Reviewer's report

Title: Intake of non-nutritive sweeteners is associated with an unhealthy lifestyle. A cross-sectional study in subjects with morbid obesity

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Reviewer: John Peters

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This paper reports on a cross sectional study of NNS usage in association with dietary and physical activity patterns in a convenience sample of morbidly obese individuals who attended a hospital clinic. The premise for the study is the relative dearth of data on lifestyle behaviors vs. just body weight as well as investigating these factors in morbidly obese individuals. The authors conclude that NNS consumption is associated with an unhealthy lifestyle.

There are a number of design and methodological issues which considerably weaken the authors interpretation and conclusions.

1. The design eliminated NNS non-users, which would have been a useful comparative group to look at dietary and exercise patterns in morbidly obese individuals...in the absence of NNS usage. Does NNS usage define a particular behavioral phenotype of morbidly obese individuals...or, do they all share similar poor dietary and exercise patterns?

2. The study population is poorly characterized for factors important to the main premise...e.g., NNS consumption was quantified in units of 100 ml for beverages and 2 NNS tablets for use in coffee/tea. Were other sources of NNS besides beverages included or not? What kinds of NNS were included...e.g., aspartame, sucralose, etc. etc. Were sugar alcohols included? Were stevia and other naturally-derived sweeteners included? They reported that intake was "clustered" into groups of roughly equal intake, but the actual intake amounts were not reported...what were actual intakes for low, medium, high and very high intakes? Were these quartiles? Other? Also, body weights were not provided, only BMI. It would be useful to know what actual body size was in these individuals. Likewise, no information is given about what specific morbid obesity, co-morbidities were the reason that patients were referred to their clinic.

3. The NNS intakes reported are puzzling. The authors report a median intake of 3.3 units of NNS beverage per day, yet the median intakes of carbonated, non-carbonated, plus coffee and tea use were 0.3, 0.1 and zero. Where was the rest of the intake coming from to equal 3.3 units/d? Since the values reported were median vs. mean intakes, it is hard to understand
how 3.3 is the median, while the median intake for the component contributors was so much less.

4. The uncertainty about the sources of NNS intake makes it difficult to interpret the correlations presented in Table 3. The authors made a point about the correlation of carbonated beverage NNS intake with sugar intake, while non carbonated beverage NNS intake was not related. This is perplexing as both sources of intake were quite low (0.1-0.3 units/d). The authors did not comment on this.

5. There is little discussion of the associations of NNS and other nutrient intakes in Table 3. The associations with specific vitamins seemed rather random as the correlations were not consistent across NNS intake sources. The consistent correlation with salt intake may simply be that salt intake increases thirst and people will drink more of whatever beverage to address this. There was no presentation of data indicating how intake of other beverages and total fluid intake was correlated with salt intake.

6. Similar to number 5, there was no discussion of the correlations with blood measures. Are the significant correlations important? Are they a signal that if you measure too many things there are bound to be some random correlations?

7. Twenty percent of the study population was diabetic and there was essentially no discussion of how the results looked in this important sub group. Likewise, the population was mostly female. How did that affect results, especially for things like heavy physical activity?

8. The authors selectively chose citations to support points about potential negative effects of NNS but did not give attention to literature reporting different findings. For example, they cite reference 42 as one of several showing adverse effects of NNS on the microbiome, yet the reference actually shows NNS associated with increasing beneficial bacterial species in the gut using a pig model, i.e., NNS were acting like a beneficial prebiotic.

9. The authors do not provide any insight into why others have seen that NNS users report higher dietary quality than non NNS users. They suggest this is due to the dietary quality studies being done in non obese individuals. The population studies used actually were representative samples and included, for example in the USA, two-thirds of the population overweight or obese.

10. The authors draw some conclusions for which they have little supportive data. For example, on page 7, line 10, they say that the association of NNS use with sugar intake "supports the hypothesis that NNS encourage sugar cravings and dependence by altered metabolism and
processing of sweet taste in the brain". Yet, there was no significant correlation with non-carbonated NNS beverage intake. So, is it the carbonation that is driving the association?

11. Given the absence of a morbidly obese group that does not use NNS as a comparison group, it is difficult to even say that the dietary, exercise and other associations observed are uniquely related to NNS consumption and not characteristics of morbidly obese individuals in general. This should be pointed out in the section on limitations.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
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No

**Are the conclusions drawn adequately supported by the data shown?**
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No

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I received funding from the American Beverage Association to conduct a one year RCT evaluating the effects of water vs. NNS beverages on weight loss and weight maintenance in 300 subjects across two sites in the USA (Denver and Philadelphia). This study was published in the journal Obesity in 2016.

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