Reviewer's report

Title: Effectiveness of a low-fructose and/or low-sucrose diet in decreasing insulin resistance. DISFRUTE STUDY: study protocol for a randomized controlled trial

Version: 0 Date: 22 Mar 2017

Reviewer: Rob Edinburgh

Reviewer's report:

The trials paper aims to investigate whether a low fructose diet (both 'free fructose' and fructose associated with sucrose consumption) over an intervention period of 24 weeks, with a subsequent follow-up of a further 24 weeks, improves insulin resistance (HOMA2-IR), lipid profile and measures associated with body composition, relative to a 'standard' diet. The research addresses a very interesting topic and applies this to a real-world setting (clinical practice). However modifications to the manuscript are required to provide greater clarity about key points, in particular the specific composition and energy content of the prescribed diets (and justification for this), as well as the two groups of participants.

Abstract:

Major Comments

At times the abstract had a lack of clarity about key aspects of the study design. For example, were the two diets energy matched? You provided a range for the age and BMI of participants, but are these/will these be matched across the two groups? Other statistics (e.g. mean and standard deviation) could be provided here to define your population more clearly to the reader. At times the text could also be more concise, especially in your discussion of the parameters being measured.

Specific Comments

Pg 2 L2. What is meant by controversial? You could be more specific with this opening sentence (i.e. 'equivocal findings in the literature' or similar).

Pg 2 L7-8. Consider the structure of the Methods section. For example, the last two sentences of this section could be combined, as similar measures were collected after 24 and 48 weeks.
Pg 2 L33-34. It is not clear whether the specified energy deficit of 30% or 40% was consistent across both the low fructose and 'standard diet'. This is essential given your outcomes. A clearer description of the two diets would be useful for the reader here.

Introduction:

Major Comments

The introduction could be made more concise (e.g. paragraphs 2 and 3), as the text is sometimes unclear. Many comments made in these sections were also not supported by citations and this should be addressed. The discussion of previous literature could also be more specific, as at times key details were missing (as outlined below). As a consequence the justification for the proposed research was not as strong as it could have been.

Specific Comments

Pg 3 L1. Consider a different word for 'abnormal' (given current trends for obesity and T2D).

Pg 3 L7. More clarity is needed here - perhaps 'the role of fructose in the development of insulin resistance'. Also consider stating the specific tissue(s) to which you are referring.

Pg 3 L18-20. Citations are needed to support these points. Under what specific circumstances or populations is this apparent?

Pg 3 L24. It is not clear what is meant by 'high energy levels'. Consider re-wording.

Pg 3 L49. Is plausible the correct word? Stating a direction (i.e. a positive relationship) would be more useful here.

Pg 3 L53-60. It is not clear whether the sucrose rich beverages were part of a diet designed to induce weight loss? What population was this study completed with?
Pag 4 L5. Does overall insulin sensitivity mean 'whole-body'? Also given that you state the time-frame as being a determining factor in mediating the effect of fructose ingestion on insulin sensitivity, this could be introduced earlier to help the reader follow your argument.

Pag 4 L22-27. More detail would be useful here. It is important to distinguish whether the diets were designed for weight loss (i.e. also inducing an energy deficit).

Pag 4 L29-31. Citation needed.

Pag 4 L33-35. Justification is needed for why the quality of trials in the review would be considered 'poor' (consider an alternative wording here also i.e. 'had some limitations'). Further detail is also needed in places to support this (i.e. how short was the 'short follow-up period', how many participants were included?)

Pag 4 L43-44. Although an attempt has been made to justify the proposed project based on the comments from the systematic review, this could be clearer. For example in L44 the manuscript states 'to test the effects', but what effects does this refer to? Also, you mention the importance of investigating fructose ingestion 'under real-world conditions' but have not highlighted this as an issue with previous literature earlier in the text.

Methods:

Major Comments

You discuss some elements of the two diets on pg 7, but key details are missing. This is the most important aspect of this project and as such this should be amended. For example, you mention that the 'low-fructose diet was designed on the basis of standard diets' but does this refer to each participant's habitual diet? Were the two diets (i.e. groups) energy matched? How did you ensure that the diets were adhered to? Some information was provided about 'counselling/reinforcement', but there was no mention of actual adherence.

Moreover (Pg 8 L 24-25) you mention that the prescribed diet is 30 to 40% less than each participant's energy requirements. This raises several points;
a) How confident are you that you calculated each person's energy requirements accurately? (i.e. basal metabolic rate and physical activity energy expenditure)

b) Why is there variation from 30 to 40%? (Did some participants have a greater diet-induced energy deficit than others?)

c) Why did you choose this energy deficit specifically (i.e. how does this relate to your study outcomes)?

The structure of the methods section could also be modified to be clearer for the reader. For example, consider first discussing the overall design (i.e. the time frame/brief overview of the different groups and outcomes measures) and then the more specific details (i.e. diet composition). Some elements (i.e. assessment of diet and physical activity) were introduced in the recruitment section and then more detail was provided subsequently. Some comments on pg 7 L39-42 (discussion of time frame of study measures) could be made in the study overview at the beginning of the methods.

Specific Comments

Pg 5 L16-24. Although you provided some information regarding a sample size estimation, it is somewhat unclear as to how this was reached. What is meant by a cut-off value for IR? How did you estimate a weight loss of 4 kg and was this expected to be consistent across both groups? Further clarity is required.

Pg 5 L8. Why did you aim to include only 40% men?

Pg 5 L31. Your inclusion criteria, includes both a large age and BMI range. Do you expect the diet to be equally effective across all individuals in this range? Do you have any measures to ensure that the groups were matched?

Pg 5 L36. What is meant by 'severe cardiovascular disease'? The paragraph regarding exclusion criteria could be made more concise for the reader.
The two groups of participants were sourced from different parts of the island and you justify this based on the concept of 'contamination bias'. However, it is unclear as to how this would specifically influence the findings of your work (i.e. adherence?). Further detail is needed here, as it is an important point.

Over what time frame were participants asked about their physical activity habits? On pg 8, you mention that physical activity is recorded for the previous 6 months. Can an accurate recall of physical activity be made over this time period?

Define TSH and T4 and consider providing some background information here.

Why was hip circumference not measured? Waist: Hip ratio would provide some useful information in this instance, and would have been an easy measure to collect.

Presumably for some participants they will purchase their own foods and for others this will be done by someone else? Do you think that this may influence diet adherence?

You mention that for some more active participants they are asked to maintain their habitual activity and for more sedentary participants, they are asked to increase their activity to 150 minutes per week. Therefore for some participants the intervention will just be a nutritional one, and for others a combination of diet and physical activity. Were the groups matched for active versus less active participants?

Well done for standardising the message given to different physicians/nurses working on the project and for comments relating to standardising equipment (i.e. pg 7 L-5). This is important given the multi-centre approach used.

How confident are you that a 4-day food diary is sufficient to accurately capture fructose intake? You briefly discuss this on pg11, but only mention the difficulty in obtaining the nutritional information (i.e. fructose content) of foodstuffs.
Do you any have plan to account for the possibility of under-reporting in food diaries? This is proposed to be particularly problematic in overweight/obese populations, and for foodstuffs that have a negative health image (i.e. high sugar foods). Both are relevant in this scenario. Macdiarmid, J., & Blundell, J. (1998). Nutrition Research Reviews, 11(02), 231-253.

Moreover, do you have a reference that a 4-day food diary is sufficient to measure fructose intake, even if under-reporting is not apparent? This would be useful to include.

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Please indicate how interesting you found the manuscript:

An article of importance in its field

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