Author’s response to reviews

Title: Metabolically healthy obese and metabolic syndrome of the lean: the importance of diet quality. Analysis of MAGNETIC cohort

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Author’s response to reviews:

Dear Editor, Dear Reviewers,

We are very excited to have been given the opportunity to resubmit the revised version of our manuscript (ID: NUTJ-D-19-00228R1) entitled “Metabolically healthy obese and metabolic syndrome of the lean: the importance of diet quality. Analysis of MAGNETIC cohort” (title changed, accordingly to the reviewer’s suggestion).

We greatly appreciate the time and efforts taken by Reviewers and the Editor to review our manuscript. We have addressed all issues indicated in the review report, and believe that the revised version can meet the journal publication requirements.
Please find our responses to the Reviewer’s comments attached. The changes in the manuscript are highlighted in yellow. Also, we have attached a PDF version of our response to the reviewers' comments as one of the supplementary files, since we wanted to include a table with metabolic syndrome definitions, this was not possible to include in the box provided in the submission system.

Yours Sincerely,

Tadeusz Osadnik

Response to the Reviewer 1 Comments

Reviewer: I appreciate this invitation to review manuscript by Osadnik K. et al. entitled: "Metabolically healthy obese and metabolic syndrome of the lean. Diet quality is more important than energy load. Analysis of MAGNETIC cohort." submitted to Nutrition Journal. Osadnik K. et al. investigated the link between diet quality and metabolic syndrome (MS) in 797 young adults, regardless of their adiposity status. The diet quality was measured with data-driven dietary patterns and diet quality scores. Authors noted that in the MS group 31% individuals were of normal weight, while in the MH (Metabolically Healthy) group 27% of participants were overweight or obese. Authors found that individuals with MS were more likely to adhere to the western dietary pattern, and have a poor diet quality when compared to metabolically healthy subjects, independently of BMI and WHR. Moreover, Authors identified the non-modifiable factors independently associated with metabolic health risks, such as male gender and age. The article is well written, and study shows very interesting new findings, with possible practical implications

Response: We are very grateful for this supportive comment and appreciate all suggestions and revision recommendations. We have gone over all the points that you have raised and we believe that the applied changes have increased the scientific value of our manuscript.
Reviewer: In the title and text (line 52; lines 78 and 286- unless it is a citation of other results, then please add reference; line 328), authors mentioned few times that "diet quality is more important than energy load" or "diet composition, not energy load, plays a pivotal role..." etc.

In my opinion authors should not conclude this way, because it has not been compared in the presented study, and authors even have not discussed results of other studies comparing energy load vs. diet quality effects. Therefore authors should rewrite and reconstruct text to avoid such a comparison, and such a conclusion. It should reconstructed underlying that diet quality can be an important, independent risk factor, etc.

Response: We agree, thank you for your suggestion. We have revised the highlighted sections in the paper.

Also, we have revised discussion, providing more supporting evidence from another study (lines 3-4, 51-52, 78-79, 301-302, 368-369, 304-309)

Reviewer: In Results a high physical activity has been presented as associated with MS, and it must be explained and discussed, since it is not an expected observation.

Response: Thank you, we have added a brief commentary to the discussion (lines 338-343)

Reviewer: Line 279-281- "Based on these findings, it can be concluded that body weight management may not be a sufficient intervention in adults with metabolic abnormalities, and more specific lifestyle modifications are required.". In my opinion it is a wrong conclusion, because based on many studies weight management is an effective intervention, and in this study it was not compared to. Therefore the mentioned sentence must be reconstructed, in a way: "Based on these findings, it can be concluded that in adults with metabolic abnormalities, not only body weight management, but more specific lifestyle modifications are required" etc.

Response: We have revised this sentence accordingly, and added a brief clarification in the following sentence (lines 290-295)
Reviewer: Lines 296, because this field is already under investigation, with isocaloric meals but different compositions, also some other articles should be referenced here.

Response: More references added (line 316)

Reviewer: Limitations are missed- please provide them. In my opinion, the lack of measuring visceral tissue is the main limitation of this study

Response: We have added the limitation section, which includes the discussion on the obesity assessment (lines 351-365)

Reviewer: In line 58- "despite" is repeated two times,

Response: Removed (line 58)

Reviewer: Lines 290-292 the reference is missed

Response: Reference added (line 312)

Reviewer: Line 304-306, "Some evidence suggests that high-sugar foods (...)"- the references are missed

Response: Reference added (line 321)
Response to the Reviewer 2 Comments

Reviewer: This is a well-written manuscript, although has some limitations that need to be addressed prior to publication

Response: Thank you for your constructive comments, which have identified important areas which required improvement.

Reviewer: Title: Metabolically healthy obese and metabolic syndrome of the lean... methods and results - structure of groups didn't meet those assumptions. Authors have classified as metabolically healthy subjects individuals without MS, but approx. 27% were overweight or obese. I have a doubt if this classification is proper. Firstly, I differently understand the criteria proposed by Buscemi et al.(ref. 2) on based whose in this study classified participants (line 112). Buscemi et al. divided participants into four groups: as normal weight or overweight-obese and also classified as MH in the presence of 0-1 and MUH if≥2 metabolic disorders, so further analysis regarded to four groups. Secondly, metabolic healthy obesity is not a "healthy" phenotype, any obesity is unhealthy and if obesity is present without the conventional cardiovascular risk factors shouldn't be classified as „healthy". Increasing evidence is now pointing that MHO individuals are at a higher risk of cardiovascular disease compared to metabolically healthy non-obese individuals, though when compared with MetS these risks are lower.

Moreover, did subjects with normal weight should be classified as with MS? Thirdly, metabolic syndrome has a different definition, and in my opinion, in this study participants shouldn't be classified as subjects with MS, if they didn't meet defined MS criterias. I suggest to divide participants into four groups, and further analyze, comparing normal-weight healthy with others.

Response: Buscemi et al. introduced criteria of metabolic health that are part of metabolic syndrome (MetS) irrespective of the adiposity status, measured with BMI/waist circumference etc. Authors of the cited paper aimed at assess what is the frequency of metabolic changes associated with MetS in normal weight and overweight subjects. In the full text of the cited paper the authors clarify that “Participants were classified as MH if they had 0-1 conditions of the following: prediabetes/T2D, hypertension, hypertriglyceridemia or low HDL cholesterolmia, and hypercholesterolaemia. Participants were defined as MUH if they had at least 2 of the conditions listed above”. The authors further divided the subjects into metabolically healthy and unhealthy within each BMI category. Similar analysis in our paper would lead to subgroup analysis with less certain results regardless of eventual statistical significance.
As for now, there is no clear definition of metabolic syndrome of the lean. Similarly, there is no definition of metabolically healthy obesity (MHO) – please see the definitions for MHO we identified in the literature (please see the table in the "Response to the Reviewers" PDF file, attached as a supplementary material). Those definitions more or less are based on the exclusion of presence of other than BMI/waist circumference criteria of MetS.

We could not agree more than in the light of recent studies an individual cannot be classified as healthy in the presence of obesity. Recently we presented results of our metabolomics study at American Heart Association in Philadelphia, comparing metabolome of healthy slim patients, patients with so called MHO and obese patients with MetS. We found very little differences between MHO and MetS patients. Both of those groups had however very distinct metabolite profile from healthy slim patients (please compare: K.Osadnik et al. Hnmr Spectroscopy Reveals Only Subtle Differences Between Serum Metabolome of Metabolically Healthy Obese Subjects and Subjects With Metabolic Syndrome. Circulation 2019;140:A13796). Nonetheless the concept of MHO had to be studied to reach those conclusions. Moreover, we agree that using word “healthy” even if someone has only one abnormality is not the most appropriate term. But in this context it is rather the absence of other MetS abnormalities. We agree, it takes more than one abnormality to have “a syndrome”.

Buscemi’s paper, among other publications, underscores the importance that metabolic abnormalities specific to MetS can be present in subjects with normal weight. Of course these criteria are not the official MetS criteria approved by WHO or other organisation, because there are no established criteria of lean MetS. Our intention in applying those used by Buscemi at all. was to add another brick to the discussion about lean metabolic syndrome.

Action:

We understand and agree that due to lack of official and widely accepted definition of metabolic syndrome of the lean, using word MetS in context of lean patients might be controversial. Therefore, we have added an appropriate information in study limitations section (lines 351-354)
Reviewer: line 154: "Anthropometric measurements: height, weight, and waist circumference", but hip circumference not mentioned, and it is need to calculate Waist-Hip Ratio (WHR). On the other hand, according to WHO, waist circumference measurement is more practical and accurate in assessing abdominal fat content and health risk associated with abdominal obesity than WHR. Both NCEP and IDF use waist circumference measurements to diagnose abdominal obesity, and the authors have measurement of WC. Why adiposity is treated as "other factors" (line 153), if it is base to diagnose metabolic health?

Response: We very much appreciate this helpful comment. We have tested the model with waist circumference (WC) instead of Waist-to-Hip Ratio (WHR). In this model (with WC) after backward selection procedure WC was dropped from the model and only BMI, western dietary pattern tertiles, sex and age were retained. After including WHR (instead of WC) the above mentioned variables, as well as WHR stayed in the final model.

We suppose that the reason for this was that although both WHR and WC alone are key indices of fat distribution, the WHR to some extent naturally corrects for gender as it includes hip circumference that is also a sex-dependent factor. Therefore, we believe that WHR in the context of multivariable analysis adds some information to the model.

Action:

Thank you for your comment regarding adiposity and metabolic health. Following your suggestion, we have:

• added waist circumference to descriptive statistics and table 2 (119, 222-223, Table 2)
• anthropometric measurements were moved to section metabolic health (114-121)
• A commentary has been added to the study limitations section (354-365)

Reviewer: line 177: My suggestion is to separate family history and NK

Response: Done (lines 180, 183)

Reviewer: Results, line 246-248: How can explain high physical activity as a factor associated with MS? I didn't find in discussion
Response: Thank you, we have added a brief commentary to the discussion (lines 338-343)

Reviewer: The discussion should be improved, a few statements are obvious: line 279-281; 282-283; a part statements weren’t be the subject of this study: line 287, 291, 300.

Response: Re:279-281: We agree this may sound obvious to readers from the human nutrition field. However, we have a few clinical practitioners among the authors of this paper, and sadly, as we observe in busy clinical settings, it is not uncommon to provide the dietary advice only to overweight or obese patients, with the recommendations most often being focused on reducing the calorific load in order to facilitate weight loss. Unfortunately, very little advice is provided regarding diet quality, especially to the patients who do not raise excessive weight concerns. We believe this is an important conclusion, directed to medical care providers, rather than dieticians or nutritionists per se. Since the other reviewer suggested revising this statement, it has been now amended accordingly (lines 290-295)

Re: 282-283: This statement summaries one of the main findings, and highlights that our hypothesis has been confirmed with the use of two dietary assessment approaches: i) data-driven dietary patterns analysis, and ii) hypothesis-driven dietary index scores. We think it would be worthwhile to retain this statement (lines 296-298)

Reviewer: The description of the relationships with male gender and age could be more complete (line 311-316).

Response: A brief comment has been added to the discussion (lines 333-335)

Reviewer: Authors should be consequently use the naming: who was classified as adults with metabolic abnormalities (line 281) metabolically unhealthy individuals (line 284), with metabolic healthy risk (line 311).

Response: We have concluded that ‘adults with metabolic abnormalities’ would be the most suitable form - corrected accordingly (lines 298, 331)
Reviewer: No reference to 15.

Response: Corrected (lines 79, 314, 460)