BMJ - Decision on
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**Body:**

04-Oct-2018

Dear Dr. Ludwig,

Manuscript ID BMJ.2018.046192.R1 entitled "Effects of a Low-Carbohydrate Diet on Energy Expenditure During Weight Loss Maintenance: A Randomized Feeding Study"

Thank you for sending us your revised paper. I sent it back to our statistician, who has some additional comments. The main one is that he feels quite strongly about the matter of the PP analysis. I am sorry if I steered you in the wrong direction. When there is a difference of opinion on these matters, we defer to our statisticians, for reasons I am sure you can understand.

I am hopeful that you will be willing to submit a revised version of the paper that takes Dr. Cole's comments into consideration. Do let me know if you have any questions.

Best,
Elizabeth Loder
eloder@bmj.com

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Reviewer: 1

Comments:
The paper describes a carefully designed, executed and described clinical trial testing the effect of dietary composition on total energy expenditure following weight loss. I have some comments on the study design, analysis, presentation and interpretation.

1.      The Abstract has a focus on the per protocol analysis results that I mentioned and deprecated in my original notes on the paper. I presume the authors include them because the between-group contrasts are larger than for ITT, though not more significant. For me the ITT results should be the gold standard, and it weakens the impact of the paper to have to rely in the Abstract on PP results. Which leads to my second point.

2.      The results in the Abstract are presented as the contrasts HI - MED and HI - LO. But the research question involves the effect of CHO% on TEE, and as such the linear trend in TEE across the three CHO% groups would be both more relevant and more parsimonious than the group contrasts. The authors point out that they include the comparison of Hi vs LO in Table 3, and state that it is algebraically equivalent to the linear trend. This would be true if the HI vs LO contrast were fitted using all the data, but not if it involved only the HI and LO groups. This needs to be confirmed.

3.      The authors do not give the linear trend any emphasis, but I should like to see the results presented as this trend. Normally it is hard to describe what is effectively an interaction in a clear way, but the concept is already mentioned in

the sample size calculation: "a predicted effect of +50 kcal/d per 10% decrease in the contribution of dietary carbohydrate to total energy intake". The advantage of this approach is that the research question is tested with a single degree of freedom rather than two, which can be presented as an effect and 95% CI in the form above, and from Table 3 it is highly significant even for ITT.

4.     Omitting PP from the Abstract would save some words, allowing the Results to be expanded. The sentence "Main outcomes were pre-specified" is redundant, and would be better replaced with a list of other outcomes, including ghrelin and insulin secretion which appear later in the Abstract.

5.     Some more minor points. The four time points in the study are labelled BSL, PWL, MID and END (Figure 1). However PWL looks (for me) like pre-weight-loss, which is confusing. I'd like to suggest instead labelling them PRE, START, MID and END, which should be less ambiguous.

6.     Where the Abstract refers to "+91 kcal/d greater" it would be better without the '+'.

7.     Page 9 What does "a physical activity factor of 1.5" mean?

8.     Page 12 line 22 lists the design factors of study site, cohort and enrolment wave. However the Supplementary Methods also refer to obesity and Hispanic ethnicity – the two lists should match.

9.     Page 12 line 35 refers to weeks 10 and 20, which would be more consistent as MID and END.

10.    Page 12 last line mentions 'hormone levels' without saying which they are.

11.    Page 13 describes the log transformation of outcomes for analysis and back-transformation for reporting. It's a well-kept secret that the back-transformation is both unnecessary and over-complicated – see my paper https://doi.org/10.1136/bmj.j3683. Multiplying the natural-log-transformed results by 100 they can be viewed as percentages – see for example the footnote to eTable 6 which laboriously concludes that -0.0101 on the log scale is "almost exactly -1%", and my paper shows it is a generalisable conclusion.

12.    Which version of SAS?

13.    Page 15 "at START, body weight did not differ across groups". Was this also true of weight loss?

14.    Give n = 120 (PP) as a percentage of ITT (n = 164 or 162).

15.    Page 16 line 8 "all pre-specified covariates". Might be worth listing them here.

16.    Line 24 "the … group effect retained statistical significance". Better to avoid mentioning significance at all.

17.    Page 17 top line implies that dietary intake was not measured in the ITT non-PP participants, which I'm sure was not the case.

18.    Page 18 the first 3 sentences need moving to the Methods.

19.     The precision of numbers in the tables needs attention. My guidelines on this are here: https://adc.bmj.com/content/100/7/608. In Table 1 % appears inconsistently in the body of the table. I doubt that CHO is accurate to 0.1g and suggest rounding. Food quotient would be better than FQ, and why the extraneous 3 columns? If the values are averages per 2000 kcal, why are the kcal 2001?

20.     Table 2 would be easier to read with two significant digits for the percentages, i.e. rounded for ≥10% and one decimal place for <10%. The same applies to eTable 4.

21.     Table 3, give full names rather than acronyms for the outcome measures. Replace the final column with results for the linear trend (effect and 95% CI), I suggest per 10% change in CHO.

22.     In eTable 7 fat would be better rounded.

23.     eFigure 1 can be simplified by combining the ITT and PP graphs and highlighting (using colour or linetype) the individuals who are ITT but not PP. It would also make it easier to see if such individuals were a biased sample.

24.     Figure 4 and eFigures 2-3 deserve more informative labels on the x-axis.

Tim Cole

Additional Questions:
Please enter your name: Tim Cole

Job Title: professor of medical statistics

Institution: UCL Great Ormond Street Institute of Child Health

Reimbursement for attending a symposium?: Yes

A fee for speaking?: No

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Funds for research?: No

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