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Response to "Metabolic Improvement with Fructose Restriction: Is It the Fructose or the Weight Loss?"

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TO THE EDITOR: Khan and Sievenpiper submit three separate criticisms. We proffer the following responses.

1. They point out that our study design did not incorporate an external control group. We addressed this in the article. Numerous studies document that dietary sugar intake by recall is notoriously underestimated (1). Had we included an external control group, we could not have matched their baseline sugar intake, thus providing flawed results. The only way to correctly match intake would be to directly monitor all home, school, and after-school behaviors for months. Instead, we incorporated five separate internal controls: (a) a weight-maintaining paradigm; (b) DXA scanning (no change in body fat); (c) repeated measures analysis of covariance adjusted for the small (0.9 kg) weight change; (d) sensitivity analysis, examining those who did not lose weight; and (e) investigator blinding throughout data collection. While lack of an external control group does not permit "categorical proof," our conclusions as stated in the article are supported.
2. They state the children exhibited "dramatic weight loss." Again, this was previously addressed in the article. (a) The children lost 0.9 kg (95% CI −1.3, −0.6); given a mean baseline weight of 93 kg (0.96%), this is hardly dramatic. (b) The weight loss occurred within the first 4 days, then returned toward baseline. This is not consistent with persistent caloric deficit. (c) DXA scanning showed the weight loss occurred within the fat-free mass compartment (water and/or muscle), the loss of either of which would not contribute to improved metabolic health. Indeed, the temporal pattern of weight change and the 5 mmHg reduction of diastolic BP argues for water loss, as hyperinsulinemia causes sodium retention (2). We dismiss this criticism.
3. They argue that pre-post t-testing is the "hallmark of an uncontrolled design," referencing Bland and Altman (3). This would be true if we were comparing pre-post testing between two treatment groups; [sic] "when there is a substantial change from baseline with *both* treatments, both tests against baseline will be significant and we can say nothing about the difference between groups." However, we are not reporting difference between two treatments. This argument does not apply to our paper. Furthermore, under "Better Approach" in the Bland/Altman paper: "'Not significant' does not mean that there is no difference; it means that there is insufficient evidence to conclude that a difference exists. This is one of the reasons for the movement to report differences in randomized controlled trials with CIs rather than *P* values, or at least in addition to them." That's exactly why we reported mean change, CI, and *P* values in our tables.

Khan and Sievenpiper state our study cannot overturn the results of their numerous systematic reviews and meta-analyses. However, these analyses suffer from flaws of their own, including publication bias; between-study heterogeneity; artifact of inadequate GI absorption in fructose-for-glucose exchange studies; random-effects modeling giving more weight to smaller studies; and, importantly, lack of subclassification of industry-sponsored vs. independent studies (4). In fact, the one meta-analysis that accounts for these concerns supports our conclusion (5). We are unmoved by their arguments.

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