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LETTERS TO THE EDITOR

Vitamin C and exercise-induced immunodepression

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Moreira *et al*. (2007) systematically reviewed the role of nutrition on exercise-induced immunodepression. However, their paper has several shortcomings.

Moreira refers to Nieman's 'J'-curve hypothesis, which proposes that moderate exercise improves the immune system and reduces the risk of upper respiratory tract infections (URI), whereas excessive physical stress impairs the immune system and increases URI risk (Nieman, 1994). In a large cohort, we found that the risk of the common cold and pneumonia was not reduced with moderate physical activity, refuting the universal validity of the 'J'-model (Hemilä *et al*., 2003, 2006).

Although excessive physical stress plausibly impairs the immune system, respiratory symptoms after a marathon run (Peters and Bateman, 1983) do not imply viral etiology because sore throat, cough and nasal symptoms can result from several hours of exceptional ventilatory exertion. Many similar studies lack evidence that respiratory symptoms were caused by infections. Pneumonia is a well-defined infection and heavy exertion is characteristic for military recruit training, and therefore, increased pneumonia risk in recruits is important when considering exercise-induced immunosuppression (Hemilä, 2004). For example, 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 (Gray *et al*., 1994). Nevertheless, irrespective of the etiology of respiratory symptoms, nutrients such as vitamin C might be beneficial for marathon runners.

Moreira states that because of their comprehensive search strategy, omission of important trials seems unlikely. Yet, several important trials are missing from their review. If the biological focus is on physical stress, then restriction to athletes is poorly justified. For example, military recruits also suffer from heavy physical stress, and trials with them can add relevant information. Furthermore, Moreira ignored earlier meta-analyses on the same topic.

In 1996, I pooled the findings of three trials with participants under heavy acute physical stress: marathon runners (Peters *et al*., 1993), Canadian troops in winter exercises (Sabiston and Radomski, 1975) and school children in a skiing camp in the Swiss Alps (Ritzel, 1961). The incidence of the common cold was significantly lower in the vitamin C groups: pooled RR = 0.50 (95% confidence interval (CI) 0.35–0.69) (Hemilä, 1996). In 2004, we updated the meta-analysis by adding three newer trials, all with marathon runners (Moolla, 1996; Peters *et al*., 1996; Himmelstein *et al*., 1998; see also Himmelstein, 1996). The estimated benefit did not change, but the confidence interval became narrower RR = 0.50 (95% CI 0.38–0.66; $P = 0.000001$) (Douglas *et al*., 2004). Moreira states that further studies are required to provide unequivocal proof of effect by vitamin C, but in our 2004 meta-analysis we already had three additional trials with physically stressed people, all consistent with the 50% benefit (Douglas *et al*., 2004). Thus, the 50% effect calculated by Moreira is not novel and it is supported by three omitted trials.

If heavy exertion impairs the immune system, vitamin C might be beneficial for infections other than URI. Vitamin C supplementation reduced pneumonia incidence by 85% in Marine recruits (Pitt and Costrini, 1979; Hemilä, 2004). Furthermore, vitamin C is an antioxidant and other antioxidants might show benefits as well. In the ATBC study, vitamin E reduced pneumonia risk in participants who exercised at leisure, RR = 0.50 (95% CI 0.30–0.84), but had no effect on those who had heavy job activity, possibly because of adaptation to regular physical activity (Hemilä, 2006; Hemilä *et al*., 2006). Vitamin E had no effect on common cold risk in physically active participants (Hemilä *et al*., 2003). Thus, these findings are partially consistent with the presumed effect of vitamin C on exercise-induced immunodepression.

Moreira calculated quality scores for the identified trials. However, because of various problems in quality scoring, the current version of the Cochrane Handbook suggests that 'Reviewers should avoid the use of 'quality scores' and undue reliance on detailed quality assessments. It is not supported by empirical evidence, it can be time-consuming, and it is potentially misleading' (Higgins and Green, 2006). Moreira calculated 8.5 points to the Himmelstein *et al*. (1998) trial, but did not mention that Himmelstein started with 52 marathon runners per study group, yet 42% (22/52) of the vitamin C group and 75% (38/52) of the placebo group dropped out during the trial. Such an extreme and significant divergence in drop-out rate (Fisher-$P(2-t) = 0.003$) may cause severe bias in the groups, but this possibility was not considered by Moreira. Thus, quality scoring camouflaged a serious shortcoming. Nonetheless, the exclusion of the Himmelstein trial would not affect the conclusions.

Proponents of evidence-based medicine argue that decisions on medical interventions should be based on clinically relevant outcomes and not on surrogates such as laboratory measurements. There are several examples where the effect on a

surrogate end point diverged from the effect on a clinically relevant outcome (Fleming and DeMets, 1996). Therefore, trials that measure URI and those that measure laboratory variables of the immune system should not be presented in the same table as Moreira did, because the latter are not relevant when evaluating the clinical effects of intervention.

Finally, Moreira claims that the risk of excessive intake of vitamin C may outweigh any potential benefits. Several independent reviewers have concluded that essentially all speculations concerning the risks of vitamin C supplementation are unfounded (e.g FNB, 2000; Hemilä, 2006). On the contrary, participants of a recent pharmacokinetic study were administered up to 100 g of vitamin C intravenously over a few hours without any reported adverse effects, indicating safety of such a high single dose in healthy people (Padayatty *et al*., 2004).

In conclusion, there is strong evidence of positive effect of vitamin C on physically stressed people and there is no valid evidence that vitamin C would be harmful to ordinary people in doses of 1–2 g/day. Therefore, physically active people, who consider that they suffer from colds frequently, can use vitamin C, while at the same time, we hope that new trials would be carried out.

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Reply to Vitamin C and exercise-induced immunodepression

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The purpose of our review and meta-analysis (Moreira *et al*., 2007) was to test the narrow and specific question of the efficacy of nutritional supplements limiting the effects of exercise induced immunodepression in athletes. We believe our emphasis in athletes is justified, particularly in these days of high-profile marketing of nutritional supplements in sports. Dr Hemilä (2007) raises the issues of several