

VIEWPOINT

Vitamin and Mineral Supplements

What Clinicians Need to Know

JoAnn E. Manson, MD, DrPH

Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts.

Shari S. Bassuk, ScD

Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Dietary supplementation is approximately a \$30 billion industry in the United States, with more than 90 000 products on the market. In recent national surveys, 52% of US adults reported use of at least 1 supplement product, and 10% reported use of at least 4 such products.¹ Vitamins and minerals are among the most popular supplements and are taken by 48% and 39% of adults, respectively, typically to maintain health and prevent disease.

Despite this enthusiasm, most randomized clinical trials of vitamin and mineral supplements have not demonstrated clear benefits for primary or secondary prevention of chronic diseases not related to nutritional deficiency. Indeed, some trials suggest that micronutrient supplementation in amounts that exceed the recommended dietary allowance (RDA)—eg, high doses of beta carotene, folic acid, vitamin E, or selenium—may have harmful effects, including increased mortality, cancer, and hemorrhagic stroke.²

In this Viewpoint, we provide information to help clinicians address frequently asked questions about micronutrient supplements from patients, as well as promote appropriate use and curb inappropriate use of such supplements among generally healthy individuals. Importantly, clinicians should counsel their patients that such supplementation is not a substitute for a healthful and balanced diet and, in most cases, provides little if any benefit beyond that conferred by such a diet.

Clinicians should also highlight the many advantages of obtaining vitamins and minerals from food instead of from supplements. Micronutrients in food are typically better absorbed by the body and are associated with fewer potential adverse effects.^{2,3} A healthful diet provides an array of nutritionally important substances in biologically optimal ratios as opposed to isolated compounds in highly concentrated form. Indeed, research shows that positive health outcomes are more strongly related to dietary patterns and specific food types than to individual micronutrient or nutrient intakes.³

Although routine micronutrient supplementation is not recommended for the general population, **targeted supplementation may be warranted in high-risk groups for whom nutritional requirements may not be met through diet alone**, including people at certain life stages and those with specific risk factors (discussed in the next 3 sections and in the **Box**).

Pregnancy

The evidence is clear that women who may become pregnant or who are in the first trimester of pregnancy should be advised to consume adequate folic acid (0.4–0.8 mg/d) to prevent neural tube defects. Folic acid is one of the few micronutrients more bioavailable in synthetic form from supplements or fortified foods than in the naturally oc-

curing dietary form (folate).² Prenatal multivitamin/multimineral supplements will provide folic acid as well as vitamin D and many other essential micronutrients during pregnancy. Pregnant women should also be advised to eat an iron-rich diet. Although it may also be prudent to prescribe supplemental iron for pregnant women with low levels of hemoglobin or ferritin to prevent and treat iron-deficiency anemia, the benefit-risk balance of screening for anemia and routine iron supplementation during pregnancy is not well characterized.²

Supplemental calcium may reduce the risk of gestational hypertension and preeclampsia, but confirmatory large trials are needed.² Use of high-dose vitamin D supplements during pregnancy also warrants further study.² The American College of Obstetricians and Gynecologists has developed a useful patient handout on micronutrient nutrition during pregnancy.⁴

Infants and Children

The American Academy of Pediatrics recommends that exclusively or partially breastfed infants receive (1) supplemental vitamin D (400 IU/d) starting soon after birth and continuing until weaning to vitamin D–fortified whole milk (≥ 1 L/d) and (2) supplemental iron (1 mg/kg/d) from 4 months until the introduction of iron-containing foods, usually at 6 months.⁵ Infants who receive formula, which is fortified with vitamin D and (often) iron, do not typically require additional supplementation. All children should be screened at 1 year for iron deficiency and iron-deficiency anemia.

Healthy children consuming a well-balanced diet do not need multivitamin/multimineral supplements, and they should avoid those containing micronutrient doses that exceed the RDA. In recent years, ω -3 fatty acid supplementation has been viewed as a potential strategy for reducing the risk of autism spectrum disorder or attention-deficit/hyperactivity disorder in children, but evidence from large randomized trials is lacking.²

Midlife and Older Adults

With respect to vitamin B₁₂, adults aged 50 years and older may not adequately absorb the naturally occurring, protein-bound form of this nutrient and thus should be advised to meet the RDA (2.4 μ g/d) with synthetic B₁₂ found in fortified foods or supplements.⁶ Patients with pernicious anemia will require higher doses (Box).

Regarding vitamin D, currently recommended intakes (from food or supplements) to maintain bone health are 600 IU/d for adults up to age 70 years and 800 IU/d for those aged older than 70 years.⁷ Some professional organizations recommend 1000 to 2000 IU/d, but it has been widely debated whether doses above the RDA offer additional benefits. Ongoing large-scale

Corresponding

Author: JoAnn E. Manson, MD, DrPH, Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Ave E, Boston, MA 02215 (jmanson@rics.bwh.harvard.edu).

Box. Key Points on Vitamin and Mineral Supplements**General Guidance for Supplementation in a Healthy Population by Life Stage**

Pregnancy: folic acid, prenatal vitamins

Infants and children: for breastfed infants, vitamin D until weaning and iron from age 4-6 mo

Midlife and older adults: some may benefit from supplemental vitamin B₁₂, vitamin D, and/or calcium

Guidance for Supplementation in High-Risk Subgroups**Medical conditions that interfere with nutrient absorption or metabolism:**

Bariatric surgery: fat-soluble vitamins, B vitamins, iron, calcium, zinc, copper, multivitamins/multiminerals

Pernicious anemia: vitamin B₁₂ (1-2 mg/d orally or 0.1-1 mg/mo intramuscularly)

Crohn disease, other inflammatory bowel disease, celiac disease: iron, B vitamins, vitamin D, zinc, magnesium

Osteoporosis or other bone health issues: vitamin D, calcium, magnesium^a

Age-related macular degeneration: specific formulation of antioxidant vitamins, zinc, copper

Medications (long-term use):

Proton pump inhibitors^a: vitamin B₁₂, calcium, magnesium

Metformin^a: vitamin B₁₂

Restricted or suboptimal eating patterns: multivitamins/multiminerals, vitamin B₁₂, calcium, vitamin D, magnesium

^a Inconsistent evidence.

randomized trials (NCT01169259 and ACTRN12613000743763) should help to resolve continuing uncertainties soon.

With respect to calcium, current RDAs are 1000 mg/d for men aged 51 to 70 years and 1200 mg/d for women aged 51 to 70 years and for all adults aged older than 70 years.⁷ Given recent concerns that calcium supplements may increase the risk for kidney stones and possibly cardiovascular disease, patients should aim to meet this recommendation primarily by eating a calcium-rich diet and take calcium supplements only if needed to reach the RDA goal (often only about 500 mg/d in supplements is required).² A recent meta-analysis suggested that supplementation with moderate-dose

calcium (<1000 mg/d) plus vitamin D (≥800 IU/d) might reduce the risk of fractures and loss of bone mass density among postmenopausal women and men aged 65 years and older.²

Multivitamin/multimineral supplementation is not recommended for generally healthy adults.⁸ One large trial in US men found a modest lowering of cancer risk,⁹ but the results require replication in large trials that include women and allow for analysis by baseline nutrient status, a potentially important modifier of the treatment effect. An ongoing large-scale 4-year trial (NCT02422745) is expected to clarify the benefit-risk balance of multivitamin/multimineral supplements taken for primary prevention of cancer and cardiovascular disease.

Other Key Points

When reviewing medications with patients, clinicians should ask about use of micronutrient (and botanical or other dietary) supplements in counseling about potential interactions. For example, supplemental vitamin K can decrease the effectiveness of warfarin, and biotin (vitamin B₇) can interfere with the accuracy of cardiac troponin and other laboratory tests. Patient-friendly interaction checkers are available free of charge online (search for *interaction checkers* on drugs.com, WebMD, or pharmacy websites).

Clinicians and patients should also be aware that the US Food and Drug Administration is not authorized to review dietary supplements for safety and efficacy prior to marketing. Although supplement makers are required to adhere to the agency's Good Manufacturing Practice regulations, compliance monitoring is less than optimal. Thus, clinicians may wish to favor prescription products, when available, or advise patients to consider selecting a supplement that has been certified by independent testers (ConsumerLab.com, US Pharmacopeia, NSF International, or UL) to contain the labeled dose(s) of the active ingredient(s) and not to contain microbes, heavy metals, or other toxins. Clinicians (or patients) should report suspected supplement-related adverse effects to the Food and Drug Administration via MedWatch, the online safety reporting portal. An excellent source of information on micronutrient and other dietary supplements for both clinicians and patients is the website of the Office of Dietary Supplements of the National Institutes of Health.

Clinicians have an opportunity to promote appropriate use and to curb inappropriate use of micronutrient supplements, and these efforts are likely to improve public health.

ARTICLE INFORMATION

Published Online: February 5, 2018.
doi:10.1001/jama.2017.21012

Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Manson and Bassuk reported that their research division conducts randomized clinical trials of several vitamins and minerals. The Vitamin D and Omega-3 Trial (VITAL) is sponsored by the National Institutes of Health but the vitamin D is donated by Pharmavite. In COSMOS, the multivitamins are donated by Pfizer. Both authors collaborate on these studies.

REFERENCES

- Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in dietary supplement use among US adults from 1999-2012. *JAMA*. 2016;316(14):1464-1474.
- Rautiainen S, Manson JE, Lichtenstein AH, Sesso HD. Dietary supplements and disease prevention: a global overview. *Nat Rev Endocrinol*. 2016;12(7):407-420.
- Marra MV, Boyar AP. Position of the American Dietetic Association: nutrient supplementation. *J Am Diet Assoc*. 2009;109(12):2073-2085.
- American College of Obstetricians and Gynecologists. Nutrition during pregnancy. <https://www.acog.org/Patients/FAQs/Nutrition-During-Pregnancy>. Published April 2015. Accessed November 20, 2017.
- American Academy of Pediatrics. Vitamin D & iron supplements for babies: AAP recommendations. <https://www.healthychildren.org/English/ages-stages/baby/feeding-nutrition/Pages/Vitamin-Iron-Supplements.aspx>. Updated May 27, 2016. Accessed November 20, 2017.
- Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. Washington, DC: National Academies Press; 1998.
- Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; 2011.
- Moyer VA; US Preventive Services Task Force. Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(8):558-564.
- Gaziano JM, Sesso HD, Christen WG, et al. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2012;308(18):1871-1880.