**Letter to the Editor**

**The Effect of Vitamin E on Mortality Is Not Uniform across the Population**

Dear Editor:

Jiang et al. analyzed the effect of vitamin E combined with other agents on all-cause mortality (1). They calculated that all-cause relative mortality was 8% lower (RR = 0.92, 95% CI, 0.86 to 0.98, *p* = 0.01) for participants administered low doses of vitamin E (<400 IU/d) combined with diverse other agents. Unfortunately, Jiang et al. ignored the strong evidence that the effects of vitamin E are not uniform across the population. Therefore such a single uniform effect estimate is not realistic.

An early analysis of the ATBC Study (2) found that the effect of vitamin E (50 IU/d) on pneumonia incidence was significantly modified by three different measures of cigarette smoking exposure (3). Another analysis focusing on common cold incidence found significant modification of vitamin E effect by age, smoking and residential neighbourhood (4). The modifying factors on respiratory infections cannot be directly extrapolated to mortality, yet those findings led to an investigation on whether vitamin E effects on mortality might also be heterogeneous in the ATBC Study. During the 5- to 8-year intervention period of the ATBC Study, overall mortality was 2% higher (95% CI, 0.92 to 1.05) in the vitamin E participants than in those taking a placebo (2). However, if the effect of vitamin E is heterogeneous, then the +2% overall estimate might not be valid for a substantial proportion of the ATBC Study participants.

In our analysis of all-cause mortality during the intervention period of the ATBC Study, we found that the combination of age and dietary vitamin C intake modified the effect of vitamin E supplementation to the extent that the heterogeneity over 6 subgroups was significant (χ² [5 df] = 22.2, *p* = 0.0005) (5). In 11,448 ATBC Study participants aged 50–62 y at the baseline who had dietary vitamin C intake above the median, vitamin E increased all-cause mortality by 19% (95% CI, +5% to +35%). In contrast, in 872 ATBC participants aged 66–69 y who had vitamin C intake above the median, vitamin E reduced mortality by 41% (95% CI, –56% to –21%). Vitamin E had no influence on mortality among those who had dietary vitamin C intake less than the median. The modifying effect of vitamin C was not explained by other substances in fruit and vegetables (5). The interaction between vitamins C and E is well documented (6, 7), and may explain the role of vitamin C as a modifying factor for some vitamin E effects.

Furthermore, in the younger ATBC Study participants (50–62 y at the baseline) who had vitamin C intake above average, vitamin E started to increase mortality only after a lag period of 3.3 y. There was no effect on mortality during the first 3.3 y of supplementation (95% CI, –18% to +19%), but thereafter mortality increased in the vitamin E participants by 38% (95% CI, +17% to +63%) (5). The effect modification by supplementation time is not easily explained by chance since the addition of a second vitamin E effect to start at 3.3 y improved the regression model significantly (χ² [1 df] = 7.1, *p* = 0.007). Thus, in addition to age and dietary vitamin C intake, the duration of vitamin E supplementation also modified the effect in this subgroup. The lag period may be explained by the fat solubility of vitamin E, since the body stores are changed slowly with changes in intake levels (8, 9).

Finally, the decrease in mortality in participants aged 66 and over by vitamin E implies that the survival time might also be influenced. A subsequent analysis found that among ATBC participants with dietary vitamin C intakes above the median who smoked less than a pack of cigarettes per day, vitamin E extended lifespan by 2 y at the upper limit of the follow-up age span (10).

These ATBC Study subgroup findings mean that there is no uniform vitamin E effect such as an 8% decline in mortality when vitamin E is combined with diverse other vitamins and minerals. It is probable that the effects of vitamin E are modified by, for example, vitamin C as found in our study, but the effects seem to depend on the characteristics of population groups so that only the oldest people benefited (5, 10). Jiang et al. (1) did not give any justification for dismissing the strong evidence of heterogeneity in the effects of low dose vitamin E on mortality (5, 10).

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**REFERENCES**


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