Reviewer's report

Title: Multi-omic signature of body weight change: results from a population-based cohort study

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Reviewer: Hector Keun

Reviewer's report:

The authors present a very substantial study of the correlation between body weight gain over 7 years and molecular measurements in blood at follow up in a population-based study. There is no doubt to me that this study will be of wide interest and that the data/findings should be in the public domain. The analyses presented are more complicated than conventional association studies due to the generation of modules which I accept may be necessary to de-correlate the data and to reduce false-discovery limitations. I don't know how easy it would be to regenerate the module eigenvalues (or estimate them for new data) with the the representation of the modules presented, this would make it difficult for others to independently verify the results. Access to the methodology for the NMR is also an issue for this, but at least the Metabolon approach/gene expression measurements would be commercially accessible. Ultimately the interpretations presented do seem to depend on the presumption of associations between individual metabolites and so I will focus on these.

Please number your comments and divide them into

- Major Compulsory Revisions

1. I presume (otherwise the authors would have included it) that no baseline metabolomic measurements at all were available to look at prediction of weight gain, stability of the signatures etc, but it would be useful if the authors explicitly state this in the text.

2. I was interested to observe clear discrepancies between the associations between metabolites(NMR) vs metabolites(Metabolon) and body weight gain. We have previously published data to show (in a vanishingly small study by comparison) that weight gain in breast cancer patients receiving chemotherapy was associated with lactate and alanine levels as detected by NMR, and one of the authors' previous NMR papers indicates an association between these metabolites and future glucose intolerance. The metabolon data seem to confirm this association to metabolic disease, but the NMR measurements do not. Can the authors please comment further (and provide more data where informative)
specifically about the discrepancies between the NMR and Metabolon data for the same metabolites? Is there an obvious explanation for the relatively low correlation between lactate (NMR) and lactate (Metabolon)? If so, which are the most meaningful measurements? I don't think these data in the Appendix are properly discussed in the text.

2. I am surprised that stratification by sex does not make a huge difference to the association to body weight gain in the module analysis. My impression is that there are big systematic differences between men and women in e.g. the lipid profile and that we might often observed statistical interactions (effect modification). Could the authors please present as supplementary data regressions for the individual metabolites stratified by gender and comment appropriately on the findings?

3. Could they also perhaps present in supplementary the individual metabolite regression coefficients with body weight gain as the dependent variable? It is my impression that this may be easier to compare to other analyses where it might be expressed as fraction of deltaBW explained by unit change in metabolites.

4. Also I am not so familiar with field, and am not clear how signatures associated with weight gain are likely to differ from those associated with gain in BMI, central adiposity, etc or indeed basal BMI etc – can the authors please indicate in some way the overlap or similarity in these profiles (At the single metabolite level).

5. Finally, I would like to have some indication of the magnitude of the corrections for day to day variation as indicated in the text

- Minor Essential Revisions

The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

1. "...these include the positive association of #BW with the tryptophane metabolites Hydroxytryptophane…" - "tryptophan" is the IUPAC name

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests