Dear Editor:

We thank Dr. Brown et al. for the comments offered in “Communication of Randomized Controlled Trial Results Must Match the Study Focus” and the opportunity to reiterate our remarks in the Discussion section of our original paper: “Secondary analyses suggest that weight status at baseline was an effect modifier of TG change during follow-up and of the MetS at the end of the study” and that “The results of both the ITT and secondary analyses indicate the need for more research in efficacy trials focused on the effect of SSB intake reduction on MetS risks and the possible differential effect according to initial weight status” (1).

We agree with the authors of the Letter to the Editor about their concern of an accurate report of results of a randomized clinical trial. It is recognized that secondary analyses within a randomized clinical trial are an important part of such types of studies; however, sometimes they can be overinterpreted (2). The credibility of secondary analyses is improved if an adequate statistical approach is used (statistical test of interaction assessing whether a different treatment effect exists between subgroups, as we did in our study), biologic plausibility exists (as there is for the interactions we tested in our study), and results are warily presented and interpreted (as we did in our study) (3). We disagree with the authors of the Letter to the Editor that the focus of our article revolves around findings related to a secondary analysis. In our article, we clearly described and stated the lack of effect in the intention-to-treat analysis throughout the Results and Discussion sections. We are clearly presenting the effect size, its variability, and statistical significance of each one of the outcomes studied, thus, not hiding anything from the intention-to-treat analysis. In addition, we clearly pointed out the results of the secondary analyses; we do not state that results from these analyses are conclusive and we state that more research is needed.

The presentation of a secondary analysis is somewhat common and, as the articles we cited noted, can be performed when handled appropriately. Eminent journals, such as The Journal of Nutrition, The New England Journal of Medicine, and Pediatrics, allow use of secondary results. Here, we will mention 2 articles by a major figure on this same topic. The first article, appearing in Pediatrics, presents a randomized controlled trial in which Ludwig’s article notes that the primary outcome was not met but that baseline BMI was a significant effect modifier (4). Second, in a trial in a more recent article in The New England Journal of Medicine, the same authors noted that the 2-y core results were not significant; however, they noted that the first year of the intervention produced significant results (5). Again, these results are described in the article and are mentioned in the abstract and the study conclusion as secondary results.

We follow the same standard as that noted in the article in The New England Journal of Medicine and in the other articles we have cited. We have been careful to separate primary and secondary analyses, but in the publications mentioned the important secondary results were highlighted in the articles, in the journal press releases, and so on. There are other examples of articles in recognized peer-reviewed journals and on several topics, such as those by Jakiric et al. (6) and Stein et al. (7).

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References

Lowering of Large Bowel Butyrate Levels in Healthy Populations Is Unlikely to Be Beneficial

Dear Editor:

We read, with interest, the recent paper by Ferrario et al. (1). In it the authors describe a study that examined the effects of a probiotic supplement on a number of fecal biomarkers, one of which was butyrate, in a group of healthy volunteers. This SCFA is an important end product of large bowel fiber fermentation and is attracting considerable attention for its potential to promote visceral function and protect against serious large bowel disease in the long term, e.g., colorectal cancer. The authors have cited our paper (2) in which we reported the wide variation in fecal butyrate levels that exists in humans. However, what was not pointed out from our study was that the butyrate levels of most individuals were increased through consumption of resistant starch and that for those individuals within the highest quartile of entry levels, the levels generally fell in response to the treatment.

Ferrario et al., the probiotic treatment increased butyrate levels when entry levels were lowest (but in only 6 individuals) and decreased levels at higher entry levels (the majority of the participants). Meaningful comparisons with our study are confounded by their report of ~10-fold higher stool SCFA levels than we and most others find. Furthermore, the method for SCFA analysis is not provided in the supplementary material as indicated in the text. A reliable picture of butyrate concentrations would enable an understanding of whether the 2 studies have a common tipping point regarding when levels begin to drop in response to treatments.

Ferrario et al. suggest that a lowering (“rebalancing”) of stool butyrate concentration is a response to protect the host. They cite some examples where butyrate may be seen as a potential contributor to adverse physiologic conditions. Although the possibility for butyrate to contribute to such conditions cannot be excluded, there is a large and growing body of evidence that indicates the benefits of butyrate. In contrast to the cited papers suggesting that butyrate might exacerbate irritable bowel syndrome, Vanhoutvin et al. (3) showed that butyrate enemas raised the pain threshold in human volunteers, suggesting a positive role in management of this condition. In this context we have also recently reported (4) that high red meat consumption increased the levels of pro-oncogenic microRNA in rectal biopsies, and increased butyrate supply (through consumption of a butyrylated-resistant starch) opposed this adverse effect in humans. Furthermore, butyrate insufficiency may contribute to the development of inflammatory conditions because the acid has been shown to induce the differentiation of colonic T regulatory lymphocytes, which suppress inflammatory and allergic responses (5). These and other findings not cited by Ferrario et al. are consistent with the observations that fecal butyrate levels are generally high in low-risk populations and vice versa [e.g., Segal et al. (6) and O’Keefe et al. (7)]. Hence, their suggestion that lowering of fecal butyrate in a majority of individuals is beneficial should be viewed with caution.

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