

Evidence-based medicine and the role of antioxidants in physically stressed people

Proponents of evidence-based medicine emphasize that conclusions regarding the effects of interventions should be based on systematic reviews of the literature and should focus on clinically relevant outcomes.¹ Neither of these demands was fulfilled in Nieman's recent discussion of the effects of antioxidants on respiratory infections in physically stressed people.²

We carried out a systematic review of the effect of vitamin C supplementation on the common cold and identified six controlled trials with participants under heavy acute physical stress.³ Four of these were with marathon runners (three in South Africa⁴⁻⁶ and one in the USA⁷), one was with schoolchildren in a skiing camp in the Swiss Alps,⁸ and one was with Canadian soldiers in a northern training exercise.⁹ We pooled the results of these six trials and found that vitamin C supplementation reduced the incidence of common cold on average by 50% (95% confidence interval [CI]: -62% to -34%). In contrast, vitamin C had no effect on common cold incidence in the general population.³

Nieman writes just two sentences about the trials testing the effect of antioxidants on clinical infection outcomes: "Several double-blind placebo studies of South African ultramarathon runners demonstrated that vitamin C (but not E or beta-carotene) supplementation (about 600 mg/day for 3 weeks) was related to fewer reports of upper respiratory tract infection symptoms (3 references). This finding, however, was not replicated by other research teams, even when 1 g of vitamin C was consumed for 2 months prior to a marathon (1 reference)".², (p. 313) The references in these two sentences are erroneous. Of the first three references, one is to Nieman's own study on quercetin and cytokines with no relationship to the sentence, another is to a US trial that administered 1 g of vitamin C per day for 2 months prior to a marathon,⁷ and only one is to a trial in South Africa.⁵ The reference at the end of Nieman's second sentence is to a vitamin E trial that has nothing to do with vitamin C and the common cold.

It seems that Nieman was trying to argue that, while Peters et al.^{4,5} and Moolla⁶ reported that vitamin C supplementation prevented colds in ultramarathon runners in South Africa, Himmelstein et al.⁷ challenged

or refuted their findings. There is, however, no justification for such an argument. First, the Himmelstein trial was small and the 95% CI (from -65% to +71%) is fully consistent with the average effect of the six trials, the results of which show no statistical heterogeneity.³ Second, Nieman ignores two trials falling into the same group.^{3,8,9} Third, the Himmelstein trial is methodologically the weakest of the six trials,³ due to an extreme and divergent dropout rate. They started with 52 marathon runners in two 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 ($P = 0.003$ for the difference in dropout rates). On the basis of such a serious weakness, the Himmelstein trial might be excluded from the meta-analysis; however, that would lead to a greater effect by vitamin C because the Himmelstein trial found the smallest effect among the six trials.³ Thus, Himmelstein's trial does not challenge our summary estimate that in six placebo-controlled trials with participants under heavy acute physical stress, vitamin C halved the risk of common cold.³ Cochrane reviews are regularly updated and the Cochrane Database provides the possibility to comment on the reviews. If Nieman considers that our estimate for the effect of vitamin C on people under heavy acute physical stress is unjustified, he should submit a detailed criticism to the Cochrane Database. Then, we will either improve our review according to his suggestions or openly describe our countercomments.

In addition to the two missing vitamin C and common cold trials with participants under physical exertion,^{8,9} Nieman ignores other trials that are relevant when considering the effect of antioxidants on physically stressed people. We published a Cochrane review on vitamin C and pneumonia, and we identified a trial with US Marine recruits in which 2 g/day vitamin C supplementation significantly reduced pneumonia incidence: seven cases in the placebo group versus one case in the vitamin C group.^{10,11} Heavy physical exertion is characteristic of recruit training, yet crowding together may also contribute to the increased risk of pneumonia: in one survey Navy and Marine recruits were at 30 times higher risk of hospital admission for pneumonia than were non-recruits.¹² Therefore, the findings with the US Marine

recruits¹¹ are relevant to the question of whether antioxidants might reduce the risk of respiratory infections in physically stressed people. A systematic review found that several vitamin C trials with military personnel or participants under comparable conditions (physical stress and/or crowding) reported a statistically significant effect on the incidence or severity of respiratory infections.¹³

Furthermore, Nieman does not discuss any vitamin E trials with clinical respiratory infection outcomes, although a few have been published. We examined the effect of 50 mg/day vitamin E supplementation on the risk of common cold and pneumonia in physically stressed participants of the Alpha-Tocopherol, Beta-Carotene ATBC Study; this included those who had physically demanding jobs and those who engaged in physical exercise as a leisure-time activity. Vitamin E had no effect on common cold incidence in either group,¹⁴ nor did it have any effect on pneumonia incidence in those who had physically demanding jobs.¹⁵ However, vitamin E reduced the incidence of pneumonia in those who exercised during their leisure time by 50%;¹⁵ furthermore, in this group ($n = 9570$), there was a statistically significant modification of the vitamin E effect by physical activity on the job ($P = 0.02$).¹⁶ Vitamin E reduced pneumonia risk by 76% (95% CI: -90% to -41%) in those who had light or very light jobs, whereas vitamin E did not differ from the placebo in those who had moderate or heavy jobs (95% CI: -57% to +68%).¹⁶ This modification of the vitamin E effect by job-related physical activity is consistent with the concept that the body adapts to physical stress arising from a regular workload, whereas sporadic heavy exercise can lead to oxidative stress against which vitamin E may protect under some conditions.

Thus, in his review, Nieman ignores several antioxidant trials with clinical outcomes and does not describe the quantitative results of the trials he does cite.^{5,7} He thereby hampers the reader from drawing his or her own conclusions regarding the published findings. Instead, Nieman discusses the effect of antioxidants on laboratory variables such as cytokine levels, even though they are surrogates. However, as well as being of questionable clinical relevance, surrogate outcomes are often misleading.^{17,18} Surrogate outcome measures, such as laboratory results, should be avoided, for example, in Cochrane reviews.¹

A number of trials indicate that vitamins C and E may affect respiratory infections in physically stressed people and further work is justified to examine their roles in more detail. As regards practical conclusions based on current evidence, it would seem reasonable for people who carry out heavy exercise and concurrently suffer from respiratory infections to test whether vitamin C might be beneficial for them. Such testing of vitamin C at the individual level seems sensible because it is safe and cheap.

The situation with vitamin E is more complicated. Although the findings of the ATBC Study indicate that vitamin E may affect pneumonia risk in some physically stressed people, pneumonia is a rare infection in the general population; the common cold was not affected by vitamin E. Furthermore, there are findings that indicate vitamin E supplementation may be harmful for some people. In the ATBC Study, vitamin E increased the risk of tuberculosis by 72% in participants who had a high dietary intake of vitamin C.¹⁹ Therefore, it seems rational to patiently wait for further trials that test the effects of vitamin E supplementation on specifically selected groups of people instead of testing it by personal experimentation.

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