Reviewer's report

Title: A randomized, controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial)

Version: 1 Date: 24 Nov 2016

Reviewer: Eiko Fried

Reviewer's report:

I'm glad to hear the authors found the prior comments useful. They went through considerable efforts to address my comments and concerns appropriately, and have succeeded to improve the quality of the paper considerably. The paper now stands out as carefully worded and preliminary study into the efficacy of dietary improvements for depressed adults.

Two concerns remain. First, given that the authors expanded the introduction and cite numerous studies and meta analysis that are consistent with their study, I am unconvinced that describing this finding as "highly novel" in the conclusion of the abstract is warranted.

My second concern pertains to this point.

My prior comment:

"Browsing the results, I see 8 p-values between 5% and 1% - I very much doubt any of these will survive multiple testing. If I understand the authors correctly, they conducted a fairly large number of tests, which calls for correcting p-values. Bonferroni may be too strict due to the correlated nature of many variables, but the authors need to apply some form of correction to counter the possibility that some of the observed effects are due to false positive findings."

Authors' response:

"Give that this is the first study to directly test the hypothesis that dietary improvement might lead to improvements in mental health, and should thus be considered preliminary, we always cited confidence intervals, but made no adjustments for multiple comparisons because they can result in a higher type II rate (falsely accepting the null hypothesis), reduced power, and increased likelihood of missing important findings (Rothman, K. J. (1990). "No adjustments are needed for multiple comparisons." Epidemiology 1: 43-46.). We have now emphasised the preliminary nature of our study and softened our conclusions to reflect this."
I strongly disagree with this argument, which was inconsistent with best statistical practices in 1990, and also best statistical practices in 2016. Not controlling for multiple testing to avoid higher rates of type II error is similar to setting the alpha level to .50 instead of 0.05. Because a study is exploratory does also not mean we need lower bars for considering something as evidence against the null hypothesis. Freedman, Cockburn & Simcoe (2015) have shown that the cumulative prevalence of irreproducible preclinical research exceeds 50%, resulting in approximately US$28,000,000,000 (US $28B)/year spent on preclinical research that is not reproducible—in the United States alone. While we have to manage type II errors, it is not appropriate to argue that we do not have to manage type I errors. Given the important nature of BMC Medicine, and the fact that this is a clinical trial for a highly prevalent disorder, I have to insist that this issue is addressed.

I see two options.

First, the authors control for multiple testing (according to any statistical textbook). Bonferroni is conservative, maybe the False Discovery Rate would be more appropriate (Benjami and Hochberg, 1995). If they want, the authors can report both p-values (controlled and uncontrolled) in the paper.

Second, the authors clearly state in the methods that they will not correct for multiple testing which can lead to false positive findings, but that they believe the benefits outweigh the costs.

To improve the quality of transparency of the review process, I always sign my reviews. Best of luck with the manuscript!

Eiko Fried, University of Amsterdam

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

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?  
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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