

Don't Believe Everything You Read: Misleading Editorial on Supplement Efficacy Presents Biased Viewpoint

Three papers on vitamin and mineral supplementation published in the Dec. 16th issue of *Annals of Internal Medicine* were accompanied by an editorial entitled “Enough is Enough: Stop Wasting Money on Vitamin and Mineral Supplements¹”. According to the editorial, “supplementing the diet of well-nourished adults with (most) mineral or vitamin supplements has no clear benefit and might even be harmful”.

The editorial seems to make the inaccurate assumption that everyone is consuming a healthy diet and obtaining everything needed from food alone. Yet government conducted surveys consistently report that many sub-groups of the population do not meet recommended intakes for a wide variety of nutrients. No one suggests that dietary supplements are a panacea for preventing or treating chronic disease. The purpose of supplementation is to help close these nutrient gaps, as well as to help people achieve intake levels of specific nutrients that correspond to risk reduction for various conditions. For example, a substantial portion of Americans typically consume less than 1-2 mg of lutein and zeaxanthin daily², whereas a daily intake of 6-10 mg has been associated with Age-related Macular Degeneration (AMD) risk reduction.

The editorial also reflects a one-sided approach that attempts to dismiss even the well-supported benefits of vitamin and mineral supplements. In the realm of ocular health for example, ample evidence supports a role for various antioxidant nutrients in lowering the risk of AMD progression^{3,4}, and supplemental B-vitamins have demonstrated a clear beneficial effect for AMD in a large randomized clinical trial⁵.

One of the papers published in the same issue of *Annals* reports that long-term daily multivitamin and mineral supplements had no favorable affect on cognitive decline in the Physicians' Health Study II (PHS II)⁶, though the authors did state that the rate of cognitive decline among the participants was smaller than expected, making a significant difference between the two groups studied more difficult to show. But despite this finding, it's important to note that salutary effects *have* been reported for other primary and secondary endpoints of the multivitamin component of the PHS II: Multivitamins reduced the risk of cataract by a significant 9%, the risk of nuclear cataract by a significant 13%, total cancer occurrence by a significant 8% (12% when prostate cancer was removed from the analysis), and a non-significant but consistent 12% reduction in cancer mortality^{7,8}. (No harm or benefit was seen for multivitamins in the cardiovascular disease or visually significant AMD portions of the PHS II).

While an 8% decrease in cancer risk may seem modest, this risk reduction would translate to about 130,000 cancers prevented every year. Similarly, the risk reduction noted for cataract would also have large public health impact because cataract is so common. Yet the editorial took the stance that “...supplements are ineffective for preventing mortality or morbidity due to major chronic diseases”.

Additionally, the 12 year follow-up of the calcium and vitamin D supplementation trial in the Women's Health Initiative recently reports a 29% reduction in the risk for hip fracture in supplement-adherent participants, a 13% reduction in vertebral fracture in intention-to-treat analyses, a 13% reduction in in situ breast cancer, and a 9% reduction in all cancers among women with low vitamin D intake at the study's start⁹. All of these findings were statistically significant and of public health import.

With regard to safety, all three of the studies published in this issue of the *Annals* commented on the safety of the multivitamins studied. It's compelling to note that none of the studies revealed any safety concerns.

According to the editorial, “beta-carotene, vitamin E, and possibly high doses of vitamin A supplements are harmful”. In contrast, a US Preventive Services Task Force report (based on a study which also appeared in the same issue of *Annals*¹⁰), found sufficient evidence that vitamin E has little or *no* significant harm, and reaffirms the general safety of multivitamins. As for beta-carotene, the adverse effects of high-doses are well known, isolated to high doses in smokers, and are not of concern to the majority of consumers taking a multivitamin.

The vast majority of large-scale studies evaluating vitamin E have not associated this nutrient with increased risk of prostate cancer or other harm. Some concerns about high dose vitamin E stem from 2005 and 2007 meta-analyses which reported an increased risk of mortality with supplementation^{11,12}. A more recent re-evaluation of the 2007 meta-analysis, however, questions its findings and concludes that any potential risk of antioxidant supplementation should be placed in the context of a benefit/risk ratio¹³.

Aside from the two meta-analyses, an intervention study that has fueled some concern is the Selenium and Vitamin E Cancer Prevention Trial (SELECT). The SELECT study observed an increase in risk of prostate cancer for men taking 400 IU daily (though no increased risk was seen in men who received *both* vitamin E and selenium)¹⁴.

The results of SELECT should be viewed in the context of other clinical trial results. According to the National Eye Institute, the independent researchers who monitored the AREDS and AREDS2 studies found no concerns about increased prostate cancer in participants receiving 400 IU of vitamin E (along with other nutrients). The PHS II also tested 400 IU of vitamin E every other day and found no effect on the incident of prostate cancer¹⁵. And notably, no safety concerns were detected in a newly published study reporting that 1200 IU of vitamin E daily slowed the functional decline of those with mild to moderate Alzheimer’s¹⁶.

In summary, the editorial appearing in the *Annals of Internal Medicine* did not recognize the scientific evidence demonstrating the value of meeting nutrient recommendations and the role of supplements in supporting good health. At the same time, potential safety concerns – not supported by the actual research published in the same issue of the *Annals* – were inflated in the editorial. Multivitamins, which are used by a majority of Americans, represent a generally safe and affordable way to fill in the nutrient gaps of our less-than-perfect diets, and to achieve optimal nutrient intakes where scientifically warranted.

References

1. Guallar E, et al. Enough is enough: Stop wasting money on vitamin and mineral supplements. *Ann Intern Med* 159:850-51, 2013.
2. Johnson EJ, et al. Intake of lutein and zeaxanthin differ with age, sex and ethnicity. *J Am Diet Assoc* 110:1357-62, 2010.
3. The Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8 *Arch Ophthalmol* 119:1417-36, 2001.
4. The Age-Related Eye Disease Study 2 (AREDS2) Research Group, Chew EY et al. Secondary Analyses of the Effects of Lutein/Zeaxanthin on Age-Related Macular Degeneration Progression: AREDS2 Report No. 3. *JAMA Ophthalmol*. Dec. 5, 2013 [Epub ahead of print].
5. Christen WG, et al. Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women’s Antioxidant and Folic Acid Cardiovascular Study. *Arch Intern Med*169:335-41, 2009.
6. Grodstein F, et al. Long-term multivitamin supplementation and cognitive function in men: The Physician’s Health Study II. *Ann Intern Med*159:806-14, 2013.
7. Christen WG, et al. A multivitamin supplement and cataract and age-related macular degeneration in a randomized trial of male physicians. *Ophthalmol* Nov 20, 2013. Epub ahead of print.
8. Gaziano JM, et al. Multivitamins in the prevention of cancer in men—The Physicians’ Health Study II randomized controlled trial. *JAMA* 308:1871-80, 2012.
9. Cauley JA, Chlebowski RT, Wactawski-Wende J, et al. Calcium plus vitamin D supplementation and health outcomes 5 years after active intervention ended: the Women’s Health Initiative. *J Womens Health (Larchmt)*. 22:915-29, 2013.
10. Fortmann SP, et al. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: An updated systematic evidence review for the U.S. Preventive Service Task Force. *Ann Intern Med* 159:824-34, 2013.

11. Miller ER 3rd et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 142:37-46, 2005.
12. Bjelakovic G, et al. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: Systematic review and meta-analysis. *JAMA* 297:842–857, 2007.
13. Biesalski HK et al. Reexamination of a meta-analysis of the effect of antioxidant supplementation on mortality and health in randomized trials. *Nutrients* 2:929-49, 2010.
14. Klein EA, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 306:1549-56, 2011.
15. Sesso HD, et al. Vitamins E and C in the prevention of cardiovascular disease in men: The Physicians' Health Study II Randomized Trial. *JAMA* 300:2123-33, 2008.
16. Effect of vitamin E and Memantine on functional decline in Alzheimer disease: The TEAM-AD VA Cooperative Randomized Trial. *JAMA* 311:33-44, 2014.

