Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-2550.

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Severe Vitamin D Deficiency: A Prerequisite for Chronic Obstructive Pulmonary Disease Responsiveness to Vitamin D Supplementation?

TO THE EDITOR: The randomized, placebo-controlled trial reported by Lehouck and colleagues (1) found that vitamin D supplementation did not improve any of a series of clinically important outcomes over 1 year in patients with moderately severe chronic obstructive pulmonary disease (COPD). It adds to an expanding body of clinical trial evidence that vitamin D supplementation does not favorably alter outcomes for many of the diseases that have been associated with lower vitamin D levels in observational studies (2). Collectively, these emerging data raise significant doubts about the role of vitamin D in the pathogenesis and management of nonskeletal disease. Therefore, it was disappointing that Lehouck and colleagues in their abstract, and Gold and Manson in their accompanying editorial (3), placed undue emphasis on the positive findings of a post hoc analysis of a secondary end point in a subgroup of 30 participants with low baseline levels of 25-hydroxyvitamin D. Such analyses should be treated with considerable caution because they are very likely to produce erroneous findings.

As is frequently observed in the vitamin D literature, Gold and Manson (3) were reluctant to consider the possibility that vitamin D is an ineffective intervention, instead offering disease heterogeneity and vitamin D–receptor polymorphisms as explanations for the null result. In skeletal biology, considerable resources were invested in evaluating the influence of vitamin D–receptor polymorphisms, to no avail.

Finally, we are less confident than the editorialists that VITAL (Vitamin D and Omega-3 Trial) will provide definitive evidence of the risks and benefits of vitamin D. In that trial, participants are permitted to take nonprotocol vitamin D supplements up to 800 IU/daily (4), potentially rendering it a comparison between low-dose and moderate-dose vitamin D rather than between vitamin D and placebo. A similar design in the Women's Health Initiative trial of calcium and vitamin D (5), in which more than 50% of participants took nonprotocol calcium supplements, obscured adverse cardiovascular effects of calcium supplements.

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IN RESPONSE: We would like to thank Dr. Grey and colleagues for their comments. There was no overall benefit of vitamin D supplementation for time to COPD exacerbation or exacerbation rates in the clinical trial by Lehouck and colleagues (1). However, when a post hoc analysis suggests a possible clinical benefit of vitamin D supplementation, with reduced exacerbations for the 20% of the population with severe vitamin deficiency at baseline (30 of 150 patients followed for 1 year), it would be worthwhile to evaluate whether these findings stand up internally to further statistical scrutiny, and whether they are reproducible.

As discussed in our editorial, the evolving pulmonary literature gives credence to the hypothesis that baseline levels of vitamin D, genetic variation, variability in disease expression, and variability in dose and timing of vitamin D supplementation may result in heterogeneity in COPD responses. There is no magic bullet for treatment of COPD, and smoking cessation remains the most effective starting point to improve prognosis. However, as the scientific community awaits findings from other ongoing clinical trials, it would be premature to conclude that there will be no patient benefit of vitamin D supplementation for either the pulmonary or extrapulmonary manifestations of this systemic and clinically heterogeneous disease.

Finally, as clinicians caring for patients with COPD await the results of ongoing clinical trials addressing pulmonary and other nonskeletal outcomes, it will be important to take into account the potential benefits of vitamin D supplementation for reducing the risk for fractures, which can contribute to COPD morbidity in this frail population with high rates of vitamin D deficiency.

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Effects of Excessive Fructose Intake on Health

TO THE EDITOR: The review by Sievenpiper and colleagues (1) has the great potential for being taken to mean that excessive intake of fructose is safe and does not promote long-term weight gain, which should be interpreted with great caution. For example, one would not expect to see a difference in weight gain for any food if both control and treatment contain the same number of calories. The way fructose increases weight gain is by altering appetite, such that it stimulates increased food intake, by inducing leptin resistance or by direct effects on the brain (2, 3). However, if food intake is forcefully kept equal, how can one expect any difference in weight gain between groups? On the other hand, the hypercaloric studies analyzed in this meta-analysis are flawed, because the median duration of the studies was only 1.5 weeks. How can anyone expect the effects of fructose on weight to manifest in such a short time? The problem is that obesity does not occur overnight—it takes years (4).

One must also consider the metabolic effects of fructose and its effects on body composition rather than on body weight. Thus, fructose (and not glucose) stimulates visceral fat accumulation, insulin resistance (with a greater increase in postprandial triglyceridemia), and drives nonalcoholic fatty liver disease (5). We have shown that these types of changes can be induced in animals with fructose or sucrose in a setting where caloric intake is kept equal (5). Sievenpiper and colleagues unfortunately address only weight gain, and hence miss this key aspect about the adverse metabolic effects of fructose. Moreover, this meta-analysis excluded studies in which fructose was administered as high-fructose corn syrup or sucrose, the largest contributors to added sugar intake (6).

The other aspect of fructose is that not all sources are the same, and not all people respond to it in the same way (4). Fructose in fruit tends to be safer because of all of the additional nutrients and antioxidants in fresh (not overripe) fruit. Fructose in sucrose and high-fructose corn syrup is much less safe, and the glucose present in these sugars can accelerate fructose absorption. Likewise, the response to fructose in young healthy people is much lower than in older obese persons. Therefore, pooling studies that contain diabetic, obese, and both old and young participants as well as those who received fructose in different ways carries great risk for diluting any real findings.

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Potential Conflicts of Interest: Dr. Johnson: *Board membership:* Amway Scientific Board, Gatorade Museum Board; *Consultancy:* Ardea, Astellas, Danone, Novartis; *Employment:* University of Colorado, University of Florida; *Expert testimony:* expert on kidney diseases; *Grants/grants pending (money to institution):* Amway, Cardero, Danone, Questcor, Sugar Foundation; *Payment for lectures including service on speakers bureaus:* honoraria associated with lectures to universities or societies; *Patents (planned, pending or issued):* have patent applications on blocking fructose metabolism or lowering uric acid as a means for preventing or treating obesity and metabolic syndrome and patent issued on allopurinol for treatment of hypertension; *Royalties:* Elsevier; *Stock/stock options:* Cardero. Dr. Sanchez-Lozada: *Grant (money to institution):* CONACyT.

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IN RESPONSE: We thank Dr. Johnson and colleagues for their comments. Their concern was that people may infer from our data that fructose intake does not promote weight gain. On the contrary, in hypercaloric trials, extreme fructose doses providing excess energy did promote weight gain despite short follow-up; however, energy was a more important factor than substrate. The weight gain was similar to that predicted from excess energy alone. We also found no effect on body weight under the same conditions of excess energy except where the comparisons were isocalorically matched. The level of energy control was unlikely to play a role in these particular comparisons, because the background diets were largely ad libitum. Even in the isocaloric trials, which provided a neutral energy balance, a new subgroup analysis did not reveal a weight-increasing effect of fructose in trials with less strict control of energy (data not shown), a situation where the ability of fructose to stimulate appetite would have been expected to manifest. Appetite effects, however, may be important.

We acknowledge that we did not consider fructose effects beyond body weight. Although fructose increases visceral fat, insulin resistance, triglycerides, blood pressure, uric acid, and nonalcoholic fatty liver in animal models, the experience in humans has been different. We and others have conducted a series of systematic reviews and meta-analyses of controlled feeding trials of the effect of fructose on related end points. We found that fructose does not increase lipid levels (1), blood pressure (2), or uric acid levels (3), and it even improves glycemic control in isocaloric trials (4); however, there is a signal for harm under certain conditions. High doses of