Author’s response to reviews

Title: Title: A systematic review on associations between dietary factors and obesity-related biomarkers - numerous limitations seem to impede current research on childhood obesity

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Author’s response to reviews:

We would like to thank all reviewers for their valuable comments on our manuscript. We have revised the manuscript according to the comments. All changes in the manuscript are highlighted in red.

Reviewer #1:

Background

Comment 1: line 56 please quote percentages of obesity prevalence in children and adolescents worldwide.

Response: We changed this accordingly (see lines 59-62).

Comment 2: I agree there are limitations in the studies when physical activity is not included in the calculations as it affects insulin resistance. Potential biomarkers to consider/control for also includes growth hormone and sex hormones such as FH, FSH, LH and testosterone. Family history and identified genes are also confounding factors to be considered.

Response: We agree with the reviewer that several hormones and genes could also be relevant confounding factors and thus added some of the suggested confounders in our statement on confounding factors in the discussion section (lines 319-321).

Comment 3: Analysis also needs to separate out those who have reached puberty and those who have not.

Response: We also agree with the reviewer that pubertal stage is an important confounding factor and (if available) we also have extracted this information from the articles. However, as only half
of all articles provided this information, we decided to name the missing adjustment for pubertal stage as one possible reason for the inconclusive findings (compare lines 278-283). In addition, we have added “pubertal stage” to our statement on confounding factors in the paragraph “Action points for the future” (lines 319-321).

Comment 4: General comments: Frankly I do not see why preventing childhood obesity should be so complicated and invasive when basic interventions such as healthy diet and physical activity are more practical and measured by anthropometric measurements including fat and muscle composition.

Response: As these basic interventions (healthy diet and physical activity) to prevent obesity in children and adolescents have shown limited success (see Summerbell et al. 2005; Ref 10 in the reference list of the manuscript), we think that biomarkers (invasive or non-invasive ones) might be helpful to identify early metabolic changes and thus to complement and improve existing prevention strategies. We now address this point in the background section (please see 68-70).

Reviewer #2:

The manuscript entitled A systematic review on associations...." is an interesting report in the field. However the article could be improved with the suggestios as follows:

Contage word ok

Abstract well expressed.

Introduction: No suggestions

Comment 1: Background: It is relevant how the overweight & obesity is defined. Authors should include the marker: BMI, % fat by (anthropometry, skinfold or body composition)

Response: We agree with the reviewer and have included this important information in the background section (see lines 59ff).

Comment 2: Methods: Literature research well searched with key words appropriate. Flowchart is very clear. Good proposal serum biomarkers of inflammation and cardiovascular biomarkers. Data selected expresed in Table I are properly included with inclusion & exclusion criteria. There are not collected any genetically study as example if parents or any other genetical member have been obese or overweight. No diabetes status is recorded.

Response:

1) According to the comment on genetically information: It is true that we did not include any genetic study/information in our review as gene-nutrition interactions are still poorly understood and the scope of our review was on dietary factors and obesity-related biomarkers and not genetics. However, we agree that family history of obesity could be an important confounding factor. We therefore have added “parental
obesity” as important confounding factor for future studies in the discussion section (lines 319-321).

2) According to the comment on diabetes status: As an inclusion criterion was “healthy children” (please see Table 1), we excluded studies with diabetic children from our review and thus we did not report “diabetes status”.

Table 2 is in accordance with methodology. as comment, that is a fact, the high quality score of the studies is scarce. Results & Discussion: Well structured and expressed. Of relevance is that only 19.2% of total observations showed relevance th relationship between diet and any obesity related biomarkers. Discussion is very well focused on the mistakes arisen from methodology in the studies. Also important in the shortcomings is the election of biomarkers. As suggestion for the future is to promote the inclusion of body composition analysis, and implement electronic tools in order to analyze the mean intake of different elements and trace.

Response: We agree with the reviewer that the techniques mentioned above would be very helpful in providing valid data on body composition and nutritional status of individuals. As these tools are very expensive, such techniques are commonly used in experimental studies with relatively low sample sizes. However, these tools may not be applicable to epidemiological studies with large sample sizes that are more common in public health research (and thus were in the focus of our review). We therefore think that adding these techniques (e.g., body composition analysis) to our argumentation in the discussion section distracts the reader from the main line of logic rather than adding value.

Completely accord with the actions points for the future. It is relevant the proposal of prospective longitudinal studies. Nowadays is key to define in other way the obesity state. Conclusion properly assessed.

Response: Thank you

Reviewer #3:

This literature review provides insight into a highly relevant topic that continues to perplex clinicians. As stated in the review, the association between childhood obesity and dietary patterns continues to be a strong area of interest. Although many original manuscripts have examined the role between various biomarkers in children and dietary intake, few have succeeded in providing concrete results. Although the authors of this paper were unable to find a strong association between selected childhood obesity markers and dietary patterns, they successfully described some of the shortcomings and limitations in the field. This review is well organized and easy to read. Please see my specific comments below:

Comment 1: Thank you

Title: I think the title could be truncated to maximize spacing and readability. Also, the paper seems to be more about which specific limitations may impede current research - instead of why.
Response: We revised the title of the manuscript (please see lines 1-2).

Comment 2:

Abstract: Although the conclusion portion of the abstract is indeed true, it does not accurately summarize the results from this review.

Response: We thank the reviewer for this valuable comment and changed the conclusion of the abstract to match with the results of the manuscript (please see lines 49-52)

Comment 3:

Background: Consider revising passive voice throughout article. Example: Line 63, "have been undertaken."

Response: We thank the reviewer for his comment and now use active voice throughout the article.

Comment 4:

The final two sentences of the Background section are awkwardly worded. Please revise (line 81-84) "If our findings will be in line with the former reviews, we will examine possible reasons for the inconclusive findings. Such an investigation may help to increase the effectiveness of future strategies against childhood obesity because inconclusive findings may impede strategy development" to past tense statements with less jargon.

Response: We revised the last sentences of the background section (please see lines 87-90).

Comment 5: Methods/Data Analyses: Robust study selection and appropriate measurements were identified for this review. Would help if the authors defined in the text the ages of the children/adolescents included in this review.

Response: We added the information on the age range of children included to the abstract and also to background section (see line 37; see line 87).

Comment 6:

Results: Would be helpful for authors to build out the results section a bit more (just a few sentences) to include the top biomarkers noted from their analyses. Although they do mention CRP specifically, it would be nice to see a few more of the measurements in the text with respective p-values- to match the table provided. Also- a bit more of an explanation of Figure 2 would be helpful in the results section.

Response: We expanded the results section accordingly and also added an explanation of figure 2.
Comment 7: On line 260 it would be helpful to change the subheading title, since that title was used previously.

Response: In order to clarify this issue we changed the subheading “Measurement errors” to “Measurement errors in dietary intake assessment” and “Measurement errors at the biomarker level (see line 232; see line 285).

Comment 8: The text on lines 286-288 is not easy to follow. Revise to improve clarity.

Response: We revised the sentences to clarify its meaning (see lines 311-314).

Comment 9: The subheadings make for easy reading and separate the text appropriately.

Response: Thank you

Comment 10: Conclusions: Adequately describe shortcomings in the field while emphasizing the need for additional research.

Response: Thank you