Vitamin supplements and mortality in older people

Dear Sir:

Macpherson et al (1) carried out a meta-analysis of multivitamin and multimineral (MVMM) tablet trials and found no effect of MVMMs on average mortality. However, their study may suffer from ecological fallacy. Ecological fallacy means that study-level (group-level) analysis can lead to different conclusions than do corresponding individual-level analyses (2). For this reason, examination of individual-level data is recommended, whenever feasible, to avoid the potential for the ecological fallacy introduced by study-level analyses (2).

Macpherson et al (1) calculated that the average age of the participants in the studies was 62 y. However, ages ranged from 17 to 86 y in the included trials (1). It is probable that the effects of all vitamins and minerals are not identical at the lower and upper ends of such a wide age range. Therefore, pooling diverse trials with young and old people to a single average MVMM effect may camouflage effects of some individual vitamins or minerals, for example, on the oldest people. In the case of vitamin E there is strong empirical evidence of effect modification by age.

In an individual-level analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study data, we found that among participants aged 50–62 y at baseline with a dietary vitamin C intake above the median, vitamin E increased mortality by 19% (95% CI: 5%, 35%; based on 1021 deaths). However, among participants aged 66–69 y at baseline with a dietary vitamin C intake above the median, vitamin E decreased mortality by 41% (95% CI: 21%, 56%; based on 195 deaths) (3).

Furthermore, because the follow-up time in the ATBC Study was up to 8 y, the participants became substantially older during the trial so that the baseline age was not a proper way to characterize them over the entire follow-up period. Therefore, the modification of vitamin E effects was also analyzed by using the follow-up age as the time variable (4). Among 10,837 ATBC Study participants who contributed follow-up time past the age of 65 y, the survival curves of the vitamin E and no–vitamin E participants significantly diverged at 71 y. Vitamin E extended life span by ~0.5 y at the upper limit of the follow-up age span (4).

Macpherson et al (1) write that in a meta-regression the estimate of the effect of MVMMs was not associated with the duration of supplementation. In the ATBC Study, the harm from vitamin E in the young participants was restricted to the supplementation period after 3.3 y, indicating that there can be a lag period of several years before the effects of some vitamins appear (3). Macpherson et al used the study-level average durations, which provide a poor basis for analyzing supplementation time–dependent effect modifications. Proper analysis of time-dependent effects requires individual-level data.

It is possible that some vitamins and minerals are beneficial for specific subpopulations. For example, age, sex, smoking, diet, and exercise might modify the effects of some vitamins and minerals, so that some restricted population groups might benefit (and some might be harmed). Such subgroups can be explored by analyzing individual-level data, whereas pooling study-level averages provides no information on relevant narrow subpopulations.

The meta-analysis by Macpherson et al (1) is important in discouraging ordinary middle-aged people from taking MVMMs. Nevertheless, their study should not be interpreted as evidence that none of the vitamins and minerals included in the MVMM tablets have effects on males and females in the age range of 17–86 y. It is possible that some vitamins, such as vitamin E, are useful for restricted groups of older people. Individual-level data analyses are needed for exploring such a possibility.

The author did not declare any conflicts of interest.

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doi: 10.3945/ajcn.113.064204.

Reply to H Hemilä

Dear Sir:

We thank Hemilä for his interest in our article entitled "Multivitamin-multimineral supplementation and mortality: a meta-analysis of randomized controlled trials" (1). Our primary finding was that, across a pooled sample of 91,074 participants, multivitamin-multimineral

(MVMM) supplementation had no significant effect on the risk of all-cause mortality, mortality due to cancer, or mortality due to cardiovascular disease.

Despite our overall finding, Hemilä asserts that some vitamins and minerals may be beneficial for specific subpopulations. We concur with his suggestion that variables such as age, sex, and lifestyle factors might modify the effects of some vitamins, such that differential effects may emerge in different subpopulations. However, as pointed out by Hemilä, we were unable to perform subanalyses to examine the modifying effect of these different variables given that only trial-level data were available.

If individual-level data were accessible we could have performed any number of subanalyses. A limitation of this approach is that each subanalysis involves an additional statistical comparison and thus a greater risk of a type I error. Furthermore, subgroup analysis based on post hoc examination of data can lead to erroneous conclusions (2). The findings discussed by Hemilä, relating to vitamin E mortality risk across different age groups, still require replication for this reason. To avoid these issues, we used a limited number of prespecified analyses to determine the overall effects of MVMM supplementation in the general population, rather than in specific subpopulations.

Our results were strengthened by the large number of trials included in our analyses, generating a large pooled sample size. Although there are several advantages to undertaking an individual-level data meta-analysis, such an analysis is not always feasible. For example, we excluded 7 relevant trials from our analysis simply because trial-level data were unobtainable. Given the difficulty in obtaining raw data from chief investigators (especially when many of the trials included in our analysis were more than a decade old), undertaking a patient-level meta-analysis would have further diminished the number of trials included in our analysis.

Hemilä states that our meta-analysis is ''important in discouraging ordinary middle-aged people from taking MVMMs.'' We are not sure how this conclusion was derived from our work given that our meta-analysis did not specifically focus on middle-aged adults. Moreover, whereas we found no effect of MVMMs on mortality across adults of all ages, this does not rule out other possible benefits to health or well-being.

Before our investigation, information on the association of MVMM use and mortality had frequently been obtained from observational studies (3). Our meta-analysis showed that, across randomized controlled trials, MVMM supplementation had no effect on mortality (1). Although we acknowledge that vitamins may have different effects in different subpopulations, it was first necessary to investigate the overall effects of MVMM supplementation in the general population. Identifying a harmful effect of MVMM use across all adults would have shown greater implications than identifying a harmful effect in one of many narrow subgroups. As discussed in our meta-analysis, we call for further research into the effects of MVMM use on all aspects of human health (1). This includes examination of MVMM use in specific subpopulations.

MPP is funded by a Menzies Foundation Scholarship in Allied Health Sciences. AP receives funding from Swisse Wellness Pty Ltd for ongoing research projects. HM holds a Postdoctoral Fellowship, which is funded by Swisse Wellness Pty Ltd. There were no other potential conflicts of interest.

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doi: 10.3945/ajcn.113.064709.

Limitations to the use of plasma osmolality as a hydration biomarker

Dear Sir:

In some laboratories, plasma osmolality (P_{osm}) is used as the gold standard for detecting dehydration (1), without consideration of its limitations; however, published data dispute this technique (2, 3), which prompts us to write in response to the recent article by Cheuvront et al (4) with regard to quantitative dehydration assessment. This article correctly states that P_{osm} is the key regulated variable in fluid balance, which means that P_{osm} is constantly regulated toward a central set point as the kidneys modify urine concentration and water excretion in response to diet and daily activities. We believe that this controlled regulation limits the efficacy of P_{osm} as an index of hydration change in many experimental designs. This article (4) also states that the ''criticisms for adopting P_{osm} as a gold standard for dehydration assessment are minimal'' (p 460). We disagree and write to describe several limitations to the use of P_{osm} as a gold standard for dehydration.

First, individuals who lose a large amount of body water (reported as % body mass loss relative to a beginning euhydrated state) may exhibit a decreased P_{osm}, contrary to anticipated hemoconcentration. For example, a summary of 2 studies (5) reported that the P_{osm} of 6 individuals (out of 39) decreased after they lost 3–8% of body mass. In a different study, men and women who consumed a 500-mL bolus of fluid acutely exhibited an increased P_{osm}, contrary to anticipated hemodilution (1); that is, after 90 min of rest, 4 of 30 P_{osm} measurements increased. These values show that P_{osm} may not reflect widely accepted physiologic principles, and that variance of P_{osm} measurements may be large.

Second, evidence suggests that P_{osm} changes are time- and protocol-specific. Unpublished observations (CX Muñoz, EC Johnson, JK DeMartini, et al, 2012) show that dehydration equivalent to 2% of body mass resulted in P_{osm} changes that were twice as large during mild cycling exercise (2.3 h; ΔP_{osm} of 9 mOsm/kg) compared with a passive exposure (5.0 h; ΔP_{osm} of 4 mOsm/kg); participants consumed no water during either trial in