Enough Is Enough

TO THE EDITOR: Guallar and colleagues (1) conclude that “the case is closed—supplementing the diet of well-nourished adults with (most) mineral or vitamin supplements has no clear benefit and might even be harmful.” However, they ignore decades of nutrition research and diet monitoring of the U.S. population to reach this misleading conclusion.

Although a well-balanced diet is the best way to get essential nutrients (except vitamin D and, for vegans and many older adults, vitamin B₁₂), few persons in the United States follow the Dietary Guidelines for Americans. Consequently, most persons in the United States are not “well-nourished” and do not meet the Institute of Medicine’s recommendations for the dietary intake of all vitamins and essential minerals.

More than 93%, 61%, and approximately 50% of adults in the United States do not get the Estimated Average Requirement of vitamins D and E, magnesium, and vitamin A and calcium, respectively, from their diet, including enriched and fortified foods (2). Further, 98% and 71% do not meet the Adequate Intake of potassium and vitamin K, respectively (2). Many of these percentages are even higher among subpopulations with increased micronutrient needs, including older adults, African Americans, and obese persons. Conversely, persons taking a daily multivitamin and mineral supplement formulated at approximately the Daily Value do fill many of these nutritional gaps effectively, safely, and at low cost: A high-quality multivitamin and mineral supplement costs as little as 3 cents per day (3), and long-term use is not associated with any adverse health effects (2, 4).

Guallar and colleagues state that “β-carotene, vitamin E, and possibly high doses of vitamin A supplements increase mortality” (1). Only approximately 0.1% of adults in the United States exceed the Tolerable Upper Intake Level of vitamin E because of high-dose supplement use, and approximately 1.1% exceed the Tolerable Upper Intake Level of vitamin A (2). It is well-known that vitamin A should not be consumed long term in amounts exceeding the Tolerable Upper Intake Level because it may cause hypervitaminosis A and birth defects and that smokers should avoid β-carotene supplements because of an increased risk for lung cancer. The meta-analysis of randomized, controlled trials (RCTs) reporting that high-dose vitamin E supplements increase mortality (1) has been refuted by several more comprehensive meta-analyses, as that of Abner and associates (5).

The known biological functions of micronutrients are to maintain normal cell and tissue function, metabolism, growth, and development by serving as essential cofactors or structural components of thousands of enzymes and other biomolecules, among other means. For example, vitamins A and D, iron, and zinc play critical roles in innate and adaptive immunity and folate is required for normal neurologic development. A multivitamin and mineral supplement containing folic acid dramatically decreases the risk for neural tube defects and is recommended for women of childbearing age.

Multivitamin and mineral supplements also may help decrease risk for chronic disease. The largest and longest RCT of a multivitamin and mineral supplement conducted to date, the PHS II (Physicians’ Health Study II), found a statistically significant 8% reduction in total cancer incidence in male physicians (12% when excluding prostate cancer) and a statistically significant 9% and 13% reduction in total and nuclear cataracts, respectively (4). These findings are consistent with those of several other RCTs and are even more impressive given that conventional RCT designs have limited ability to reveal benefits of nutrients—in contrast to drugs—for chronic diseases (6).

Therefore, taking a daily multivitamin and mineral supplement not only helps fill known nutritional gaps in the diet of most persons in the United States (thereby ensuring normal body function and supporting good health) but may have the added benefit of helping to reduce the risk for some chronic diseases. To call the case closed; deny the value of further research; and label multivitamin and mineral supplements useless, harmful, and a waste of money (1) is wrong, is not based on the established science for their primary indication, and misinforms the public and the medical community.

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References
TO THE EDITOR: Guallar and colleagues (1) purport that their opinions are facts. They state that most supplements “do not prevent chronic disease or death . . . and they should be avoided.”

The authors totally disregard the best and most comprehensive study to date, PHS II (2). This study followed nearly 15,000 male physicians aged 50 years or older for up to 13 years. It revealed that use of a Centrum Silver (Pfizer, New York, New York) multivitamin alone reduced the risk for cancer in men from any source by 8%. The study also found that multivitamin use decreased site-specific cancer (except for prostate cancer) by 12% and suggested a 12% reduction in deaths caused by cancer.

According to SciTech Daily, “Recent studies have looked at whether vitamins such as C, E and B12 could prevent cancer. They found that multivitamin use decreased the risk for cancer in men from any source by 8%.” (3)

If Guallar and colleagues are correct in their assumptions, then every ophthalmologist who prescribes antioxidant vitamins with lutein to treat macular degeneration and every obstetrician–gynecologist who prescribes prenatal vitamins to prevent spina bifida, meningomyelocoele, and other neural tube defects in the neonate is wrong. These regimens are factual and proven. If Guallar and colleagues are correct, then most urologists who prescribe time-release vitamin C for recurrent urinary tract infections are wrong. This protocol obviates the need for long-term antibiotic use, which creates drug-resistant bacterial strains. Bacteria have a difficult time living in an acidic environment (ergo, the vitamin C).

If Guallar and colleagues are correct, then another excellent study (4) is wrong. This 2-year, double-blind study discovered that use of vitamin B slowed brain shrinkage and atrophy of gray matter in the brain affected by Alzheimer disease by 30% and, in some cases, by more than 50%. As the principal investigator of this study states, “[T]he subject of the latest research study . . . showed that vitamin B is the first and only disease-modifying treatment that’s worked” and “we have proved the concept that you can modify the disease” (5).

How do you know that your antioxidant vitamins are working? Your hair and nails will grow rapidly. Your body needs rapid cell turnover; it prevents cancer of the gastrointestinal system, which is activated by cell stagnation. Also, rapid turnover of skin cells helps to prevent skin cancer.

I recommend that Guallar and colleagues be thought fools rather than put their opinions in print and remove all doubt. The authors cite a collection of poor studies that they claim to be factual. I recommend that patients who find a physician who states that persons receive all of the vitamins and minerals that they need from the food that they eat should find another physician. Enough is enough!

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References

TO THE EDITOR: I am concerned about how Guallar and colleagues’ editorial (1) was presented. I believe that a large set of persons should take vitamins: pregnant women. As a matter of fact, any woman of childbearing age should take vitamins because we do not always know whether we will become pregnant, even if we use protection (2).

Guallar and colleagues did not address this problem. I am worried that even one woman of reproductive age may stop taking a multivitamin to the detriment of a fetus that she may be carrying.

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References

TO THE EDITOR: Guallar and colleagues (1) declare that vitamin and mineral supplementation in well-nourished adults is pointless in the prevention of “chronic disease.” They neglect to mention that the large RCT PHS II showed that daily multivitamins and minerals significantly reduced the risk for cataract formation (2). More important, they do not mention the effectiveness of vitamin and mineral supplementation in the prevention of severe vision loss and blindness from age-related macular degeneration (3, 4), a common chronic disease of considerable importance.

Blindness is a most feared disability and is linked strongly to increased mortality, rates of hospitalization, and length of hospital stays. Despite its effect on a patient’s well-being, blindness is often excluded from the symptom list during hospital stays (5). Thus, it is not surprising that Guallar and colleagues’ editorial omitted one of

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References
the primary reasons for vitamin supplementation among older adults: ocular health.

As a principal investigator in AREDS (Age-Related Eye Disease Study) and AREDS II, I have seen the role of supplements for the prevention of vision loss in age-related macular degeneration become well-established. Unfortunately, Guallar and colleagues were apparently oblivious to the needs of patients with this condition, the most common cause of blindness in adults in the United States.

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References

TO THE EDITOR: Guallar and colleagues (1) draw attention to mounting evidence that most vitamin and mineral supplements do not prevent chronic diseases and in some cases may be harmful. We share the authors’ concerns and have released 2 related reports (2, 3) that further highlight risks of dietary supplements based on our review of their labels. Manufacturers make claims on these labels that the U.S. Food and Drug Administration (FDA) has limited authority to review; however, consumers rely on those claims in purchasing supplements.

In the first report, we found that claims made on dietary supplement labels may be misleading. Specifically, we reviewed the substantiation for structure/function claims found in a sample of supplements marketed for weight loss and immune support. The FDA requires that supplement manufacturers have substantiation to support such claims on their products’ labels and has issued guidance on the scientific support necessary to do so.

The substantiation for structure/function claims was not consistent with FDA recommendations that evidence be derived from high-quality human studies. Most studies that we reviewed did not involve the actual supplement or test the supplement or its active ingredients in humans. Furthermore, 20% of the supplements’ labels bore claims that the FDA prohibits, such as claims that it prevents or treats disease.

In the second report, we found that the FDA may have difficulty locating dietary supplement companies in emergencies related to their products. We contacted the companies responsible for the supplements in our sample and found that 28% had facilities that failed to register with the FDA as required. Of those that did register, 72% had incomplete or inaccurate contact information. In addition, 20% of sample labels lacked the required contact information for reporting adverse events.

On the basis of our research, we share Guallar and colleagues’ view that consumers should be wary of dietary supplements’ claims of effectiveness and call on the FDA to seek explicit authority to review those claims. Furthermore, the FDA should improve the accuracy of its registry to ensure that it can respond to a public health emergency related to dietary supplements.

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References

IN RESPONSE: Dr. Frei and colleagues believe that our current knowledge based on nutritional research and dietary monitoring justifies daily use of multivitamin and mineral supplements by most persons in the United States. We disagree. In contrast to many prevention strategies, vitamin and mineral supplements are pill-based interventions that are amenable to rigorous evaluation in large-scale clinical trials with clinically relevant outcomes. The lack of efficacy and the adverse effects observed in clinical trials of antioxidant supplements, confirmed once again in a recent Cochrane review (1), should be a constant reminder of our limited ability to infer the consequences of interventions from mechanistic considerations or surrogate end points of uncertain clinical relevance.

Dr. Frei and colleagues and Dr. Mason mention a possible signal of benefit in PHS II (2) and the SU.VI.MAX (Supplementation en Vitamines et Minéraux Antioxydants) study (3). PHS II was a double-blind, placebo-controlled trial in 14 641 male physicians in the United States. After a median follow-up of 11.2 years, men receiving a daily 30-component multivitamin supplement (Centrum Silver) had lower overall cancer incidence than those receiving placebo (hazard ratio, 0.92 [95% CI, 0.86 to 0.99]). The SU.VI.MAX study was a double-blind, placebo-controlled trial in 13 017 French...
men and women. After a median follow-up of 7.5 years, there were no major differences in cancer incidence between participants receiving a daily 5-component multivitamin supplement and those receiving placebo. However, a sex-stratified analysis showed a reduced risk for cancer incidence in men receiving multivitamins (relative risk, 0.69 [CI, 0.53 to 0.91]) but not in women (relative risk, 1.04 [CI, 0.85 to 1.29]). Because the observed possible benefits were limited to men, were modest (as in PHS II), or were evident only in subgroup analyses (as in the SU.VI.MAX study) and did not consistently extend to reductions in mortality, these findings are only weak signals compatible with small or no benefit.

As Ms. Stepp indicates, our editorial did not address the use of prenatal vitamin and mineral supplements, which are not for long-term use but rather for use during a limited, well-defined period. Our editorial specifically dealt with long-term use of multivitamins.

We also did not address the use of antioxidant vitamins in the treatment of age-related macular degeneration. There is no evidence that antioxidants or multivitamins prevent or delay the onset of this condition (4), but antioxidants may delay progression once it has started (5). However, use of antioxidants in this setting should be part of a formal therapeutic plan supervised by an ophthalmologist.

Finally, we share Ms. Fargnoli and associates’ concerns about misleading claims on dietary supplement labels and support their call to increase the authority of the FDA to review such claims.

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References

Insurance Status and the Transfer of Hospitalized Patients

TO THE EDITOR: We read Hanmer and colleagues’ article (1) with great interest. A patient’s status as “insured” is probably the principal element in his or her likelihood to undergo interhospital transfer directly from the emergency department or after admission.

Specifically, patients insured and enrolled in a managed care product, accountable care organization, or otherwise who are subject to the constraints of a specifically designated network of care and who present and are admitted to an out-of-network facility on an emergency or unplanned basis will be of great interest to their designated provider network for financial reasons. Patients and their provider networks will have a financial incentive to “repatriate” patients back to an in-network facility. Uninsured patients are not subject to utilization management, prior authorization rules, network enforcement, case management, or other resources typically found in managed care environments with an incentive to enforce in-network utilization and inpatient admission.

This phenomenon of interhospital transfers is likely to grow as “accountable care” or other shared-risk arrangements become more pervasive. Physicians and hospitals alike will have a keen incentive to attend to their financial accountability for patient care.

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Reference

Observation

Tanning Beds and Hypervitaminosis D: A Case Report

Background: Vitamin D is synthesized in the skin in response to ultraviolet B rays during sun exposure. Several vitamin D metabolites circulate in the blood, but measurement of serum levels of 25-hydroxyvitamin D [25-(OH)D] is a standard method to assess vitamin D status. Hypervitaminosis D usually occurs as a result of excessive intake of vitamin D preparations and can lead to hypercalcemia, hypercalciuria, hyperphosphatemia, and low parathyroid hormone levels.

Case Report: A primary care physician referred a 26-year-old asymptomatic white woman to our endocrinology clinic because of high serum 25-(OH)D levels (>339 nmol/L [reference range, 75 to 185 nmol/L]) discovered during an annual health examination in July 2012. We saw her 6 months later, because of our clinic’s wait...
The patient did not excessively consume milk or receive over-the-counter vitamin D preparations or other medications. She reported minimal sun exposure but had been using a tanning bed 3 or more times weekly for at least 6 months. Her medical history included polycystic ovarian disease. She was following a low-fat, low-carbohydrate diet and other lifestyle changes to lose weight. Serum levels of calcium, phosphorus, 1,25-dihydroxyvitamin D, and parathyroid hormone were normal (Table).

We advised her to stop using tanning beds because we could not identify another cause for hypervitaminosis D. On repeated measurement 1 month later, 25-(OH)D levels were lower (182 nmol/L). The patient did not return for other follow-up visits.

**Discussion:** Vitamin D levels are higher in persons with lighter-colored skin, in summer than in winter, and in persons who expose their skin to the sun to promote tanning (1–5). How these associations affect this patient is difficult to determine because she had lighter-colored skin, persistently high vitamin D levels during winter, and minimal sun exposure. Furthermore, she lived in Worcester, Massachusetts, where the latitude of 42 degrees is intermediate for year-round sun intensity. We believe that the patient’s use of tanning beds is the probable explanation for her elevated 25-(OH)D levels: Tanning beds produce ultraviolet B rays, and the patient’s 25-(OH)D levels were elevated after exposure to tanning beds and decreased when she stopped using them.

Other such cases have not been reported to our knowledge, and we alert clinicians that patients who use tanning beds may have elevated vitamin D levels. If tanning beds can lead to hypervitaminosis D, they might be useful alternatives for patients who need higher vitamin D levels but do not benefit from oral replacement therapy because of intestinal malabsorption or adherence issues, as long as the benefit from higher vitamin D levels outweighs the increased risk for skin cancer.

**Table. Serum Levels**

<table>
<thead>
<tr>
<th>Serum Level</th>
<th>Normal Range</th>
<th>19 July 2012</th>
<th>30 January 2013</th>
<th>28 February 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-(OH)D, nmol/L</td>
<td>75–185</td>
<td>&gt;339</td>
<td>&gt;299</td>
<td>182</td>
</tr>
<tr>
<td>1,25-(OH)2D, pmol/L</td>
<td>47–187</td>
<td>135</td>
<td>137</td>
<td>135</td>
</tr>
<tr>
<td>Calcium, mmol/L</td>
<td>2.13–2.55</td>
<td>2.35</td>
<td>2.42</td>
<td>2.35</td>
</tr>
<tr>
<td>mg/dL</td>
<td>8.5–10.2</td>
<td>9.4</td>
<td>9.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Phosphorus, mmol/L</td>
<td>0.77–1.32</td>
<td>1.26</td>
<td>1.29</td>
<td>1.26</td>
</tr>
<tr>
<td>Intact parathyroid hormone, ng/L</td>
<td>15–65</td>
<td>38</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

25-(OH)D = 25-hydroxyvitamin D; 1,25-(OH)2D = 1,25-dihydroxyvitamin D; ND = not done.

**Disclosures:** Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L13-1122.

**References**


