

Dear Dr. Timothy Koch,

We would like to thank you for your thoughtful review. In this document, we would like to indicate the changes made and inquire further about some suggestions presented by the reviewer.

Review:

This manuscript has been carefully examined. My questions are summarized below: 1) The authors state that they are utilizing the 2009 PRISMA strategy. The manuscript is however not organized along these guidelines. The authors should provide a reference for the 2009 PRISMA strategy. The manuscript needs to be reorganized (for example, the Abstract does not follow a Structured Summary; the Results does not contain “Results of Individual Studies” or “Synthesis of Results”; and the present Discussion needs to be reorganized with information moved to Results and a new discussion can follow the guidelines of the 2009 PRISMA strategy. 2) What is the AIM of this study? In the Abstract the authors state “responses in models of healthy and non-insulin dependent”. Models would represent animal studies. This manuscript however summarizes studies performed in animal studies and in humans with diabetes mellitus. 3) The Introduction continues this uncertainty. The authors have not clearly summarized data from animal studies and then data from human studies in order to form the basis for the AIM of this manuscript. For example: reference 10 is not an in vitro study but is rather an in vivo animal study (that does not induce caloric restriction as stated by the authors), while in Introduction, paragraph 1 when summarizing potential factors for understanding the increasing incidence of type 2 diabetes, we see no mention about obesity. The first sentence in the Introduction itself discusses the “incidence of type 2 diabetes” and provides 3 references. Reference 1 refers to prevalence; Reference 3 is not the correct reference but I believe that the reference intended is in the same issue of the Annals of Internal Medicine and it describes prevalence. The authors need to be more cautious in their terminology when describing this disease, and they need to recheck their references. 4) Figure 5 is not necessary as this manuscript is not designed to study potential mechanisms. 5) Table 1 can be summarized in the Methods section and eliminated. 6) Table 3 can be summarized in the Results section and eliminated.

1. Thank you for this suggestion. The content of the results and discussion sections has been altered to better suit the PRISMA guidelines. Results of Individual Studies is shown in Tables 1,2,3 and the synthesis of results is observed in the evidence appraisal (GRADE, tables 4 and 5) and the effectiveness paragraph (now under results).
2. The aim has been re-worded in the abstract to be more clear about the study population, with animal models and human trials being separated.
3. Description of findings in reference 10 have been reworded to be more accurate of its findings. Obesity has been added to the introduction. References have been reviewed and fixed as necessary.
4. Figure 5 has been removed.
5. Table 1 has been removed in favour of a brief description of methodology.
6. We feel that table 3 is an important table as it summarizes included studies, many of which are referred to throughout the paper. Additionally, as per PRISMA, we feel that it is important to present the findings of the individual studies.

In addition, all formatting requirements outlined in the revised Microsoft Word document have been adhered to. This includes: defining abbreviations in tables, adding article highlights at the end of the document, adding sentences to describe sections that previously only had tables or figures, adding a fax number for contact, and modifying word fonts.