

# Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention

## Systematic Review and Meta-analysis

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**Context** Antioxidant supplements are used for prevention of several diseases.

**Objective** To assess the effect of antioxidant supplements on mortality in randomized primary and secondary prevention trials.

**Data Sources and Trial Selection** We searched electronic databases and bibliographies published by October 2005. All randomized trials involving adults comparing beta carotene, vitamin A, vitamin C (ascorbic acid), vitamin E, and selenium either singly or combined vs placebo or vs no intervention were included in our analysis. Randomization, blinding, and follow-up were considered markers of bias in the included trials. The effect of antioxidant supplements on all-cause mortality was analyzed with random-effects meta-analyses and reported as relative risk (RR) with 95% confidence intervals (CIs). Meta-regression was used to assess the effect of covariates across the trials.

**Data Extraction** We included 68 randomized trials with 232 606 participants (385 publications).

**Data Synthesis** When all low- and high-bias risk trials of antioxidant supplements were pooled together there was no significant effect on mortality (RR, 1.02; 95% CI, 0.98-1.06). Multivariate meta-regression analyses showed that low-bias risk trials (RR, 1.16; 95% CI, 1.05-1.29) and selenium (RR, 0.998; 95% CI, 0.997-0.9995) were significantly associated with mortality. In 47 low-bias trials with 180 938 participants, the antioxidant supplements significantly increased mortality (RR, 1.05; 95% CI, 1.02-1.08). In low-bias risk trials, after exclusion of selenium trials, beta carotene (RR, 1.07; 95% CI, 1.02-1.11), vitamin A (RR, 1.16; 95% CI, 1.10-1.24), and vitamin E (RR, 1.04; 95% CI, 1.01-1.07), singly or combined, significantly increased mortality. Vitamin C and selenium had no significant effect on mortality.

**Conclusions** Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study.

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