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Hemilä, Harri

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[Letter to the Editor]

Hemilä H

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Harri Hemilä
Department of Public Health, POB 41
University of Helsinki,
FIN-00014
Finland
harri.hemila@helsinki.fi
http://www.ltdk.helsinki.fi/users/hemila

Experts of controlled clinical trials argue that decisions on medical interventions should be based on clinically relevant outcomes and not on surrogates such as laboratory measurements. There are quite a few examples in which the effect on a surrogate end point substantially diverged from the effect on a clinically relevant outcome [1,2].

In this respect, the recent paper by Bruno et al. is problematic as it proposed higher vitamin E intakes for smokers on the basis of greater disappearance rate of \(\alpha\)-tocopherol in the plasma of smokers [3]. The disappearance rate is a surrogate end point with no validated relation to any clinically relevant outcome.

In our analyses of the ATBC Study cohort, we found that smoking modifies the effect of 50 mg/day vitamin E supplementation; however, the modification takes place in the direction opposite to that proposed by Bruno et al. In the \(\geq72\)-year-old ATBC Study participants who smoked \(\geq15\) cigarettes per day at baseline, vitamin E supplementation increased common cold incidence by 42\% (95\% CI: \(+18\%\) to \(+70\%\)), whereas in those who smoked less, vitamin E reduced common cold incidence by 29\% (95\% CI: \(-9\%\) to \(-46\%\)) [4].

Similarly, smoking modified the effect of vitamin E on pneumonia incidence. In the ATBC Study participants who had initiated smoking at later age, vitamin E reduced pneumonia incidence in those who quit smoking during the follow-up by 79\% (95\% CI: \(-40\%\) to \(-93\%\)), but had no effect on those who continued smoking (95\% CI: \(-47\%\) to \(+19\%\)) [5].

Thus, in the case of these two respiratory infections, vitamin E supplementation appeared beneficial for those who were smoking less, but it was harmful or ineffective for those who smoked heavily at baseline or continued smoking during the follow-up. These findings with clinically relevant outcomes thus contradict the surrogate-based proposal by Bruno et al. that smokers would benefit of higher vitamin E intakes and it would seem necessary for them to consume at least 15 mg/day of vitamin E [3]. Furthermore, the current US RDA recommendation level for vitamin E, 15 mg/day, is not based on any clinically relevant outcome either and is arbitrary [6]. The divergence in the effects of vitamin E supplementation in the ATBC Study cohort indicates that caution should be maintained in any proposals that people should increase their consumption of vitamin E until its effects are better understood.
References


