Reviewer’s report

Title: Lifestyle precision medicine: the next generation in type 2 diabetes prevention?

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Reviewer: Jordi Merino

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Review of:

P.M. Mutie et al. “Lifestyle precision medicine: the next generation in type 2 diabetes prevention?”

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In this manuscript, PM. Mutie and colleagues conducted an extended and up-to-date revision of the literature on the translation of novel emerging findings from high-throughput technologies into better lifestyle therapeutic strategies for diabetes prevention in the next future. Mutie et al described evidence of differential response to lifestyle interventions based on particular genetic and other omics layers of information. Authors offered an evidence-based view that there are many ways in which lifestyle interventions could be optimized to better prevent and stratify individuals based on the amount of information offered by novel technologies. However, they also make the point that many challenges on analytical aspects, lack of lifestyle trials for precision medicine and innovative aspects to better capture lifestyle exposures are needed before translating findings.

The topic, as pointed out by the authors, is of high interest given preliminary evidence that genetic variation and relevant downstream biological alterations can be a valuable source of information to better prevent T2D and stratify individuals based on individual's unique characteristics. The identification of candidate biological factors interacting with dietary intake, physical activity or a lifestyle intervention on intermediate glycemic traits or diabetes incidence holds the promise to be translated into personalized lifestyle strategies to curb the epidemics of diabetes and related comorbidities.

This paper has the following strengths:

1. Focus on an interesting and relevant question in contemporary medicine
2. Potential translational implications
3. Comprehensive and accurate revision including different layers of omics information
4. Authors are leaders in the field

However, different suggestions and minor comments have emerged from the revision and a number of considerations have to be made before taking the extend of this revision as a valid evidence.

1. Why the authors did not use a standard method to score studies included in the revision? As far as I know there are validated scoring methods such as MOOSE for prospective studies or JADAD for clinical trials. Also, authors should provide a broad score quality information when reporting evidence.

2. Is there any robust evidence from RCT regarding diet and T2D prevention worth to mention? What about RCT for physical activity? Is the key for T2D precision medicine implementation to randomize individuals to a broad lifestyle interventions and gather evidence from these studies? Please comment on that.

3. Connected with the above, the authors should provide detailed information about reference 81 given that is a matter of debate and quite relevant for the revision.

4. The authors reported relevant information from different layers of omics techniques interacting with lifestyle factors. I am wondering whether evidence about the interplay between lifestyle characteristics and multi-omics integration studies on T2D is available (i.e., studies integrating lifestyle, metabolomics and genomics). If not, please discuss why this is not available and whether we should conduct this kind of studies.

5. Why the authors did not focus on other examples of relevant T2D biological candidates like insulin resistance linking lifestyle and T2D risk? They only provided information about TBC1D1, but other genetic or metabolomics insights on other relevant pathways would be of interest.

6. The authors should consider socioeconomic status as a potential factor accentuating complex diseases genetic susceptibility such as obesity or T2D.

Minor comments:

1. Introduction section should include appropriate references (i.e., page 3 lines 34, 50 and 5, or page 4 lines 45, 51 and 55).

2. Findings from FGF21 and sweet and alcohol preference are likely to be robust and relevant. How can this information would be translated into tailored therapeutic interventions? Please, discuss briefly about potential lifestyle approaches.

3. I do not understand why the authors consistently showed the following; "unlike drugs, lifestyle prevention has widespread effects". I do not think individuals have a uniform drug response, especially in T2D.
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.

Unable to assess

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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Please indicate the quality of language in the manuscript:

Acceptable

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