



## CRN ANALYSIS

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### **“Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention: Systematic Review and Meta-analysis”**

*Bjelakovic et al., February 28, 2007, Vol. 297, No. 8, JAMA*

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**Background:** A new meta-analysis examining the effect of antioxidant supplements and all-cause mortality will be published Feb. 28, 2007 in the *Journal of the American Medical Association (JAMA)*. The authors of the analysis conclude that “treatment with beta-carotene, vitamin A, and vitamin E may increase mortality.” The Council for Responsible Nutrition (CRN) finds this conclusion unfounded, inappropriate and not relevant to consumers who regularly use antioxidant supplements to maintain health.

- There is a large body of data, including observational studies and randomized clinical trials, which show that supplemental antioxidants provide a number of health benefits (including reduced risk for cardiovascular disease and some cancers, immune support and reduced progression of eye disease). This meta-analysis, which seems to be a predetermined conclusion in search of a method to support it, will inappropriately confuse and alarm consumers who can benefit from supplementing with antioxidants.
- The conclusions from this meta-analysis should not be generalized to a healthy population. The overwhelming majority of the clinical trials included in the meta-analysis focused on “secondary prevention” (i.e., treatment) in patients who already had serious illnesses such as cancer, cardiovascular disease, liver disease, etc., and therefore the results are not applicable to the general healthy population who take antioxidant supplements as part of the lifestyle choices they make to maintain and promote good health.
- This meta-analysis used methods which raise questions as to the validity of the results.
  - Meta-analyses can be useful and valid when the included studies are very similar in design and study population. However, this meta-analysis combined studies that differ vastly from each other in a number of important ways.
  - This meta-analysis included clinical trials that varied widely in terms of dosage, duration, study population and nutrients tested. For example, a study lasting one day with a vitamin A dose of 200,000 IU in elderly nursing home residents was included along with other studies lasting years.
  - Many of the clinical trials included in the analysis tested other nutrients beyond those that were the focus of the article (vitamins A, C, and E; beta-carotene; selenium), including lutein and zinc. Therefore, it is difficult to interpret the findings of the study.
  - The clinical trials, which overwhelmingly focused on secondary prevention, may have statistically skewed the results. Mixing secondary prevention and primary prevention trials and then making conclusions for the entire population is an unsound scientific approach.
  - Overall, the study authors conclude that there was no effect of antioxidant supplements on all-cause mortality. Only after the researchers divided the chosen clinical trials into “high risk bias” and “low risk bias” groups, using their own criteria, did they observe a statistically significant effect on mortality.

- The study's conclusions are in direct conflict with a 2006 report from Johns Hopkins University which concluded "we find no convincing evidence to suggest vitamin E supplement use increases the risk of death per se."<sup>1</sup>
- The study authors acknowledge that their results are in conflict with observational studies that have shown beneficial effects of supplemental antioxidants; these studies (both retrospective and prospective in nature) have examined primary prevention (or risk reduction) in healthy populations, not treatment of sick patients.
- The meaning and relevance of all-cause mortality is unclear, even to the study authors. In a literal sense it means death from any and all causes, including accidents. The study authors acknowledge not knowing what the actual causes of death may have been in the individuals in the trials. This absence of information raises doubt about the validity and relevance of their findings.
- Healthy consumers can feel confident in continuing to take antioxidant supplements for the benefits they provide. Consumers with serious illnesses, such as cancer, heart disease, liver disease, etc., should consult with their physician on anything they put into their body. This meta-analysis does nothing to change those facts.

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<sup>1</sup> Huan HY, Caballero B, Chang S, Alberg A, Semba R, Schneyer C, Wilson RF, Cheng TY, Prokopowicz G, Barnes II GJ, Vassy J, Bass EB. Multivitamin/Mineral Supplements and Prevention of Chronic Disease. Evidence Report/Technology Assessment No. 139 (Prepared by The Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018). AHRQ Publication No. 06-E012. Rockville, MD: Agency for Healthcare Research and Quality. May 2006. Pgs. 62-63.