Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: an updated systematic evidence review for the US Preventive Services Task Force
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CRD summary
This review concluded that evidence for an effect of nutritional doses on cardiovascular disease, cancer, or mortality in healthy individuals without nutritional deficiencies was limited. In most cases there were insufficient data to draw any conclusion but for vitamin E and beta-carotene a lack of benefit was consistent across several trials. This conclusion is likely to be reliable.

Authors' objectives
To evaluate the benefit and harms of vitamin and mineral supplements in community-dwelling, nutrient-sufficient adults for the primary prevention of cardiovascular disease and cancer.

Searching
Results from four previous systematic reviews on the same topic (see Other Publications of Related Interest) were supplemented by update searches of MEDLINE, EMBASE and The Cochrane Library (including CENTRAL and DARE databases) to identify studies published between January 2005 and January 2013. Further studies were sought from bibliographies of relevant reviews, websites of government agencies and professional bodies, and by contacting experts in the field.

Study selection
Fair- and good-quality randomised controlled trials (RCTs) that assessed the effectiveness or safety of supplements in the primary prevention of cardiovascular disease, cancer or all-cause mortality in community-dwelling nutrient-sufficient adults who had no chronic disease were eligible for inclusion. Secondary prevention RCTs were included if they hypothesized effects on outcomes relevant to the review but not present at baseline in the study. Eligible studies had to be conducted in countries with a Human Development Index of “very high” and used supplement doses below the upper tolerable limit set by the U.S. Food and Nutrition Board. Fair- and good-quality observational studies were also included to assess potential harms.

Included studies that evaluated multivitamin, individual or paired supplements were conducted in USA, Canada, New Zealand, Australia and Europe. Individual and paired supplements were beta-carotene, vitamin E, selenium, vitamin A, vitamin C, folic acid, vitamin D, calcium and vitamin D in combination with calcium. Where reported, mean age ranged from 22 to 77 years; mean age was older than 50 years in most studies. Three per cent to 100% of participants were smokers and most had history of prior supplement use. Most trials compared vitamin supplementation to placebo; some had non-use of supplements as a control.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Two reviewers independently assessed studies as being good, fair or poor quality according to U.S. Preventive Services Task Force criteria. Observational studies were assessed using National Institute for Health and Clinical Excellence criteria. Any disagreements were resolved through discussion.

Data extraction
One reviewer extracted study characteristics and outcomes and a second reviewer checked these data for accuracy. Unadjusted relative risks and 95% confidence intervals were calculated for each outcome.

Methods of synthesis
Where appropriate, pooled relative risks and related 95% confidence intervals were calculated using the fixed-effect Mantel-Haenszel method. Results were stratified by type of supplement.
Results of the review
The review included 103 articles reporting the results of 26 studies. Study sample sizes ranged from 128 to 79,752 participants. Follow-up ranged from six months to 16 years (most studies were less than 10 years). There were some discrepancies in the number of included RCTs and cohort studies but the authors stated in the text that multivitamin supplementation was evaluated in four RCTs and one cohort study. Individual or paired supplements were evaluated in eighteen RCTs and five cohort studies.

Pooling of three RCTs suggested no significant overall reduction in risk of all cause mortality in people taking multivitamins (RR 0.95, 95% CI 0.89 to 1.01). Two large RCTs (27,658 participants) reported lower cancer incidence in men taking a multivitamin for more than 10 years, but not for women in the one RCT with a mixed population (overall RR 0.94, 95% CI 0.89 to 1.00). Multivitamin supplementation had no effect on cardiovascular disease incidence (RR 1.02, 95% CI 0.94 to 1.10; two RCTs).

The 24 studies (324,653 participants) of single and paired nutrients were clinically heterogeneous and showed no consistent evidence of either benefit or harm on any of the measured outcomes. Neither vitamin E nor beta-carotene prevented cardiovascular disease or cancer. Beta-carotene appeared to increase lung cancer risk in high risk subgroups (smokers and asbestos workers).

Further results for specific outcomes and supplements were reported in the article.

Authors' conclusions
Evidence for an effect of nutritional doses on cardiovascular disease, cancer or mortality in healthy individuals without known nutritional deficiencies was limited. In most cases there were insufficient data to draw any conclusion, although for vitamin E and beta-carotene a lack of benefit was consistent across several trials.

CRD commentary
This review used appropriate methods to identify and synthesise relevant evidence for the effects of vitamin and mineral supplements for the primary prevention of cardiovascular disease and cancer and made efforts minimise the potential for errors and bias throughout. Readers should be aware that the duration of follow-up in the included studies was generally shorter than 10 years and effects on cardiovascular disease and cancer may take longer than this to emerge.

The authors discuss the limitations of the available evidence in detail and their carefully constructed conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors added that these findings did not apply to populations deficient of nutrients or high risk individuals.

Research: The authors made extensive recommendations for future research: future studies investigating calcium and vitamin D supplementation should be conducted separately and include the full range of hypothesised benefits, including fracture prevention; and multivitamin trials should be properly powered, recruit from a general and representative population, use a multivitamin similar to popular commercially available preparations, investigate important subgroups and have at least 10 years' follow-up. The authors also stated that the available evidence was sufficient to discourage further studies of beta-carotene or vitamins A, C, and E in general populations that are not deficient in these nutrients.

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