indicate that the in vitro methodology used by Jin et al. (9) was too short and not vigorous enough to be a good predictor of the human digestion process. Gastric digestion of a solid meal in humans is variable but is often much longer than 1 h. The median half gastric emptying time for a solid meal was recently reported to be 127 min (10). A longer, more vigorous in vitro simulated digestion procedure as used by other researchers (11, 12) might improve the equilibration between native iron and extrinsic tags. The in vitro technique as used by Jin et al. (9) has only been used to evaluate the extrinsic tag technique in beans, and we would suggest that further studies should be made with a greater variety of meals, including meals used in the human validation experiments, in which we are sure that the extrinsic tag predicts the absorption of native food iron. Evidence of poor equilibration of extrinsic and native iron in the in vitro technique of Jin et al. (9) would indicate that this method does not adequately simulate gastric digestion in humans. Evidence of good equilibration would indicate that the problem could be specifically with colored beans.

We consider the results of Jin et al. (9) to be a particularity of the simulated digestion method used. The reason is that human iron absorption studies with red and black beans have reported good agreement between the absorption of intrinsically labeled native absorption studies with red and black beans have reported good agreement in absorption and utilization between extrinsic and intrinsic tags. The in vitro technique of Jin et al. (9) would indicate that this method does not adequately simulate gastric digestion in humans. Evidence of good equilibration would indicate that the problem could be specifically with colored beans.

Glahn stated that close agreement in humans between absorption of intrinsically labeled native iron and an extrinsically labeled iron tag is not an indication of close equilibration. We would disagree with this. We believe that good agreement in absorption and utilization between extrinsic and intrinsic tags indicates that the tags have behaved in a similar way at all stages of the digestion and absorption process, including similar equilibration in a common iron pool. We thus conclude that, apart from the few exceptions discussed above, there is strong evidence that the extrinsic tag technique performs as it was designed to do, and usefully estimates the absorption of native food iron from individual foods and composite meals.

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References

Communication of Randomized Controlled Trial Results Must Match the Study Focus

Dear Editor:

We read with interest the recent article by Hernández-Cordero et al. (1) that adds another data point to a growing body of randomized, controlled evidence demonstrating that sugar-sweetened–beverage-reduction initiatives attempted, to date, do not have large or reliable effects on obesity (2). We express concern about how this article may be interpreted, however, because the article’s title and focus revolves around findings related to a secondary analysis of the primary outcome and a tertiary analysis of a tertiary outcome. By focusing the title and abstract on secondary and tertiary analyses, the article may distract readers from the statistically nonsignificant primary findings in favor of statistically significant exploratory findings.

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Letters to the Editor 1027
The choice of which outcomes to analyze and in what ways can influence type I error rates (i.e., the probability of obtaining a statistically significant finding when a true difference does not exist). To put the issue into perspective in this particular case, the authors prespecify the following outcomes in the trial registry (NCT01245010): a single primary outcome of blood TGs and at least 13 secondary outcomes including body weight, fasting insulin, fasting glucose, homeostasis model assessment, HDL cholesterol, LDL cholesterol, total cholesterol, systolic and diastolic blood pressures, waist circumference, glycated hemoglobin, hydration status (assumed to mean serum and urine osmolality), and 24 h-dietary recalls (each of which includes numerous data points to analyze). However, insulin and homeostasis model assessment are not mentioned in the published article, but the authors add metabolic syndrome, BMI, and physical activity to their measurements listed in the article that were not in the trial registry document. The authors declare a primary intent-to-treat analysis and a secondary analysis stratified by overweight and obese status in the article, but not in the trial registry. Therefore, there are at least 12 outcomes planned or added that were compared in at least 2 ways for a total of 24 declared comparisons.

With a type I error rate set to 0.05 across all comparisons, and assuming all comparisons were independent, one would expect to see an average of 1.2 significant comparisons across all similar studies if there were no true differences between treatments. Indeed, they reported 1 nominally significant result from their secondary analysis of the primary outcome (TGs stratified by weight status; \( P = 0.02 \)), which would become nominally insignificant if corrected for multiple comparisons (the threshold for nominal significance at \( \alpha = 0.05 \) when Bonferroni corrected for 24 comparisons is \( 0.05/24 = 0.002 \)).

The Bonferroni correction mentioned previously, however, may not be correct because it is unclear how many comparisons were actually calculated. The article also includes a tertiary analysis of a tertiary outcome that was not registered with clinicaltrials.gov. The use of change-in-physical-activity as a postrandomization covariate, which has been discouraged (3), in the logistic regression for metabolic syndrome prevalence implies that more comparisons were conducted in producing this publication than we are aware [so-called “researcher degrees of freedom” (4)]. To make the concern more clear, consider that conducting 59 comparisons were actually calculated. The article also includes 12 comparisons. Therefore, there are at least 12 outcomes planned or added that were compared in at least 2 ways for a total of 24 declared comparisons.

Exploratory data analyses can lead to interesting hypotheses and important investigative avenues, but even the strongest proponents of exploratory data analysis suggest such analyses “should be described as such, and conveyed with a strong note of caution” (6). We commend the authors for what appears to be a well-conducted study and note that we would not have been able to critique these finer points of reporting and analysis had the authors not reported their results as thoroughly as they have. However, this study should have been appropriately titled and communicated to recognize the design and main findings as planned, rather than using “specific reporting strategies... to highlight that the experimental treatment is beneficial, despite a statistically nonsignificant difference for the primary outcome” (7).

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Reply to Brown et al.

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 any information 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 note, 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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Letters to the Editor 1029