

Vitamin E is likely to affect mortality even at low doses
[Letter to the Editor]

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Clinical Trials: Journal of the Society for Clinical Trials. 2009; 6: 392-393

Published version: <http://dx.doi.org/10.1177/1740774509340211>

Post-print version of the manuscript

Reply to this comment by Donald Berry:

<http://dx.doi.org/10.1177/1740774509339843>

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Berry *et al.* [1] studied the between-trial variation in the effect of vitamin E on mortality in 22 trials, concluding in the abstract that “vitamin E intake is unlikely to affect mortality regardless of dose.” However, their discussion of the vitamin E literature is biased to such an extent that it does not provide a proper context for their paper.

Berry *et al.* referred to Meydani *et al.*'s small trial with 617 participants followed up for 1 year [2], stating that this “trial demonstrated a protective effect of vitamin E supplementation on upper respiratory tract infections for elderly residents in nursing homes” [1 p. 38]. In their ITT analysis reported in Table 3, Meydani calculated 13 *P*-values, one of which was significant, but very marginally so at the level of $P = 0.048$ [2]. Such a *P*-value in a series of 13 calculations is explained by random fluctuation and does not “demonstrate” that vitamin E is protective. Thus, Berry did not pay attention to the multiple comparison problem in Meydani's paper.

In addition, Berry *et al.* ignored our analysis of 21,796 ATBC Study participants followed up for 4 years, which showed no overall effect of 50 mg/day vitamin E on common cold incidence [3]. However, even though we found no overall effect, we found a statistically highly significant 28% reduction in common cold incidence in a subgroup of elderly less-smoking city dwellers [3]. This

finding led us to analyze the heterogeneity more thoroughly and we found that vitamin E increased or decreased common cold risk in old participants depending on their smoking background and residential neighborhood [4].

We also found significant modification of the vitamin E effect on pneumonia risk by the age of smoking initiation [5]. The concept of heterogeneity in vitamin E effect was underscored by further analyses of the ATBC Study focused on pneumonia and tuberculosis [6-8]. Thus, strong evidence of heterogeneity in the effect of vitamin E on respiratory infections was published well before Berry's study [3-5]. Whereas those findings do not prove that the effect of vitamin E on mortality is also heterogeneous, the prior information indicates that age and smoking should be considered as potential modifying factors when examining the effects of vitamin E.

The heterogeneity in the effect of vitamin E on respiratory infections motivated us to test whether the effect on mortality was also heterogeneous. We found strong evidence that the effect of vitamin E on the mortality of ATBC Study participants is modified by the combination of age and dietary vitamin C intake [9]. In 11,448 ATBC participants aged 50-62 years who had higher than median vitamin C intake, vitamin E supplementation increased all-cause mortality by 19% (95% CI: 5-35%), whereas in 872 participants aged 66-69 years, who had higher than median vitamin C intake, vitamin E decreased mortality by 41% (-56% to -21%). Furthermore, harm from vitamin E in the young ATBC participants was restricted to the follow-up period after 3.3 years of supplementation, so that thereafter mortality was increased by 38% (17-63%), whereas vitamin E had no effect on mortality over the earlier period. Berry reported that in their between-trial comparison "there is little evidence that these covariates (age and follow-up duration) matter as regards any effect of vitamin E" [1 p. 34]. Berry's findings are based on trial-level mean ages and durations of the trials. Our within-trial analysis of the ATBC Study suggests that Berry's findings are not valid.

Finally, the ATBC Study used a vitamin E dose of 50 mg/day, which is among the lowest, that have been used (see Berry's table 1). Thus, it seems that it may be primarily the subject characteristics and not the dose that determines whether vitamin E causes harm or benefit. Nevertheless, when there is difference in mortality between two vitamin E levels, it is obvious that there must be dose-dependency, which refutes Berry's conclusion.

In line with the negative findings of most vitamin E trials, our study suggests that vitamin E self-supplementation by the general public should be discouraged; however, our study also indicates that further research on people over 65 years is warranted [9].

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