# **JAMA Clinical Evidence Synopsis**

# Antioxidant Supplements to Prevent Mortality

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**CLINICAL QUESTION** Are antioxidant supplements associated with higher or lower all-cause mortality?

**BOTTOM LINE** Antioxidant supplements are not associated with lower all-cause mortality. Beta carotene, vitamin E, and higher doses of vitamin A may be associated with higher all-cause mortality.

Excessive oxidative stress may be implicated in a variety of diseases. By reducing oxidative stress, antioxidant supplements may prevent diseases and prolong survival. This updated Cochrane Collaboration systematic review includes 78 randomized clinical trials that have assessed antioxidant supplements for prevention of all-cause mortality. The randomized adult participants came from the general population (primary prevention) or were patients with stable, chronic diseases (secondary prevention).<sup>2</sup>

#### Summary of Findings

Seventy-eight randomized clinical trials (296 707 participants; mean age, 63 years; 46% women) fulfilled our review inclusion criteria. Twenty-six of the trials assessed 215 900 healthy participants. The remaining 52 trials assessed 80 807 participants with stable, chronic diseases (eg, coronary disease, diabetes mellitus, Alzheimer disease, and age-related eye disease). All antioxidants were administered orally, either alone or in combination with vitamins, minerals, or other interventions. The mean duration of supplementation was 3 years. Fifty-six trials covering 82% of the participants had a low risk of bias.

Overall, the antioxidant supplements were associated with neither higher nor lower mortality in a random-effects model meta-analysis (relative risk [RR], 1.02 [95% CI, 0.98-1.05]), but a fixed-effect model meta-analysis showed statistically significant higher mortality (RR, 1.03 [95% CI, 1.01-1.05]). Heterogeneity between studies was low, with an  $I^2$  of 12%. The risk of bias and the type of antioxidant supplement were the only significant predictors of intertrial heterogeneity in a meta-regression analysis. The meta-regression analysis did not find a significant difference in the association of antioxidants with mortality among people without any chronic disease vs among those with chronic disease.

In the 56 trials with a low risk of bias, the result obtained with both fixed-effect model and random-effects model metaanalyses showed that the antioxidant supplements were associated with higher mortality (18 833 deceased per 146 320 participants [12.9%] vs 10 320 deceased per 97 736 participants [10.6%]; RR, 1.04 [95% CI, 1.01-1.07]) (Figure).<sup>2</sup> Trial sequential analysis, designed to control for sparse data and multiplicity in cumulative meta-analysis,<sup>3</sup> confirmed this association.<sup>2</sup> In these analyses, beta carotene (RR, 1.05 [95% CI, 1.01-1.09]) and vitamin E (RR, 1.03 [95% CI, 1.00- 1.05]) were associated with significantly higher mortality, whereas vitamin A (RR, 1.07 [95% CI, 0.97-1.18]), vitamin C (RR, 1.02 [95% CI, 0.98-1.07]), and selenium (RR, 0.97 [95% CI, 0.91-1.03]) were not associated with higher or lower mortality (Figure). However, in a univariate metaregression analysis, higher doses of vitamin A were associated with higher all-cause mortality (RR, 1.0006 [95% CI, 1.0002-1.001], P = .002).

#### Discussion

When trials with a low risk of bias were analyzed separately from trials with a high risk of bias, the antioxidant supplements were associated with statistically significantly higher all-cause mortality. The higher risk of all-cause mortality was observed for beta carotene and vitamin E, and in some analyses for higher doses of vitamin A. Vitamin C and selenium were associated with neither higher nor lower all-cause mortality.

## Limitations

First, the examined populations varied. The associations between supplements and all-cause mortality were assessed in the general population and in patients with stable, chronic diseases. However, associations of antioxidants with mortality in these 2 populations were not significantly different.<sup>2</sup> Second, the trials were mostly conducted in countries without overt deficiencies of specific antioxidants. Accordingly, we could not assess whether anti-

### **Evidence Profile**

No. of randomized controlled trials: 78

Study years: Published, 1977-2012 No. of participants: 296 707

Men: 54% Women: 46% Race/ethnicity: Unavailable

Age, mean (range): 63 (18-103) years

**Settings:** Primary or secondary prevention trials in healthy participants and participants with stable, chronic diseases

Continents: Europe, North and South America, Asia, and Australia

**Comparison:** Antioxidant supplements (beta carotene, vitamin A, vitamin C, vitamin E, and selenium) vs placebo or no intervention

Primary outcome: All-cause mortality

Figure. Associations of Antioxidant Supplements vs Placebo (Collectively and Individually) on All-Cause Mortality

			Antioxidants		Placebo							
Source	No. of Trials	No. of Participants	Deaths, No.	Participants, No.	Deaths, No.	Participants, No.	Relative Risk (95% CI)		Favo Antioxida		avors lacebo	
Trials with both a low risk and a high risk of bias								_				
Trials assessing all selected antioxidant supplements	78	296707	21484	183749	11479	112958	1.02 (0.98-1.05)			-	-	
Trials assessing all selected antioxidant supplements <sup>a</sup>	78	296707	21484	183749	11479	112958	1.03 (1.01-1.05)			<b>4</b>		
Trials with a low risk of bias												
Trials assessing all selected antioxidant supplements	56	244056	18833	146 320	10320	97736	1.04 (1.01-1.07)			<b>-</b>		
Trials assessing beta carotene	26	173 006	13202	96 003	8556	77003	1.05 (1.01-1.09)			4		
Trials assessing vitamin A	12	41144	3444	24596	2249	16548	1.07 (0.97-1.18)					
Trials assessing vitamin E	46	171244	11689	97 523	7561	73721	1.03 (1.00-1.05)			•		
Trials assessing vitamin C	29	65942	3637	36659	2717	29283	1.02 (0.98-1.07)					
Trials assessing selenium	17	62740	2670	39779	1468	22961	0.97 (0.91-1.03)					
								0.8	0.9 Relative	1.0 Risk (9!	1.1 5% CI)	1.2

Relative risks are from a random-effects model.

oxidant supplements were associated with all-cause mortality in populations with specific nutritional needs.

### Comparison of Findings with Current Guidelines

Our results are consistent with the 2010 Dietary Guidelines for Americans and the National Institutes of Health-sponsored State-of-the-Science conference conclusions that there is no evidence to support the use of multivitamin or mineral supplements. <sup>4,5</sup>

#### Conclusion

Antioxidant supplements are not associated with lower all-cause mortality. Beta carotene, vitamin E, and higher doses of vitamin A may be associated with higher all-cause mortality. Therefore, our re-

view does not support the use of antioxidant supplements as a primary or a secondary preventive measure.

#### Areas in Need of Future Study

Future randomized placebo-controlled clinical trials should try to define levels of malnutrition in otherwise healthy people where antioxidant supplements may offer more benefits than harms. Future randomized placebo-controlled clinical trials should also examine if antioxidant supplements may offer more benefits than harms in secondary prevention as well as in tertiary prevention for specific disease states with defined levels of malnutrition. Such trials need to be conducted with low risks of systematic errors (bias) as well as with low risks of random errors (play of chance).

## ARTICLE INFORMATION

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**Submissions:** We encourage authors to submit papers for consideration as a JAMA Clinical Evidence Synopsis. Please contact Dr McDermott at mdm608@northwestern.edu.

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<sup>&</sup>lt;sup>a</sup>These data are from a fixed-effects model.