Of course, we agree with Falk et al that breastfeeding is a major contributor to the immunologic health of infants, even when provided in limited amounts, and that this is a confounding variable. Nevertheless, exclusive formula feeding in this population would shorten the time that infants receive the formula, limit the range and total time of observation, and raise ethical concerns. Because the primary goal of this trial was to assess safety and tolerance in this population of infants attending day care, a design was considered that maximized the number of infants and length of follow up.

The children were included in the study on the basis of their parents’ willingness to participate in the trial after being approached by the research team. Although still far from ideal, breastfeeding rates and length of breastfeeding in the United States have increased. Given that the longest possible length of follow-up of infants consuming study formulas is essential to reasonably assess their safety and potential health effects, a compromise in design was reached to allow the entry of infants who were already in the process of weaning from breastfeeding (ie, had started taking formula) before being approached for participation. Breastfeeding ≥3 times/d was a study exclusion criterion. For obvious ethical reasons, the study did not discourage the amount or the frequency of breastfeeding, which was determined entirely by the parents. This design allowed infants in the process of weaning to participate, thus increasing our recruitment rate, allowing for a longer duration of follow-up during the weaning period and beyond, and resulting in observations that were actually closer to a “real-life situation” for most of the infants.

Careful randomization yielded homogeneous groups relative to all baseline anthropometric and demographic characteristics. There were differences between the groups in the percentage of infants being breastfed at the time of randomization: 23% in the high-supplement group, 28% in the low-supplement group, and 15% in the placebo group. These differences were not statistically significant. However, we also analyzed the potential for breastfeeding as a confounder in several other ways.

First, we assessed in each study group the average number of times that infants who were still being breastfed were being put to the breast at the time of enrollment: 2.2, 2.7, and 2.2 times for the high-supplement, low-supplement, and placebo groups, respectively. Second, we analyzed in each group the average number of days of continued breastfeeding (duration of weaning) during study participation: 56.2, 53.3, and 49.5 d for the high-supplement, low-supplement, and placebo groups, respectively. Finally, we analyzed the average actual number of times per day that each infant in each group was being put to the breast while participating in the study, until they weaned completely to formula: 1.8 (range: 1.5–2.2), 2.2 (1.0–2.6), and 1.8 (1.0–2.1) times/d for the high-supplement, low-supplement, and placebo groups, respectively. None of these differences were significant.

In total, the infants studied were at least partially breastfed for a grand total of 1070 subject-days, or only 4.3% of the total 24,830 subject-days of follow-up. Although, ultimately, the true effect of breastfeeding cannot be ascertained, the effect on the outcomes observed could be reasonably considered minimal if at all contributory to any differences in outcomes.

With regard to colic and irritability, Falk et al are correct that definitions of colic vary, as does the age at which infants can be diagnosed as having colic. The purpose of the inclusion of “colic or irritability” in the weekly questionnaire was to identify—as perceived and reported by the parents—any potential and apparent abdominal discomfort not attributable to other changes in the child’s routine. The ultimate reason for this was to identify any potential gastrointestinal intolerances (in conjunction with the other questions related to upper and lower gastrointestinal symptoms). Given the age span of the group in the study, we preferred to use the term “colic or irritability” to better describe the responses given by the parents to the standardized questionnaire. This is how the results and conclusions are reported.

Regarding antibiotic use, although a 1-d difference in antibiotic use per 100 subject-days may not appear to some to be “clinically significant,” for a child in their first 2 y (730 d) of life, this equates to 7 d of antibiotic use or one standard course of antibiotic treatment for common illnesses requiring antimicrobials. Although this is obviously an extrapolation of the results, a decrease of one course of antibiotic treatment in a child receiving a formula containing probiotics in their first 2 y of life is not only clinically significant and relevant but is of potentially great epidemiologic effect, particularly in our current environment of indiscriminate antibiotic prescription and growing antibiotic resistance.

This is the most detailed and carefully controlled study yet to follow infants consuming a probiotic-supplemented formula for an extended period of time and to document safety and tolerance. The purpose of this single study was not to recommend changes across the board in standard clinical practice but to add to the growing body of evidence of safety and potential beneficial effects of specific agents for their use as probiotics in infant nutrition.

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Vitamin E from supplements has good bioavailability

Dear Sir:

The results of a study published in the January 2004 issue of the Journal suggest that synthetic vitamin E in capsules is less bioavailable than is synthetic vitamin E in fortified cereal (1). As the manager of VERIS, a nonprofit information service on vitamin E and other antioxidants, I had the opportunity to review the results of numerous studies on vitamin E for >15 y. Several of these studies have shown benefits of supplemental vitamin E in amounts higher than are regularly consumed in the diet. The results have been somewhat variable, however, most likely due to differences in the dosages and forms of the vitamin E supplements evaluated. For example, research suggests that the bioavailability of natural-source vitamin E is approximately twice that of synthetic vitamin E (2–4).

Although it is recommended that vitamin E supplements be taken with a meal containing fat (because dietary fat generally promotes vitamin E absorption), no fat was provided with the vitamin E supplements in the study by Leonard et al. In addition, the physical form of the vitamin E added to the cereal differed from the vitamin E capsules used in the study. In contrast with the results of this study,
the results of other published studies have shown a high bioavailability of vitamin E from capsules when consumed with a meal providing adequate fat (2, 5).

Fortification of foods with vitamin E is of course a means of significantly increasing vitamin E intake, and the results of the study by Leonard et al suggest that formulation characteristics can affect the absorption of fat-soluble nutrients. Unfortunately, the study does not provide a meaningful comparison of the bioavailability of vitamin E from fortified cereal and that from capsules, because no fat was consumed with the vitamin E supplements. Further research is needed to provide a valid comparison of the bioavailability of vitamin E from fortified cereal and that from supplements consumed with fat.

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REFERENCES

Reply to S Landvik

Dear Sir:

Landvik states that “results [of vitamin E studies] have been somewhat variable, ... most likely due to differences in the dosages and forms of the vitamin E supplements evaluated.” We concur that the outcomes of vitamin E supplementation studies have been variable, but the question is why. Studies of patients with fat malabsorption have shown that vitamin E absorption requires normal digestive processes involved in the absorption of dietary fats (1). However, the amounts and forms of fat required for optimal vitamin E absorption are unknown, and the causes of the variability in responses to supplements are also unknown. The purpose of our study was not to compare the bioavailability of vitamin E consumed with different amounts or kinds of dietary fat, but to design a study to evaluate the bioavailability of vitamin E in commonly consumed sources of the vitamin, namely, supplements and fortified breakfast cereal (2). Indeed, we anticipated that fortified breakfast cereal might not be an ideal vitamin E source because of its low fat content; therefore, one arm of our study included cereal that was intentionally upfraportified with vitamin E (eg, 400 IU per serving).

In an effort to make our results applicable to typical consumers, we considered that many persons take vitamins as part of their definition of a healthy lifestyle and thus take vitamins with breakfast or in the morning while they remain fasting. Thus, vitamin and mineral supplements, including vitamin E, are commonly consumed on an empty stomach in the morning with juice, tea, coffee, or nonfat milk. On the basis of these observations, the question we wanted to answer was, Is there a difference in the bioavailability of vitamin E when consumed as part of a low-fat breakfast cereal compared with that of a supplement consumed with a nonfat drink? Landvik also states that “it is recommended that vitamin E supplements be taken with a meal containing fat.” Two studies in humans have shown that plasma vitamin E increases to a greater extent when vitamin E supplements are taken with fat-containing foods (3, 4). Our study showed that vitamin E supplements are not effectively absorbed if they are taken on an empty stomach with a glass of nonfat milk (2). Therefore, we believe that our data support the advice that vitamin E supplements should not be taken alone, but rather should be consumed with food, perhaps foods containing higher amounts of fat in an effort to improve absorption.

Landvik claims that “the physical form of the vitamin E added to the cereal differed from the vitamin E capsules.” In point of fact, the same deuterium-labeled vitamin E (d9-all-rac-α-tocopheryl acetate) was added to the cereal as was in the capsule. The study cereal was fortified in a manner identical to the commercially available cereal (Total; General Mills Inc, Minneapolis, MN) and was prepared by the same manufacturer so that the results of the study would be applicable to cereal available for purchase by average consumers. The vitamin E used was dissolved in the commercially used emulsion (Hoffmann-La Roche, Nutley, NJ), sprayed on the cereal, and then dried. The emulsion applied to the cereal was not included in the encapsulated vitamin E, but neither is it in commercially encapsulated vitamin E supplements. The differences in vitamin E absorption when the pill was consumed along with cereal suggest that the emulsion on the surface of the cereal does not increase vitamin E absorption from the supplement. Moreover, Roxborough et al (5) also observed a large degree of variability in subjects who consumed deuterium-labeled vitamin E with toast for breakfast. Thus, our findings concerning the lack of consistency in vitamin E absorption when the supplement is consumed with a low-fat meal are not unique.

From our results, we conclude that consumers wishing to increase their vitamin E intakes would benefit from eating their vitamin E supplement after a fat-containing meal, eating a vitamin E–fortified food such as breakfast cereal, or a combination of both. Food fortification with vitamin E appears to optimize vitamin E bioavailability from a low-fat diet, because we showed that the breakfast, which contained <5% fat (consisting of vitamin E–fortified cereal plus fat-free milk), unexpectedly increased vitamin E bioavailability. These findings are significant because fortified breakfast cereals are a major source of vitamin E in the American diet (6, 7). Further efforts to educate consumers regarding the consumption of vitamin E through fortified foods or supplements should be considered.

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