other studies that showed that circulating pentadecanoic acid concentrations reflect the intake of dairy products, whereas free concentrations of heptadecanoic acid are predominantly synthesized by endogenous metabolic pathways (3, 4) (i.e., by the use of propionyl-CoA for fatty acid synthesis). Interestingly, recent studies indicate that heptadecanoic acid is linked to insulin sensitivity (5, 6), whereas pentadecanoic acid shows no association (4). This highlights the importance of heptadecanoic acid as a biomarker of dietary fiber intake and thus provides a new explanation for its positive association with insulin sensitivity. In summary, we support the assumption that mainly heptadecanoic acid is a valid biomarker for fermentable dietary fiber intake and a good predictor of insulin sensitivity.

None of the authors had a conflict of interest.

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Dietary whole grains and zinc nutriture

Dear Editor:

In a recent article in the Journal, Vanegas et al. (1) provided 81 adults with whole grains or refined grains in mixed diets for 6 wk. Dietary fiber contents were ~41 or 21 g/2500 kcal. Outcomes included "a very modest effect on the gut microbiota composition, SCFAs [short-chain fatty acids], and certain indicators of the immune response" in the subjects who consumed whole grains. In our opinion, the report is incomplete: phytate-to-zinc molar ratios of the diets were not disclosed.

Relevant to phytate-to-zinc molar ratios, Hunt et al. (2) conducted a feeding study in 109 adults in which the fiber contents of diets were similar to those in Vanegas et al. (1), in which outcomes were the intestinal absorption of zinc. Each subject received 1 of 10 diets. Five diets provided 21–39 g dietary fiber/2500 kcal daily for 4 wk. In contrast, the other 5 diets provided 18 g dietary fiber/2500 kcal daily for 4 or 8 wk. The respective phytate-to-zinc molar ratios were 15–23 and 2–7. The higher fiber-phytate diet significantly decreased intestinal absorption of ^{65}Zn. Plasma zinc concentrations did not reflect the changes in zinc absorption, and no metabolic changes were recognized.

The suppression of intestinal absorption of certain essential metals by dietary phytate has been known since the 1920–1930s. As reviewed (3), in 1961, Prasad and colleagues proposed that zinc deficiency was the cause of growth stunting and hypogonadism in 11 Iranian subsistence farmers who frequently ate clay; later, Prasad led the team who studied 40 stunted hypogonadal Egyptian farmers in a controlled environment. All subsisted on diets based on whole grains and were afflicted by hookworm and schistosomiasis. Zinc treatment and an omnivorous diet facilitated growth and development, in contrast to diet alone. Prasad also found zinc deficiency in 16 subsistence farmers living in 2 desert oases who were not afflicted with hookworm or schistosomiasis. In addition, colleagues in Iran confirmed the efficacy of zinc in stunted hypogondal Iranian subsistence farmers and clarified the role of zinc-binding dietary ligands (e.g., phytate, dietary fibers, lignin) in the illness (3). The practical importance of these findings for US women was suggested by Velie et al. (4). Their case-controlled study found associations between preconceptional maternal nutrition and neural tube defects (NTDs) in 859 mother-infant pairs that included 430 instances of NTDs. The risk of NTDs was inversely associated with maternal preconceptional zinc intake. Also, phytate seemed to modify the zinc-NTD association. The effect of zinc per se was consistent with Meadows et al. (5): fetal growth related directly to the zinc content of maternal and fetal leukocytes and maternal muscle. More recently, Hambidge et al. (6) and Miller et al. (7) confirmed the key role of phytate in human zinc nutriture. Phytate-to-zinc molar ratios $\geq$12 increase the risk of zinc deficiency, and phytate can account for 88% of the variance in human zinc absorption.

Prasad and colleagues (8, 9) showed immunologic markers to be highly sensitive to zinc status, in contrast to plasma zinc. Of high importance is serum active thymulin, a hormone produced by the thymus. Thymulin mediates the proliferation and differentiation of T-helper cells and the generation of mRNAs of IL-2 and interferon γ (IFN-γ) by T-helper 1 cells. More recently, Zyba et al. (10) reported that low zinc status impairs DNA integrity. We suggest that the indexes reported by Prasad and colleagues (8, 9) and Zyba et al. (10) might be useful in research on the safety of the habitual consumption of whole grains and other seeds, in contrast to foods based on seeds from which phytate and other metal-binding ligands have been removed.

Neither of the authors had conflicts of interest concerning the contents of this letter.

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Reply to HH Sandstead and AS Prasad

Dear Editor:

We appreciate the interest of Sandstead and Prasad in our recently published article (1). In this study, we provided healthy men and postmenopausal women [aged 40–65 y; BMI (in kg/m^2) <35] a diet containing whole grain (WG) or refined grain (RG) for 6 wk after a 2-wk run-in period. The results showed that participants who consumed WG relative to RG had increased plasma total alkylresorcinols (an indicator of WG intake), stool weight and frequency, total stool short-chain fatty acids (SCFAs), and SCFA producer Lachnospira and decreased proinflammatory Enterobacteriaceae. In addition, we found a modest difference between the WG and RG groups in immune and inflammatory responses (i.e., higher percentage of terminal effector memory T cells and LPS-stimulated ex vivo production of TNF-α in the WG group than in the RG group), which were positively associated with plasma alkylresorcinol concentrations.

In our article, we discussed several possibilities for the lack of a more dramatic and comprehensive impact of increasing WG consumption on immune and inflammatory responses; however, we did not consider the possible contribution of low zinc absorption potentially resulting from increased WG consumption. Sandstead and Prasad pointed out that we should have reported the phytate-to-zinc ratio, because WG consumption may increase this ratio, which, in turn, could reduce zinc absorption. Given the importance of zinc in maintaining and improving immune cell function, reduced zinc concentrations might be a factor contributing to the lack of substantial immunologic benefit from WG consumption. We appreciate the relevance of their suggestion, and thus revisited the diet record data and calculated the phytate-to-zinc ratio after converting the daily intake of each, recorded in milligrams, to molar units. We then conducted a statistical analysis by using the same methods as described in the original article (1). As expected, the results showed that the WG diet provided substantially more phytate and slightly more zinc, resulting in a significantly higher phytate-to-zinc ratio compared with the RG diet (**Table 1**).

Phytate is abundant in foods that are rich in dietary fiber, including WGs (2). Dietary phytate has long been known to decrease zinc bioavailability because it forms poorly soluble complexes with zinc in the intestine, resulting in reduced zinc absorption and reabsorption (3, 4). Thus, in practice, the molar ratio of phytate to zinc in the diet is often used as a useful indicator to estimate the zinc absorption status. In our study, the phytate-to-zinc ratios at baseline were not different between the RG and WG groups; however, the ratios at the end of the intervention became significantly different, with a much higher increase observed in the WG group (3.77–14.15) than in the RG group (3.78–4.45) (Table 1). The increased phytate-to-zinc ratio is mainly due to the increased phytate intake (778 to 3720 μmol/d) through the WG diet rather than reduced zinc intake because daily zinc intake, in fact, even increased from 207 to 263 μmol. On the basis of the classification by the WHO (5), phytate-to-zinc ratios <5 are indicative of "high" zinc absorption, whereas ratios of 5–15 are indicative of "moderate" zinc absorption. Therefore, the postintervention phytate-to-zinc ratios in the WG group (14.15) compared with the RG group (4.45) strongly suggest that WG consumption may have significantly reduced the absorption and thus the tissue concentrations of zinc.

Zinc as an important trace element has a variety of biological functions. One of its well-recognized functions is to regulate immune cell development and to maintain their appropriate functionality; zinc deficiency has been linked to impaired immunity and an increased risk of infection, which can be corrected by zinc supplementation (6, 7). This is particularly important in older populations with an already dysregulated immune response. Thus, it is reasonable to speculate that a compromised zinc status resulting from the consumption of a WG diet may offset some potential immune benefit of WG consumption, which might have otherwise been detectable. We thank Sandstead and Prasad for noting this possibility

TABLE 1
Phytate-to-zinc molar ratios of participants at baseline (week 2) and at follow-up (week 8)[1]

Measure	RG group				WG group					
	Baseline	Follow-up	Δ RG	*P*	Baseline	Follow-up	Δ WG	*P*	Δ WG − Δ RG	*P*
Phytate, μmol	768.3 ± 22.0	976.8 ± 29.2	208.5 ± 26.8	0.0032	778.2 ± 18.6	3719.8 ± 77.3	2941.6 ± 77.3	<0.0001	2733.1 ± 52.1	<0.0001
Zinc, μmol	203.6 ± 4.7	219.8 ± 6.5	16.3 ± 4.7	0.0022	207.5 ± 5.4	263.2 ± 5.8	55.7 ± 3.4	<0.0001	39.4 ± 4.3	<0.0001
Phytate:zinc	3.8 ± 0.1	4.5 ± 0.1	0.7 ± 0.1	<0.0001	3.8 ± 0.1	14.2 ± 0.1	10.4 ± 0.1	<0.0001	9.7 ± 0.1	<0.0001

[1] Values are means ± SEMs; $n = 40$ in the RG group and $n = 41$ in the WG group. There were no differences between groups at baseline. *P* values were obtained by using ANCOVA controlling for baseline values, BMI, age, and sex. RG, refined grain; WG, whole grain; Δ, change.