Do dietary supplements have beneficial health effects in industrialized nations: what is the evidence?

Marik PE, Flemmer M

CRD summary
The review concluded that, except for vitamin D in older populations and omega-3 fatty acids for cardiovascular disease, there was no supporting evidence for dietary supplement use in westernised populations; sometimes it may be harmful. The reliability of the authors' conclusions is unclear given the absence of statistical data, and the unclear quality and large differences between the included trials.

Authors' objectives
To evaluate the effects of dietary supplements on safety and efficacy clinical outcomes in adults in industrialised countries.

Searching
MEDLINE was searched from 1966 to December 2010 for articles published in any language. EMBASE and the Cochrane Database of Systematic Reviews were also searched. MeSH headings and search terms were reported. References of retrieved articles and relevant reviews were handsearched. A search for grey literature including studies published only in abstract form was also carried out.

Study selection
Randomised controlled trials (RCTs) that evaluated dietary supplements in adults in industrialised countries were eligible for inclusion. Trials of paediatric or pregnant participants or participants that were undernourished or with nutritional diseases were excluded. Trials appear to have been excluded if they did not have a placebo arm. Trials with less than 200 participants and/or less than one year old were excluded.

The dietary supplement evaluated (alone or in combination) in included RCTs were: beta-carotene; vitamins A, B6, B12, C, D and E; folic acid; calcium; selenium; omega-3 fatty acids; Ginkgo biloba; glucosamine; saw palmetto; milk thistle; and zinc. Dosages varied between trials. Many trials included only participants with specific health conditions or risks, such as cardiovascular disease, cancers, or dementia. Many trials focused solely on older populations (lowest age ranged from 50 to 70 years). Some trials included only people who smoked. A variety of outcomes were reported, such as fractures, falls, death, pain, disability, progression or onset of specific illnesses, or health conditions. Included trials were conducted in the USA, Australia, Canada, UK, France, Italy, the Netherlands, Finland, Norway, New Zealand, Japan and Spain.

Two authors carried out the MEDLINE search independently. It was unclear how the remainder of the study selection was carried out.

Assessment of study quality
It was unclear whether the authors assessed study quality.

Data extraction
The main findings from each trial were extracted. Trials were categorised as showing no benefit (no significant difference between groups), showing benefit (significant differences in favour of dietary supplement), or harmful (significant difference against dietary supplements).

Two authors independently performed the data extraction.

Methods of synthesis
The outcome for each trial was presented in tables as no benefit, benefit or harm. The overall number of trials for each category (no benefit, benefit or harm) was presented. Trials that showed significant differences between groups were summarised in a narrative synthesis.
Results of the review
Sixty-three RCTs were included for review (428,357 participants). Trial duration ranged from one year to 12 years (mean 4.7 years).

Overall, 45 trials showed no benefit, four trials showed harm and 12 trials showed a benefit. Two trial had mixed results.

Six trials showed a benefit of vitamin D on falls, fractures or cancer. Five trials showed no benefit of vitamin D on falls, fractures, death, cardiovascular event or cancer. Two trials of high dose once yearly vitamin D found that vitamin D was harmful with regards to fractures and falls.

Three trials showed a benefit of omega-3 fatty acids on cardiovascular events.

One trial (2,002 participants) found a benefit of vitamin E on cardiovascular events. However, nine other trials found no benefit of vitamin E on cardiovascular events.

One trial (818 participants) found a benefit of folic acid on cognitive function in participants aged over 50 years, with raised homocysteine levels. However, two trials (685 participants) found that folic acid had no effect on cognitive function in participants with Alzheimer's or in people over 65 years with raised homocysteine levels.

One trial found a benefit of Ginkgo biloba on cognitive function in participants with Alzheimer's (309 participants), but a larger trial (3,069 participants aged over 75 years) found no benefit on cognitive function.

Two trials showed an increased risk of cancer and cancer deaths: one trial (18,314 participants) evaluated vitamin A and beta-carotene use in participants who smoked or were exposed to asbestos; and one trial (6,837 participants) evaluated folic acid and vitamins B6 and B12 in participants with coronary artery disease.

One trial found an increased risk of type II diabetes, but a decreased risk of cancer and death, in patients with prior skin cancer who were given selenium. However, the benefit of selenium on cancer was not found in another trial in 35,533 men (aged 50 or older) given selenium and vitamin E.

One trial found an increased risk of acute myocardial infarction, but a reduced risk of fractures, with calcium supplementation in people younger than 80 years with recent adenoma.

Authors’ conclusions
With the possible exception of vitamin D in older populations and omega-3 fatty acids for cardiovascular disease, there was no evidence to support the use of dietary supplements in westernised populations. In some instances, dietary supplementation may be harmful.

CRD commentary
The review addressed a clear question. Inclusion criteria for intervention, populations and outcomes were broad, resulting in large differences between trials. No language restrictions were applied, which minimised the risk of language bias. A search was made for unpublished material, so attempts were made to minimise publication bias. It was unclear whether appropriate steps were taken in the study selection processes to minimise the risk of reviewer error and bias.

The authors stated that there were limited or no high quality data available for some supplements. However, they did not report on any quality assessment process, so it was difficult to ascertain the quality of included trials. In light of the large differences between trials, the authors decision to combine the trials in a narrative synthesis was appropriate. However, no statistical data were reported, which made it difficult to ascertain the clinical and statistical significance of the findings. The large differences between trials in populations, interventions and outcomes, made it difficult to draw overarching conclusions about the efficacy and safety of dietary supplements in westernised adult populations. It appeared that supplements may have been compared with placebo, but the comparator conditions were not explicitly stated; this made it difficult to conclude what each supplement was being compared against.

Given the absence of statistical data, the unclear quality of the included trials and large differences between trials, the
reliability of the authors' conclusions is unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that dietary supplements should be held to the same evidence and regulatory standards as traditional medicines.

**Research:** The authors stated that further long-term RCTs were needed to investigate the efficacy of dietary supplements on health outcomes. Where long-term RCTs were not economically viable, long-term prospective cohort and case-control studies should be conducted on vitamin use for chronic health problems.

**Funding**

Not stated.

**Bibliographic details**

Marik PE, Flemmer M. Do dietary supplements have beneficial health effects in industrialized nations: what is the evidence? Journal of Parenteral and Enteral Nutrition 2012; 36(2): 159-168

**PubMedID**

22275325

**DOI**

10.1177/0148607111416485

**Original Paper URL**

http://pen.sagepub.com/content/36/2/159.abstract

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Developed Countries; Dietary Supplements /adverse effects /utilization; Fatty Acids, Omega-3; Fractures, Bone; Ginkgo biloba; Humans; Neoplasms; Outcome Assessment (Health Care); United States; Vitamins

**AccessionNumber**

12012013842

**Date bibliographic record published**

26/04/2012

**Date abstract record published**

14/11/2012

**Record Status**

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