Cost-effectiveness studies are warranted and can be informed only by data from prospective, randomized trials that show safety and efficacy of the antibiotic envelope, which WRAP-IT has provided.

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Vitamin D Supplementation and Prevention of Type 2 Diabetes

TO THE EDITOR: In the randomized, placebo-controlled Vitamin D and Type 2 Diabetes (D2d) trial involving persons at risk for type 2 diabetes, Pittas et al. (Aug. 8 issue)[1] found that vitamin D_3 supplementation at a dose of 4000 IU per day did not result in a significantly lower risk of diabetes than placebo. Investigators emphasized that the trial was planned not only for participants with vitamin D insufficiency, given ethical considerations. Although the mean baseline vitamin D levels are well balanced between the trial groups and above insufficiency limits, more than 20% of the participants in the placebo group had a vitamin D level of less than 20 ng per milliliter. Furthermore, 43 participants (3.6% of the group) had a vitamin D level of less than 12 ng per milliliter, which is currently considered vitamin D deficiency.[2] Vitamin D has crucial roles not only in bone health and calcium metabolism but also in muscle health. Observational studies have shown an association between vitamin D deficiency and muscle weakness, hypertension, or cancer.[3-5] We have ethical concerns about this trial, given that a substantial number of participants had a low vitamin D level at entrance to the trial.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the trial by Pittas et al. of vitamin D supplementation in a cohort of adults with prediabetes, the mean serum 25-hydroxyvitamin D level at baseline was 28.0 ng per milliliter (approximately 70 nmol per liter), which National Institutes of Health (NIH) guidelines consider to be adequate for bone and overall health.[1] Only 103 participants (4.3%) had serum 25-hydroxyvitamin D levels that are associated with vitamin D deficiency, according to NIH guidelines (<12 ng per milliliter, or 30 nmol per liter).[1] Vitamin D deficiency is prevalent globally, particularly in cohorts in which there are persons with elevated rates of obesity and increased diabetes risk.[2] In the current trial, post hoc analysis of data from participants with baseline serum 25-hydroxyvitamin D levels of less than 12 ng per

milliliter showed greater benefits of vitamin D supplementation (hazard ratio, 0.38; 95% confidence interval, 0.18 to 0.80), a finding consistent with those of previous meta-analyses.[3] Furthermore, participants met criteria for prediabetes at baseline, when evidence of beta-cell dysfunction may already be apparent. Future studies should determine whether vitamin D supplementation is more effective at earlier stages of type 2 diabetes, before beta-cell dysfunction, and in persons with baseline vitamin D deficiency.

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Dr. Hewison reports receiving advisory and consultancy fees from Internis Pharmaceuticals. Dr. Gittoes reports receiving advisory and consultancy fees from Consilient Health. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The work of Pittas et al. shows that supplementation with vitamin D does not prevent diabetes. However, the mean baseline 25-hydroxyvitamin D level was 28.0 ng per milliliter. A significant difference between the vitamin D group and the placebo group was found in the post hoc analysis of data from participants with a level of less than 12 ng per milliliter (hazard ratio, 0.38). Why was that level not studied in the primary analysis? The conclusion of the work should be that vitamin D does not prevent diabetes in participants who have vitamin D sufficiency. The risk was 62% lower with vitamin D supplementation than with placebo among participants with insufficient levels of less than 12 ng per milliliter.

The same problem was present in the Vitamin D and Omega-3 Trial (VITAL),[1] in which vitamin D supplementation in nondeficient people did not prevent cancer or major cardiovascular events. In contrast, the meta-analysis by Martineau et al.[2] showed that daily or weekly administration of vitamin D prevented respiratory infections in the subgroup of participants who had a level of less than 25 nmol per liter, or 10 ng per milliliter (odds ratio, 0.30). I wonder why the authors of different trials continue to conclude that vitamin D supplementation does not prevent pathologies, when the intervention is studied in populations not lacking this vitamin.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Aktaş and Öztürk Aktaş raise concerns about the enrollment of participants with low vitamin D levels. All participants were encouraged to meet the National Academy of Medicine Recommended Dietary Allowance for vitamin D (600 or 800 IU per day, depending on age), which is the intake that meets the needs of 97.5% of the population.[1,2] For practical reasons, the trial design allowed participants to take up to 1000 IU per day of vitamin D on their own from all supplemental sources and did not limit vitamin D intake from food sources. To respect the principle of equipoise in relation to the primary hypothesis and ensure the generalizability of results, and in accordance with guidelines that do not recommend screening to assess vitamin D status in the general healthy population,[1-3] the investigators remained agnostic to the blood 25-hydroxyvitamin D level throughout the trial.[4] Therefore, our trial was designed and conducted to maintain equipoise while ensuring participant

safety, as confirmed by the data and safety monitoring board and the institutional research board at each of the 22 collaborating clinical sites.

Hassan-Smith et al. suggest that vitamin D supplementation may be of benefit if started earlier in the natural history of type 2 diabetes. Despite its theoretical appeal, testing for an effect of early supplementation presents multiple challenges. For example, the risk of disease progression is expected to be very low; therefore, a very large and long trial would be needed to test the hypothesis. Furthermore, because there are no data to predict the rate of progression to diabetes from normal glucose tolerance, population size and length of follow-up would be unpredictable, creating logistical issues (e.g., participant and investigator fatigue, funding insecurity, and evolving clinical practices) that would compromise trial integrity. For these reasons, in the D2d trial, we recruited a population at high risk for the development of diabetes.[4]

We agree with Mansur as well as with Hassan-Smith et al. that the high percentage of participants with adequate levels of vitamin D at baseline may have prevented detection of a significant effect in the entire cohort. We also agree that vitamin D supplementation may be of benefit among people at risk for diabetes and low vitamin D status, as suggested (but not proven) by the post hoc analysis that showed a 62% lower incidence of diabetes with vitamin D supplementation than with placebo among the small group of participants with a baseline serum 25-hydroxyvitamin D level of less than 12 ng per milliliter (30 nmol per liter).

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Liraglutide in Children and Teens with Type 2 Diabetes

TO THE EDITOR: Although it is widely accepted that glucagon-like peptide-1 (GLP-1) receptor agonists do not cause hypoglycemia,[1] the recent Evaluation of Liraglutide in Pediatrics with Diabetes (Ellipse) trial conducted by Tamborlane et al. (Aug. 15 issue)[2] appears to call this statement into question. The higher incidence of hypoglycemia in the liraglutide group cannot be explained by a higher proportion of participants using basal insulin at baseline; the absolute difference is too small to explain the observed effect. However, there could be an imbalance in the proportion of patients who started taking insulin during the trial. Such a difference in proportion might affect not only the difference in the incidence of hypoglycemia but also the difference in glycated hemoglobin levels. Furthermore, hypoglycemia has been described after gastric bypass, which suggests that GLP-1 is a major cause.[3] Even though the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial did not show a positive correlation between liraglutide use and the incidence of hypoglycemia, the results might have been confounded by a discrepancy in the use of hypoglycemic medications between the groups.[4]

Therefore, to better understand the role of liraglutide in the development of hypoglycemia, it would be helpful if the authors provided data