Author’s response to reviews

Title: Feasibility and Acceptability of a Beverage Intervention for Hispanic Adults: A Protocol for a Pilot Randomized Controlled Trial

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Version: 1 Date: 09 Jan 2018

Author’s response to reviews:

Associate Editor: Thank you for submitting your protocol to Nutrition Journal. As both reviewers point out, the topic of study is novel and timely, and is therefore very interesting. However, there are also several areas of concern that would need to be fully addressed before we can further consider the manuscript and re-review. In addition to the reviewer's comments, please find my own below:

1. Please add the abstract to the manuscript file.
   a. The abstract has been added to the manuscript file.

2. The format of your article will have to be somewhat altered to meet the submission criteria for Nutrition Journal. Please refer to https://nutritionj.biomedcentral.com/submission-guidelines/preparing-your-manuscript/study-protocol.
   a. Thank you for the note - changes were made according to the submission guidelines provided.
3. The protocol reads as if the study will still need to be conducted, but clinicaltrials.gov suggests recruitment has been completed in August 2017. This information should be added to the protocol.

   a. The manuscript has been updated to reflect that the study recruitment was completed as of August 2017. This includes relevant changes in word tense. Notably, at the time of the manuscript submission, the intervention was still underway with study assessments and randomization in progress. This is noted to provide clarity for the reader.

4. Thank you for adding the SPIRIT checklist. I am somewhat surprised by the relatively high number of "N/As", and I think that some several of these items can be addressed in the protocol (particularly in the ethics & dissemination and appendices section). If you feel you cannot incorporate them, please explain the rationale for not being able to report on this in your reply to the reviewers and myself.

   a. Thank you for this very important comment. The SPIRIT checklist and manuscript has been updated to address the N/As, particularly the ethics and dissemination section. Please note, less robust exploratory outcomes (e.g., biological samples) have also been included in this resubmitted draft of the manuscript to provider greater adherence to SPIRIT guidelines. This includes our IRB approved consent documents, in both English and Spanish. We also include our plan to disseminate our research findings. Please note, the page numbers for the SPIRIT checklist are for the manuscript submission with no track changes.

5. There are some discrepancies between the submitted manuscript and the registration on clinicaltrials.gov (for example, history of cancer as exclusion criterion), which need to be resolved before we can consider publication - both should convey exactly same information. Did the protocol change? If so, please add the version number and version date to the protocol.

   a. Thank you for bringing this to our attention. This was an error on the author’s part – the information on the registration on clinicaltrials.gov is correct. We did not exclude any individuals from participation due to history of cancer. This was confirmed in a review of our recruitment screening forms as well.

6. If you decide to keep the flowchart in addition to the SPIRIT figure, it would be helpful to indicate the group sizes and add inclusion and exclusion criteria, following the Consort statement as much as possible at this stage.

   a. Thank you for the suggestion. At the time of submission, not all participants were randomized to the study. Given our primary outcomes are recruitment and retention, we would like to include this information in the outcomes manuscript. Therefore, we will remove the Figure 1 flowchart from this manuscript.
7. For the green tea preparation, tea bags will be steeped in water for 3-5 minutes. Does duration not affect the concentration and thereby potential biological effects?
   a. Preliminary work by our team indicates that 3-5 minutes for the steeping of green tea led to optimal release of GT catechins/polyphenols as assessed in our preliminary sample bioanalysis. While preparing the beverages, our research staff was diligent in following the beverage intervention preparation protocol to ensure consistency weekly and reduce the potential for influencing biological effects.

8. Please describe the findings of the validation studies of the global PA questionnaire rather than saying the GPAQ was validated. A validation study can have been conducted and show that a tool is not valid for use in a specific setting.
   a. This information has been added.

9. Please expand on your power calculation. What are your margins of error (0.14?) and what proportion do you expect?
   a. Thank you for the note. We have clarified this as follows:
   “…that are no wider than 0.28 (margin of error = 0.14), conservatively assuming a base proportion of 0.5, which maximizes the standard error.”

10. Please remove the first sentence of the section on our data management plan. Even though your funding agency doesn't require one, Good Clinical Practice requires you to have a plan in place, and this needs to be presented in this section.
   a. Thank you for this comment. The first sentence has been removed and we expanded the section to include our efforts to follow Good Clinical Practice Guidelines for data management.

Reviewer #1: This is a study design paper for a pilot beverage intervention among Hispanic adults. Obesity prevalence is higher in Hispanics than other race/ethnicity groups in the US. General American populations consume large proportion of energy from beverages. There is a strong evidence that consumption of sugar sweetened beverages (SSB) is associated with increased risk of obesity, type 2 diabetes, hypertension and other obesity-related complications. Therefore, reduction in SSB intake has been proposed as a potential approach to reduce obesity. This study targeted in beverage intervention and Hispanic population which is quite interesting. My specific comments are:

1. The authors missed several important publications in SSB/beverage interventions. For example, Ruyter et al., 2012 NEJM; Ebbeling et al., 2012 NEJM; Hedrick et al., 2017 AJCN.
a. Thank you for the note. Our intention was not to ignore these studies, but rather focus on SSB/beverage interventions in adults specifically. Per your suggestion, we have added the above references, in addition to a few others, to acknowledge the work that has been done in children, as well as adults.

2. Page 4, line 34, reference 18. The study, although analyzing the data from the PREMIER trial, it an observational analysis by nature. Authors seems misunderstand the design of this study and mislead the reader.

a. Thank you for the comment. When we addressed the reviewer’s comments above, the PREMIER trial was removed as a reference in this section.

3. It is well-known that FFQ is not a sensitive dietary assessment tool for short term dietary changes. 24-hour dietary recall is a better choice.

a. Given the pilot nature of the study and budget constraints, we were unable to complete repeat 24-hr recalls. Further, repeat recalls over a few weeks may not adequately capture habitual beverage patterns. This will be addressed in our outcomes manuscript.

4. It will be very helpful if authors can provide a table to compare the nutrients contents and other bioactive components across the green tea, Mediterranean Lemonade, and the control beverage.

a. Thank you for this suggestion. We added a table including relevant nutrient information (estimated using the Nutrition Data System for Research 2017 nutritional analysis software) and included the key bioactive components for green tea (EGCG) and Mediterranean lemonade (d-limonene) based on our prior chemical analysis.

5. After randomization, can study participants to switch to different beverage groups (cross over)?

a. Participants were only able to switch to an alternative beverage if they experienced a significant adverse event related to the originally assigned beverage. This information can be found under “Participant-Reported Tolerance or Toxicities” on pages 16-17.

6. Are there any strategies to prevent the beverage being consumed by other family numbers?

a. There was no objective measurement in place to monitor beverages being consumed by family members or others. However, during weekly check-ins, research staff asked each participant how the previous week had been for consumption and reviewed a tracking sheet to open up the conversation to routinely extract this information. Based on these interactions and weekly log
sheets, we did not find this to be an issue; participants seemed to follow instructions to consume the beverage themselves, not share with others and return any unconsumed beverage to the clinic.

7. **Statistical analysis plan:** It is little confusing how and why mixed-effect model will be applied. For example, it seems to be used to "compare each of these outcomes post-intervention", but also account for "longitudinal nature of the data”. So will only post-intervention outcomes be compared or both baseline and post-intervention measures, or the changes between baseline and post-intervention?

   a. The changes between baseline and post will be compared. We have clarified this as follows:

   Mixed models will be used to compare arms in each of these outcomes’ change from baseline. We will include fixed effects of intervention arm, time and their interaction to allow for different patterns of change between the arms, as well as a random participant effect to account for the longitudinal nature of the data. Baseline values of the outcomes will be included in the dependent variable vector. The changes from baseline, and the differences between arms in change from baseline will be estimated using contrasts from the mixed models.

8. **For those who do not complete the 8-week intervention, what is the plan for data imputation?**

   a. No explicit imputation is carried out. Maximum likelihood based models, however, use an implicit form of imputation, which is why they are more robust to missing data than using a t-test, for example. We have added the following:

   “Mixed models yield unbiased estimates for data that are missing completely at random (when missingness does not depend on any observed or unobserved data) and missing at random (when missingness may depend on observed data, such as the baseline value of the outcomes), as these models perform an implicit imputation”.

9. **Does the primary analysis follow the intent-to-treatment method?**

   a. Following the CONSORT 2010’s recommendation, we did not use the term intention-to-treat, as this term is widely misused. However, we did add this clarification: “Data from all patients who are randomized will be analyzed in the arm that they were randomized to.”

Reviewer #2: This study describes in a comprehensive manner an intervention study aimed at reducing obesity prevalence among the Hispanic population living in the US by changing habits of beverage consumption. The authors describe all study phases, potential biases, control of all the aspects related to the recruitment and intervention, and the expected impact. The study is moreover well-written and synthesized, though the style could be tailored to fit it to a scientific publication. Few additional comments to improve the current version of the manuscript are:
Introduction:

1. Is the data on obesity prevalence among Hispanics related to the US? This could be made clear. However, the obesity epidemic is also affecting many other populations. While the authors justify that the Hispanic population is more prone to consume SSB, other populations could also benefit from an intervention based on restricting consumption of these beverages. This could be mentioned as well.

   a. Thank you for the suggestions. The data on obesity prevalence among Hispanics were specific to the U.S. We have clarified this in the manuscript. We agree, SSB consumption is an issue affecting other populations as well. To acknowledge this information, we have broadened our introduction to include more information on other racial/ethnic subgroups in regards to SSB consumption, along with additional citations.

2. What is Mediterranean lemonade made of? While this is described later on, it is unclear from the beginning whether this is a certainly a healthy beverage.

   a. Mediterranean lemonade is made by blending two full lemons (with peels) and water. We have added more information (and relevant citations) to the introduction to support Mediterranean lemonade as a potential healthy alternative to SSBs.

Methods

1. With the defined selection criteria, some potential obese subject’s won’t be recruited. Could the authors justify the convenience of some of these criteria, such as for example diabetes? Would be these conditions (criteria) self-reported by the participants or a physician?

   a. Our exclusion criteria reflect our interest in having a more homogeneous group given our small sample size for this pilot work. Further, we were interested in exploring the effect of beverages on cardiometabolic biomarkers (although not statistically powered to do so) and therefor excluded individuals with abnormal values that were clinical diagnostic of diabetes. History of diabetes was self-reported, however, at baseline participants completed a blood draw to assess cardiometabolic biomarkers which included HbA1c. In the occurrence that an individual had at an HbA1c ≥6.5%, he or she was referred to a physician and was no longer eligible to participate in the study. Other ineligibility criteria (e.g. currently being treated for psychological issues, history of liver disease, uncontrolled blood pressure, etc.) were self-reported without objective verification given the pilot nature of this work.

2. What data source (i.e. food composition database) was used to estimate energy and nutrient intake?
a. Our food composition database is from the 2009 National United States Department of Agriculture (USDA) Nutrient Data Bank. This information has been added to the manuscript.

3. The authors do not report how they are going to measure the biochemical parameters (glucose, cholesterol, hs-CRP, etc.). For this purpose, sampling of biological samples would be needed before and after the intervention. This is, however, not sufficiently described.

   a. Thank you for this comment. On page 18, we note that fasting blood samples were collected at baseline and 8-weeks (before and after intervention) by a trained phlebotomist. We also provide greater detail for the reader that the laboratory tests for the cardiometabolic measures were performed by an independent clinical lab blinded to the study outcomes.

4. Besides, apart from these parameters, is weight change over the intervention study and follow-up an additional endpoint?

   a. Body weight was measured at baseline and 8-weeks to ensure we can examine changes overtime given weight loss/gain could influence our study findings. These data will be included in the outcomes manuscript.

5. What is meant with mixed models under the presence of missing values? Would the authors carry out imputation of these values?

   a. We have added the following in hopes that it addresses the reviewer’s concerns, but note that the field of statistical analysis in the presence of missing data can be quite technical. We have added an additional reference also.

   “Mixed models yield unbiased estimates for data that are missing completely at random (when missingness does not depend on any observed or unobserved data) and missing at random (when missingness may depend on observed data, such as the baseline value of the outcomes), as these models perform an implicit imputation”.

   “Mixed models yield unbiased estimates for data that are missing completely at random (when missingness does not depend on any observed or unobserved data) and missing at random (when missingness may depend on observed data, such as the baseline value of the outcomes), as these models perform an implicit imputation”.

   “Mixed models yield unbiased estimates for data that are missing completely at random (when missingness does not depend on any observed or unobserved data) and missing at random (when missingness may depend on observed data, such as the baseline value of the outcomes), as these models perform an implicit imputation”.