

Health effects of vitamin and mineral supplements

Growing numbers of healthy people are taking dietary supplements but there is little evidence that they protect against non-communicable diseases, say **Fang Fang Zhang and colleagues**

Vitamin and mineral supplements are the most commonly used dietary supplements by populations worldwide.¹⁻⁴ The amount of micronutrients they provide ranges from less than recommended intakes to much more, making them important contributors to total intakes. While supplements can be used to correct micronutrient deficiency or maintain an adequate intake, over-the-counter supplements are most often taken by people with no clinical signs or symptoms of deficiency. However, the effect of vitamin and mineral supplements on the risk of non-communicable diseases in “generally healthy” populations is controversial. We examine patterns of supplement use and the evidence on their effects from randomised trials.

Who uses supplements?

Vitamin and mineral supplements have a large worldwide market, but we will focus on their use in North America and Europe, where there is most evidence on patterns of use and health outcomes. The use of vitamin, mineral, and fish oil supplements⁵ is common among adults in North America

(fig 1).⁶ The prevalence of use has increased for some individual nutrients—for example, there was a fourfold increase in use of vitamin D supplements among US adults from 1999 to 2012, excluding intake obtained from multivitamin and mineral.⁷ The use of omega-3 fatty acid supplements also increased sevenfold.⁷

Supplement use is generally less prevalent in other countries than in the US and Canada but varies widely (eg, Denmark 51%, South Korea 34%, Australia 43%, UK 36%, Spain 6%, Greece 2%).²⁻⁴ Different methods for assessing supplement use may contribute to the different prevalence in high income countries. National survey data for supplement use in the general population remain scarce for low and middle income countries.

Supplement use varies considerably among population subgroups within North America and Europe. In the US, >70% of adults aged ≥65 years use supplements⁸ compared with a third of children and adolescents.⁹ More women than men use supplements.⁶ Supplement use correlates positively with educational and socioeconomic status.¹⁰ It also clusters with healthy lifestyle factors such as not being a smoker or heavy drinker, not being overweight or obese, and being physically active.⁶ Importantly, people who use supplements tend to have a better overall diet quality than those who don't use them and their nutrient intake from foods mostly meets recommended intake levels.^{11 12}

Are supplements needed?

Use of supplements contributes substantially to total vitamin and mineral intakes at the population level.¹³ Intake of vitamin B₆, thiamin, and riboflavin among US adults is at least five times higher from supplements than from foods, and intakes are 15 to 20 times higher for supplements for vitamins B₁₂ and E.⁶ Consequently, supplement use considerably reduces the proportion of the general population with inadequate nutrient intake (box 1).

This is especially true for vitamins and minerals identified as “shortfall” nutrients

such as calcium and vitamin D (fig 2).¹⁴ Despite the high use of supplements, inadequate intakes of micronutrients are still common in high income countries, where dietary patterns are typically energy rich but nutrient poor.

In low and middle income countries, where specific micronutrient deficiencies are prevalent (eg, of iodine, iron, zinc, and vitamin A), supplementation is recommended when food based approaches such as dietary modification, fortification, or food provision are unable to achieve inadequate intake.¹⁵ In the US and other countries, food fortification and enrichment such as the addition of iodine to salt, vitamin D to milk, and B₁ and B₃ vitamins to refined flour have contributed to the virtual elimination of their syndromes of deficiency (goitre, rickets, beriberi, and pellagra, respectively).^{16 17}

The widespread use of vitamin and mineral supplements in high income countries seems to contribute to an increase in population prevalence of intake above the upper tolerable level (box 1).⁶ Although the overall proportion of US adults with intakes above the upper level is below 5% for most nutrients (fig 2), some population subgroups may have high rates of excess intake. For example, in a Canadian national survey, over 80% of children aged 1-3 years who took dietary supplements consumed vitamin A and niacin at levels above the upper limit.¹⁸ In the US, excessive intake was noted for vitamin A (97%) and zinc (68%) among toddlers who were given supplements.¹⁹ High quality evidence is lacking on the long term adverse effects of excess intake for several nutrients so it is unclear whether this is a cause for concern.

Do supplements protect against non-communicable diseases?

It remains controversial whether supplements are effective in reducing the risk of non-communicable diseases. In contrast to results of observational studies, the accumulated evidence from randomised controlled trials does not support benefits of

KEY MESSAGES

- Randomised trial evidence does not support use of vitamin, mineral, and fish oil supplements to reduce the risk of non-communicable diseases
- People using supplements tend to be older, female, and have higher education, income, and healthier lifestyles than people who do not use them
- Use of supplements appreciably reduces the prevalence of inadequate intake for most nutrients but also increases the prevalence of excess intake for some nutrients
- Further research is needed to assess the long term effects of supplements on the health of the general population and in individuals with specific nutritional needs, including those from low and middle income countries

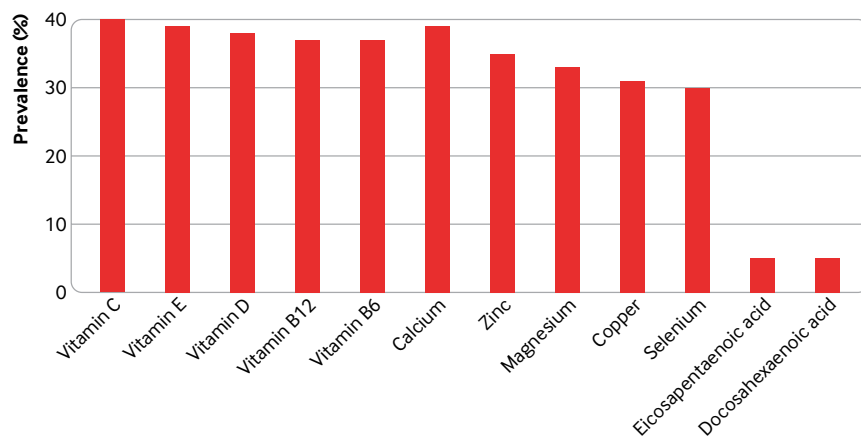


Fig 1 | Proportion of US adults taking commonly vitamin, mineral, and fish oil supplements, National Health and Nutrition Examination Survey 1999-2014⁶

supplements in reducing risks of cardiovascular disease, cancer, or type 2 diabetes in healthy people with no clinical nutritional deficiencies.

Cardiovascular disease

An updated systematic review of 15 randomised trials published after the 2013 US Preventive Service Task Force (USPSTF) review²⁰ confirmed the lack of benefits of supplements on cardiovascular events, mostly among patients with risk factors.²¹ Although randomised trials of folic acid, alone or in combination with vitamins B₁₂ or B₆, found significant reductions in plasma homocysteine levels, total cardiovascular events were not reduced. Another systematic review reported a reduced risk of stroke in association with supplementation of homocysteine lowering B vitamins,²² but the result was largely driven by one large trial in China.²³ Overall, there is no consistent evidence to support the use of antioxidant supplements for reducing cardiovascular risk.^{22 24}

The Vitamin D and Omega-3 Trial (VITAL), one of the few randomised trials of supplements for primary prevention of cardiovascular disease, found no effect

of vitamin D supplementation (2000 IU/day) on its primary endpoint (myocardial infarction, stroke, or cardiovascular death) in healthy people.²⁵ Previous large scale trials such as the Women's Health Initiative Calcium and Vitamin D Supplementation Study²⁶ and the Vitamin D Assessment Study²⁷ also showed vitamin D supplements, alone or in combination with calcium, had no effect on cardiovascular risk.

Supplementation with omega-3 fatty acids (1 g/day) did not reduce the risk of major cardiovascular events among healthy people in the VITAL trial.²⁸ However, benefits were found for some secondary endpoints such as total myocardial infarctions. This result is largely consistent with findings from meta-analyses that fish oil supplementation did not have substantial effects on the primary or secondary prevention of cardiovascular disease.^{29 30} However, a meta-analysis including the most recent trials reported a significant reduction in risk of myocardial infarction.³¹ Further studies are needed to determine whether fish oil supplementation has a greater effect on risk of heart disease than of stroke.³²

Box 1: Population nutrient intake—definitions

- *Estimated average requirement* is the daily level of nutrient intake estimated to meet the requirement of half of healthy people in a population
- *Inadequate nutrient intake*—The population prevalence of inadequate intake is estimated as the percentage of the population with nutrient intake below the estimated average requirement
- *Tolerable upper intake* is the highest daily nutrient intake that is likely to pose no risk of adverse health effects to almost all healthy people in a population. As intake increases above the upper level, the potential risk of adverse effects increases.
- *Excess intake*—The population prevalence of excess intake is estimated as the percentage of the population with nutrient intake above the upper level

Cancer

Current evidence does not support a role of vitamin and mineral supplements in reducing cancer risk, with some evidence suggesting potential harm. β -Carotene supplementation increased the risk of lung cancer among high risk individuals in two randomised trials. The α -Tocopherol, β -Carotene Cancer Prevention Study reported an 18% increase in relative risk among smokers randomised to β -carotene (20 mg/day) compared with those who did not.³³ The β -Carotene and Retinol Efficacy Trial found that β -carotene (30 mg/day) plus vitamin A as retinol (25 000 IU/day) increased risk by 28% among smokers and workers with occupational exposure to asbestos.³⁴ The Selenium and Vitamin E Cancer Prevention Trial found that vitamin E (400 IU/day) supplementation was associated with a 17% increase in prostate cancer risk among men.³⁵

Although maternal folic acid supplementation has been proved to reduce the risk of neural tube defects, concerns have been raised that high folic acid exposure may promote cancer progression, especially in countries with mandatory fortification.³⁶ Most notably, folic acid supplementation at ≥ 1 mg/day may promote the growth of undiagnosed colorectal adenomas.³⁷ However, a meta-analysis of 11 randomised trials concluded that folic acid supplementation neither increased nor decreased site specific cancer risk within the first five years of supplementation.³⁸

Randomised trials have failed to detect a benefit of vitamin D supplementation, alone or combined with calcium, on cancer risk at either high or low doses^{25 39} despite some evidence suggesting reduced total cancer mortality.^{25 40} The limited evidence on fish oil supplementation suggests it does not reduce cancer risk.^{28 41}

Type 2 diabetes

Current evidence does not support the use of supplements with vitamins C or E, β -carotene, or fish oil to reduce the risk of type 2 diabetes, although the overall evidence from randomised trials is limited.^{42 43} A recent placebo controlled trial of vitamin D supplementation (4000 IU/day) failed to reduce the risk of type 2 diabetes despite significantly increasing serum 25-hydroxyvitamin D concentrations.⁴⁴

Osteoporosis

Recent evidence regarding the effects of vitamin D and calcium supplementation is inconsistent. A meta-analysis of trials in community living older adults found that

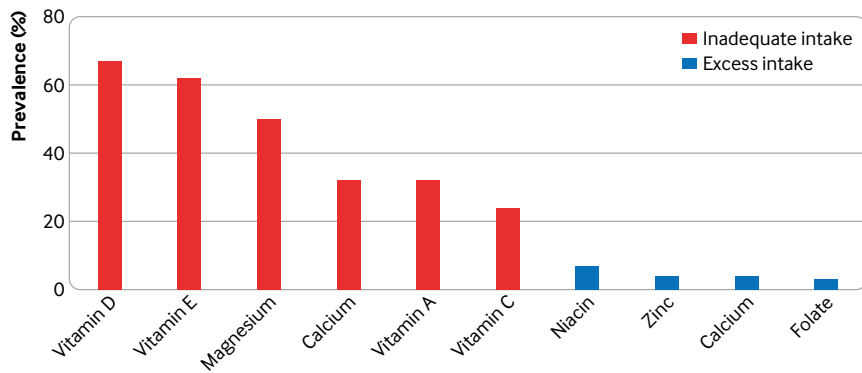


Fig 2 | Prevalence of inadequate and excess nutrient intake among US Adults, National Health and Nutrition Examination Survey 1999-2014⁶

vitamin D or calcium supplementation did not reduce the risk of hip fracture or total fracture,⁴⁵ whereas another meta-analysis reported that while vitamin D alone did not reduce fracture risk, combined calcium and vitamin D supplementation decreased the relative risk of hip fracture (16%) and all fractures (6%) among older adults.⁴⁶ Ongoing research is assessing the effect of high dose vitamin D supplements on several health outcomes, including fractures,⁴⁶ but a recent three year trial of 400, 4000, or 10 000 IU/day reported that the higher doses reduced volumetric bone density, suggesting potential for harm.⁴⁷ In the absence of clear evidence on supplementation, it is prudent to ensure that dietary recommendations on calcium and vitamin D intakes are met through food and supplementation.

What next?

To date, randomised trials have largely shown no benefit of vitamin, mineral, and fish oil supplements on the risk of major non-communicable diseases in people without clinical nutritional deficiency. These results contrast with findings from observational studies, where supplemental nutrient intakes are often associated with a reduced risk of these diseases. The apparent associations from observational studies may result from unknown or unmeasured confounding factors such as socioeconomic status and lifestyle factors, including a better overall diet.

Although randomisation reduces confounding, relying exclusively on the results of randomised trials also has limitations. Trials are often conducted among high risk populations with pre-existing conditions, so the findings may not be applicable to healthy individuals. Supplements may also have health benefits for population subgroups, such

as people with inadequate nutrient intake from foods, but randomised trials are not usually designed to evaluate subgroup differences. Furthermore, financial and practical constraints mean that most trials are able to investigate only a single dose, which may result in selection of a dose that is either too low (no efficacy) or too high (untoward outcomes).

Nutrients obtained from foods and supplements may confer different health effects. The Cancer Prevention Study (CPS)-II Nutrition Cohort found that supplemental calcium intake at ≥ 1000 mg/day was associated with an increased risk of all-cause mortality in men whereas high levels of calcium intake from foods had no harm.⁴⁸ Among US adults in the National Health and Nutrition Examination Survey, adequate intake of nutrients from foods, but not supplements, was associated with a lower risk of all-cause mortality.⁶ The benefits of nutrient intake from foods may reflect synergistic interactions among multiple nutrients and other bioactive substances in foods.

The effect of supplements in specific populations warrants further investigation. Older adults are at an increased risk of malnutrition because of reduced nutrient intake and age related decreases in the bioavailability of some micronutrients. Vitamin D supplementation is recommended for breastfed infants before the introduction of whole milk and solid

foods. Supplements may be more effective in reducing the risk of non-communicable disease in specific ethnic groups or people with low micronutrient intake from foods.²⁸ With a recent increase in the proportion of people reporting that they follow restricted dietary patterns such as ketogenic, Palaeolithic, vegan, and vegetarian diets, the value of supplements to meet the needs of these specific populations requires evaluation. In addition, potential nutrient-gene interactions have rarely been examined in studies of dietary supplements. Future studies on the role of nutrigenetics should help refine and personalise targeted recommendations for supplement use (box 2).

It is also important to recognise that the need for nutrient supplements is different in countries where nutrition deficiency is common. Ensuring adequate nutrition through food fortification and nutrient supplementation can be crucial to prevent serious adverse outcomes of nutrient deficiencies in low and middle income countries, especially among children <5 years, for whom malnutrition contributes to more than half their deaths.¹⁵

In summary, current evidence does not support recommending vitamin or fish oil supplements to reduce the risk of non-communicable diseases among populations without clinical nutritional deficiency. Continuing efforts are warranted to further understand the potentially different roles of nutrients from foods versus supplements in health promotion among a generally healthy population as well as individuals or groups with specific nutritional needs, including those living in low and middle income countries. These efforts, coupled with the integration of new research approaches, will better inform clinical practice and public health policies.

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Box 2: Areas for research in vitamin and mineral supplementation

- Differing health effects of nutrients obtained from foods versus supplements
- Synergistic interactions among multiple nutrients and with other bioactive substances
- Subpopulation studies (eg, elderly people, ethnic groups, vegans)
- Nutrigenetics and “omics” sciences
- Personalised supplementation
- Specific needs in low and middle income countries

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