Letter to the Editor

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The effect of nutrition on exercise-induced immunodepression was reviewed by Gleeson.[1] In the vitamin E section of the review, he discussed the findings of Graat et al.[2] (N = 652) with ≥60-year-old, non-institutionalized participants and those of Meydani et al.[3] (N = 617) with ≥65-year-old nursing home residents.

Gleeson commented that self-evaluation of the common cold might have been unreliable in Graat's trial[2]; however, Gwaltney states in a major textbook of infectious diseases that "the manifestations of the common cold are so typical and familiar that self-diagnosis by the patient is usually correct."[4] Furthermore, even if the outcome may be inaccurate, such inaccuracy cannot explain the increase in the number of participants with fever ($P = 0.009$) after vitamin E supplementation in a trial that is double-blind.[2] Irrespective of etiology, the net increase in fever indicates unquestionable harm in those participants.

Statisticians prefer intention-to-treat analysis (ITT), and in their paper, Meydani et al.[3] presented their ITT results in tabular format. Meydani calculated 13 different *P* values, only one of which was statistically significant, but very marginally so ($P = 0.048$), and easily explained by the multiple comparison problem. Furthermore, even if the effect of vitamin E on the number of participants with one or more respiratory tract infection might be real, it is small (risk ratio [RR] = 0.88; 95% confidence interval [CI]: 0.76–1.00).[3]

Moreover, neither of these trials[2,3] tested whether vitamin E has effects on people who exercise. A further study, not mentioned in the review, focused on the question of whether 50 mg/d of vitamin E supplementation affects the incidence of the common cold in physically active 50- to 69-year-old male smokers in the ATBC Study cohort.[5] In participants who performed heavy physical activity on the job (N = 2211), vitamin E had no effect on common cold incidence (RR = 1.08; 95% CI: 0.99–1.18); vitamin E was also ineffective (RR = 1.10; 95% CI: 0.96–1.27) in those who exercised heavily during their leisure time (N = 916).

The effect of vitamin E on the incidence of pneumonia in physically active males was recently analyzed in the ATBC Study cohort.[6] In participants whose jobs were moderately or very active (N = 7493), vitamin E had no effect on pneumonia risk (RR = 1.29; 95 % CI: 0.79–2.11); however, in those who exercised moderately or heavily in their leisure time (N = 9570), vitamin E reduced pneumonia risk by half (RR = 0.50; 95% CI: 0.30–0.84). These findings may seem inconsistent because both subgroups were selected on the basis of physical activity; however, physical activity at work and at leisure differed such that vitamin E reduced pneumonia risk only in those who carried out exercise in their leisure time and had a physically light job.[7] This may be explained by the adaptation of the body to physical stress arising from a regular workload, whereas physically light jobs leave people unadapted to oxidative stress caused by occasional exercise at leisure.[7]

A meta-analysis focusing on the effects of vitamin C on the common cold identified six trials with participants under heavy acute physical stress (combined N = 642),[8] and in this group of studies vitamin C reduced the common cold risk by half (RR = 0.50; 95% CI: 0.38–0.66). Four of these trials had marathon runners as participants, the fifth studied Canadian soldiers in a winter exercise, and the sixth studied Swiss schoolchildren in a skiing camp.[7,8] The Himmelstein trial mentioned by Gleeson is not in conflict with the pooled RR estimate because it is small and has a wide confidence interval.[8,9]

Thus, there is evidence that vitamins C and E may affect, under some conditions, the risk of respiratory infections in people who are under physical stress, but assessment of the practical significance of these findings needs further work.

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The Author's Response

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Although the trial of Graat et al.[1] involved a large cohort and a 2×2 factorial, double-blind treatment design, the health assessment by self-evaluation can be considered to be a limiting factor, particularly in an elderly population whose cognitive function was not described. The recent large trial by Meydani et al.[2] used a more reliable method (weekly documentation by nurses and physicians, thus justifying greater confidence in the results) and showed protection against upper respiratory infections with vitamin E supplementation. Furthermore, the elderly do not develop an effective fever response to infection and have a lower body temperature than young people. Thus, more fevers in the study by Graat et al.[1] could be considered a beneficial effect of vitamin E supplementation rather than what Hemilä describes as "unquestionable harm." Indeed, the authors reported that the number of medications did not differ between groups, even though severity did.[1]

My failure to mention the Hemilä et al.[3] study in my review[4] was an unfortunate omission. However, the reported lack of effect of vitamin E supplementation in 50- to 69-year-old men with physically active jobs in this study may have been due to the lower dose of vitamin E (50 mg/d) used in this study compared with other studies that have shown beneficial effects on respiratory infection incidence[2]; it could also have been due to the fact that the subjects were smokers. The higher risk of colds in men taking vitamin E supplements and performing heavy exercise in their leisure time is interesting and worthy of further investigation. In the more recent Hemilä et al.[5] study, which was not available at the time I wrote the review,[4] it seems that the effect of vitamin E supplementation in relation to pneumonia incidence in men performing heavy exercise in their leisure time was the opposite to that reported in the Hemilä et al.[3] study on cold and flu risk. In the more recent study, vitamin E supplementation reduced the pneumonia risk in leisure-time active male smokers by 50%.[5] I certainly agree with Hemilä that further work is required on the practical relevance of antioxidant supplements (both vitamins and others such as polyphenols) on infection incidence in physically stressed individuals.

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