Author’s response to reviews

Title: Dietary patterns and physical activity in the metabolically (un)healthy obese: The Dutch Lifelines Cohort Study

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Reviewer reports:

We are pleased to read that both reviewers are positive about the quality of the manuscript and the importance of the topic. Furthermore, we would like to thank both of them for the constructive feedback and suggestions to improve our manuscript. Below we will elaborate on the comments from the reviewers. We hope that we have to their satisfaction expanded the text and discussed the issues raised.
Reviewer #1: General comments:

Metabolically healthy obese (MHO) phenotype subjects constitute a fascinating group for medical research. As is concordant with the findings of this study, it seems to be more prevalent in women than men, and its prevalence decreases with age.

Specific comments:

Abstract

- Please change "modifiable factors may be contributing" to "modifiable factors may be at play."
- Please change "tirtile" to "tertile".

#1 This has been changed.

Introduction

- It should be mentioned that MHO individuals are not 'without risk' because they still present a risk for mortality, as shown by a recent meta-analysis (Zheng R, Zhou D, Zhu Y. The long-term prognosis of cardiovascular disease and all-cause mortality for metabolically healthy obesity: a systematic review and meta-analysis. J Epidemiol Community Health. 2016 Apr 28:jech-2015). These individuals are also exposed to other obesity-associated complications, such as osteoarthritis and obstructive sleep apnea.

#2 Thank you for sharing this more recently published meta-analysis. In the introduction we have mentioned that it remains controversial whether MHO is a truly healthy state due to their increased risk for CVD and T2D. The suggested meta-analysis does however show that adults with MHO do not have an increased risk for all-cause mortality. This new information has been implemented in the introduction on page 4.

- Please change "Which determinants account for the metabolic differences observed between MHO and MUO is uncertain" to "The determinants accounting for the metabolic differences observed between MHO and MUO remain uncertain".

#3 This has been changed.
Methods

- "Differences between groups were tested by t-test for continuous variables or Kruskal-Wallis test when appropriate, and Chi-Square test for categorical variables." With multiple t-tests, the likelihood of incorrectly rejecting a null hypothesis (i.e., making a Type I error) increases. Bonferroni correction should have been done to compensate for this.

#4 Thank you for pointing this out. In fact, when performing the tests we have applied the Bonferroni correction, however, did not mentioned that in the Statistics section. This has now been added in the text on page 10.

Discussion

- In the discussion of limitations, the difficulty to adequately standardize the identification of MHO individuals should be mentioned. This may render findings and/or conclusions difficult to interpret. Besides the presence of an obese state (high BMI), different methods (three insulin sensitivity indices: hyperinsulinemic-euglycemic clamp, OGTT and HOMA and two methods based on several metabolic risk factors) have been used to identify MHO individuals. The clinical relevance and feasibility of these methods should also be discussed if these findings were to be translated into clinical practice.

#5 We have elaborated on this point by adding an additional paragraph on page 22 & 23: “In the literature MHO is still defined by the different classification systems that use different methods to measure metabolic abnormalities as well as different cut-off points or set of parameters to define MetS and/or its components. This makes it difficult to compare and interpret findings of studies on MHO. We defined previously a harmonized set of criteria for MHO within an international collaborative project (BioSHaRE-EU Healthy Obesity Project) [11]. The definition is based on the most widely used criteria for MetS (NCEP ATPIII) and also strict regarding metabolic health status (i.e. according to the classification none of the metabolic disturbances may be present (except for waist circumference) and no history of CVD). A major strength of our definition for MHO is that it can be easily applied in clinical practice and it may also have a greater utility to estimate differences in risk for T2D, CVD and mortality. Future work with longitudinal data should be encouraged to examine the influence of (changes in) dietary patterns on developing adverse metabolic outcomes and more ideally to examine the effect on hard endpoints (i.e. T2D, CVD and mortality).”
- As seen in Table 1, perhaps, it could be suggested that waist circumference be excluded as a potential marker because most obese individuals have large waist circumferences; and thus this phenotype becomes non-discriminatory in the identification of MHO individuals.

#6 This is correct. Almost all obese subjects meet the criteria for enlarged waist circumference. Therefore the waist component has been excluded from the definition for MHO. We have used this definition for MHO in a previous publication (van Vliet-Ostaptchouk et al. BMC Endocr Disord. 2014 Feb 1;14:9. doi: 10.1186/1472-6823-14-9) as described in the section ‘Definition of the metabolic health phenotypes ’on page 7:

“MHO was defined according to the criteria established by the BioSHaRE-EU Healthy Obesity Project [10] this means that subjects with obesity had none of the MetS risk factors, except for WC, according to the revised NCEP ATPIII [21] (using the WHO cut-off of ≥6.1 mmol/L for impaired fasting glucose [22]), and had no previous diagnosis of CVD (defined as self-reported myocardial infarction, stroke, or vascular intervention).”

See also Additional file 1 for the detailed information of the applied criteria/definition.

- In addition, for future work, hard end points, such as incidence of diabetes and CVS disease or mortality should be highlighted as the criteria that might be the most clinically useful.

#7 We fully agree with the reviewer. In the discussion on page 23 a statement about this has been added, see also the reply on comment #5.

Reviewer #2: NUTJ-D-17-00330

This study aims to evaluate cross-sectional associations of dietary patterns and physical activity with metabolic health in obese individuals. This is currently a hot topic in obesity research. The study is well conducted and based on a high-quality dataset. I only have a few minor suggestions that the authors may consider in a revised version.

In the introduction you may wish to refer to a recent Eur Heart J publication on this topic (PMID: 29020414).

#8 Thank you for sharing this recent publication. We have added the reference in the introduction.
Please specify how the standardisation of food intakes was performed.

#9 We have now specified this in M&M section, page 9, by mentioning that standardisation was performed by calculating the Z-scores for men and women separately.

Add whether two-sided p-values were reported.

#10 Correct. It has been included in the text.

Add specific adjustments in footnotes of Tables (e.g. 4) for models 1 and 2.

I am assuming that dietary patterns and physical activity were included in the same model, please explicitly state whether that was truly the case.

#11 This is indeed the case. To make this more clear we have changed the title of table 4 into: Multivariable-adjusted odds ratios for the associations of dietary patterns and physical activity with metabolically healthy obesity.

Furthermore in the footnote of table 4 we now have specifically stated for which variables the models have been adjusted.

The author mention that they see diet being part of a broader lifestyle, so I wonder whether authors consider testing a sort of healthy lifestyle score combining diet, physical activity, and maybe smoking.

#12 We have mentioned on page 22 the following: “We consider it likely that dietary patterns are not isolated, but part of a broader lifestyle and subject to someone’s phase in life.” This conclusion has been generated from the results seen in table 3. This table represents the demographic, physical activity and other lifestyle characteristics within the first and fourth quartile of the dietary patterns. The results show that within the dietary patterns there is a variability in other lifestyle factors, such a physical activity, smoking and alcohol use. Within this study it was, however, not our intention to generate a lifestyle score. Our focus was on diet and physical activity.

Related to this previous comment, did the authors evaluate correlation structure between physical activity and dietary patterns? For example, one could imagine that men with higher physical activity levels have higher scores on the "fruit and vegetables" pattern and less so in women,
which could explain why one does not see an association with healthy patterns, but with physical activity. This should be evaluated and briefly mentioned in the discussion.

#13 This is an important point, which we have addressed in our analyses. Due to the nature of the data it is however difficult to make direct comparisons between men and women using continuous data. Dietary pattern scores are generated based on the standardised intake of food groups for men and women separately, representing the z-scores. To elaborate on your suggestion we have additionally analysed the moderate to vigorous physical activity in minutes per week within the quartiles of the dietary patterns stratified for men and women. As a result, the following paragraph has been added in the discussion (page 21): “In general, men engaged in more physical activity compared to women. To illustrate this, within the ‘fruit, vegetables and fish’ pattern and the ‘bread and potatoes’ pattern men engaged in more moderate to vigorous physical activity compared to women. At the same time men were also more physical active in the lowest vs. highest quartile of the ‘fruit, vegetables and fish’ pattern, and more physical active in the highest vs. lowest quartile of the ‘bread and potatoes’ pattern. This was not seen in women (data not shown). We hypothesize that this results in the stronger positive association between vigorous physical activity and MHO seen in men.”

Please indicate in the discussion whether the authors would find it worthwhile to evaluate their analysis in a prospective setting?

#14 This is indeed important to fully understand the relationship between diet, physical activity and health. On page 23 this had been added to the discussion. See also our reply on comment #5.