjects and conditions.

Five small trials found significant reduction in the incidence of colds with vitamin C.^{19,24-27} All of these trials were short, lasting at most a few weeks, and the subjects underwent extraordinary conditions involving heavy acute physical stress.¹⁴ Heavy exertion has been associated with the speeding up of the depletion of the vitamin C pool and with causing a frank deficiency when dietary vitamin C intake is low.³¹ In this respect, heavy exertion is an interesting element that these five small trials have in common. Two of these trials^{19,24} reported a significant effect of vitamin C on the constitutional symptoms of the common cold, such as general malaise and headache, but a smaller effect on the duration of mild symptoms. Three additional small trials found that vitamin C supplementation had no effect on common cold incidence.²⁰⁻²² These latter trials involved no extraordinary exertion, setting them apart from the former set.

Two large-scale trials^{16,23} found evidence indicating that vitamin C supplementation may affect the risk of pneumonia. Nonetheless, it is noteworthy that the incidence of pneumonia was exceptionally high in the control groups of Pitt and Costrini¹⁶ and Glazebrook and Thomson:²³ 120 and 30 cases per 1,000 person-years, respectively. In comparison, the average incidence of pneumonia in Marine and Naval recruits in the 1970s was also high, 60 per 1,000 person-years, whereas the incidence in young nonrecruits was only 2 per 1,000 person-years.¹ Two studies of young adults in Western countries reported an incidence of pneumonia of 1 to 4 per 1,000 person-years.^{32,33} Consequently, the findings of Pitt and Costrini¹⁶ and Glazebrook and Thomson²³ cannot be generalized to the population of ordinary young adults, but may have relevance to populations at high risk of pneumonia, such as military recruits.

Furthermore, Kimbarowski and Mokrow¹⁸ observed a reduced risk of pneumonia in influenza patients and Dahlberg et al.¹⁷ reported 50% lower incidence of respiratory infections more severe than the common cold in their vitamin C group, but the difference was not statistically significant.

Amount of Vitamin C in Diet and in Supplements

One particular problem in the interpretation of vitamin C trials is the great variation in the dietary intake levels and supplementation dosages. A different value of outcome between vitamin C and control groups may result from a particularly low dietary intake in the control group ("marginal deficiency") or from the high-dose supplementation in the vitamin C group. In the former case, a small dosage of supplement might produce a similar effect, whereas the latter case requires the particularly high dosage. Previously, low dietary intake of vitamin C, rather than high-dose supplementation, was proposed better to explain the decrease in common cold incidence found in trials with British men.¹³

The trials in Tables I and II vary widely in dietary vitamin C intake. Sabiston and Radomski¹⁹ estimated that the food rations contained at most 40 mg/day of vitamin C, which is considerably lower than the current U.S. recommendation for men (90 mg/day).³⁴ Pitt and Costrini¹⁶ failed to estimate dietary vitamin C intake, but in their subjects, the mean vitamin C level in plasma was rather high initially, 57 $\mu\text{mol/L}$, corresponding to a dietary intake of 100 mg/day or more.³⁵ Glazebrook and Thomson²³ estimated that their control students obtained only 15 mg/day of vitamin C in foods. On the other hand, the control

group of Peters et al.^{26,27} received some 500 mg/day of vitamin C from foods and self-supplementation. Thus, vitamin C intakes among the control groups vary up to 30-fold. The dosage of supplements also varied dramatically, from 0.05 to 2 g/day (Tables I and II). Accordingly, the supplement dosages vary up to 40-fold.

Such dramatic variations in dietary vitamin C intakes and in supplement dosages preclude any simple comparisons of the trials in Tables I and II and any straight generalizations to other population groups, although all of the trials test whether vitamin C supplementation affects respiratory infections.

Conclusions

Several trials with military personnel and with participants under conditions comparable to those of military recruits have found that vitamin C substantially reduced the incidence or severity of respiratory infections. Although there is great variation in the technical quality of the analyzed trials, eight of the trials were double blind and placebo controlled. Furthermore, the technical shortcomings in two less satisfactory trials^{18,23} fail to discount their findings.

The estimates of benefit calculated in Tables I and II require cautious interpretation. If vitamin C does affect respiratory infections, it seems evident that no single estimate applies to all population groups because various factors, such as the dietary intake level of vitamin C, the dosage of supplements, the definition of outcome, and the level of exertion, most likely modify the effect. Consequently, the estimates presented in the tables in all probability do not directly apply to other population groups. Nevertheless, the large number of statistically significant benefits observed in these trials seems to warrant further examination of the role of vitamin C in respiratory infections, particularly in military recruits.

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