Author's response to reviews

Title: The prevalence of Metabolic Syndrome and Metabolically Healthy Obesity in Europe: a collaborative analysis of ten large cohort studies

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Version:2 Date:15 November 2013

Author's response to reviews: see over
To:
Joanna Denyer, PhD
Assistant Editor
BMC Medicine

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Re. Manuscript
1644101373104866

Dear dr. Denyer.

It is my pleasure to resubmit -on behalf of all authors- our original manuscript entitled ‘The prevalence of Metabolic Syndrome and Metabolically Healthy Obesity in Europe: a collaborative analysis of ten large cohort studies (MS)’.

We are very happy with the possibility offered by you to resubmit our manuscript, intended now for BMC Endocrine Disorders. In this new version, we have indicated in yellow the parts of the text which have been added or amended, according to your instructions and the valuable comments and suggestions made by the reviewers.

I hereby confirm that neither the manuscript nor any part of it has been published or is being considered for publication elsewhere.

We do hope that with the additions provided in the current manuscript we have been able to indicate its novelty and importance, and we look forward to receive comments from you and your staff.

Yours sincerely,

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The prevalence of Metabolic Syndrome and Metabolically Healthy Obesity in Europe: a collaborative analysis of ten large cohort studies


Referee 1:

Reviewers report

Title: The prevalence of Metabolic Syndrome and Metabolically Healthy Obesity in Europe: a collaborative analysis of ten large cohort studies

Version: 1 Date: 12 September 2013

Reviewer’s report:

In this collaborative analysis on over 163,000 cohort participants in Europe, authors aimed primarily to determine the prevalence of metabolically healthy obesity (MHO), and also that of obesity and MetS. Ten cohorts of 7 countries served for this purpose. The prevalence of MHO was approximately 10%, ranging from 4.6% to 18% in the cohorts, while the prevalence of overall obesity was 17% (12% to 26%). Authors emphasized the variability in the prevalence of MHO.

This large but descriptive study, although pursuing a worthy primary aim, seems to have added little novelty to current knowledge because few variables have been collected. Following issues need further to be addressed.

1) Though the prevalence of obesity is strongly age-related, and participants’ age ranged widely from 18 to 80 years, prevalence values provided refer to the whole cohorts without considering a threshold (say 40 years), whereas cohorts’ age ranges vary widely.

This is correct, and – also based on the comments of the reviewer 2 - we have added age-standardized prevalence values for metabolic syndrome and MHO for men and women separately in Figure 3, and the percentage current smokers in Table 1. This allows for even better comparison of the cohorts, and we thank the reviewer for this important remark. In Figure 4 we clearly demonstrate that healthy obesity depends on age, see also the next point.

2) The above-stated age-relatedness applies even more strongly to MetS and MHO. Providing the Fig. 4 A and B is insufficient to determine the variation in the prevalence, let alone the key characteristics in each gender. It is better that participants younger than 40 years are removed from the study, and focus rests on the remainder. Analysis may preferably be performed in two age groups.

We thank the reviewer for this comment. However, we do not feel that omitting the groups below 40 years will add to a better understanding. As can be clearly seen in Figures 4A and 4B, there is a gradual decrease in the percentage of healthy obese, and these data add to the knowledge and understanding that when judging the prevalence of healthy obesity, the specific age of an individual or group of individuals needs to be taken into account. A high prevalence of metabolic syndrome in those < 40 years is a good indicator of poor health in the specific cohort / country, and as can be seen from this figure, especially the Finnish males are already unhealthy at a young age.

3) Two studies predominate in size (the NL LifeLines and the HUNT2 survey) so that the remaining 8 cohorts make up less than one-quarter of the total sample.
Since MetS and MHO prevail quite differently in the two large studies, authors might consider the advantages of presenting certain data of the remaining 8 cohorts in a combined fashion (such as those in Tables 1-3).

Unfortunately, due to the currently decentralized analysis we do not yet have the possibility to perform a joint analysis on aggregated data. In addition, despite the lower number of individuals in the other 8 cohorts, joining these data would obscure important knowledge on the prevalence of obesity and health in these specific cohorts and countries, for instance the very high percentage of unhealthy obesity in the Finnish cohorts. As for the differences between the two largest cohorts, both a difference in age and a difference in smoking prevalence account for these differences, as can now be clearly seen in the adjusted Table 1.

4) Omission of less strict criteria (which compound the plethora of data) and an approach as described in items 2 and 3 may allow focusing primarily on triglycerides (and on HDL-C) which are key apparent factors for MetS (please, consult also Onat A, J Clin Lipidol 2010; 4:89) and MHO, as well as on gender differences, and yet, not discussed at all. Non-fasting TG values are apparently harmonized for comparison.

We agree with the reviewer that the less strict criteria add another set to the already abundant data. However, we have included these data to convince the readers that the prevalence of healthy obesity strongly depends on the set of criteria applied to the population, as recently reviewed by Phillips et al (PLoS One. 2013 Oct 17;8(10):e76188.). It becomes apparent that raising the cut-off values for blood pressure strongly and significantly influences results. We have shortened the results in this respect, and also adapted Figure 3, in which data in MetS and MHO are now given separately for men and women, and data on less strict criteria omitted. We do agree that TG and HDL-cholesterol are important factors, yet – as can be observed in table 2 – blood pressure appears to be the strongest driver in the metabolic syndrome cluster.

5) Total lack of data on waist circumference is striking, given MHO is largely related to WC. It would be beneficial to add available data on WC, at least in Table 1. Is this issue reflected or explained by the divergence of MetS prevalence among obese subjects between CHRIS and DILGOM (40%-72% in text; and 24%-33% in Table 3)?

Data on waist circumference was already shown in Table 1 (the sixth variable from the top) of our original submission, except for the Italian cohorts, in which these data were not available. As >96% of people with obesity have a waist circumference above the threshold for the metabolic syndrome according to NCEP-ATP III criteria, we have simplified our analysis accordingly. The difference between CHRIS and DILGOM is mainly explained by the striking difference in health, thus MetS, between Italian and Finnish cohort participants.

6) The lack of data on smoking status is conspicuous and needs remediing, separately stratified to sex, due to its close relation to the examined topic (please see Onat A Atherosclerosis 2007; 193:380, Metabolism 2011; 60:499; [Polish women] Kwasniewska M, Menopause 2012; 19:194, and Rasouli, Diabetes Care 2013, 36:604 [the HUNT study].

We agree with the reviewer that smoking is an important factor in its influence on certain metabolic syndrome criteria, and we have now included data on smoking in Table 1 of the revised manuscript. In addition, we refer to a more detailed analysis on this to a recent paper in BMC Medicine (Slagter et al, BMC Med. 2013; 11: 195. Published online 2013 September 3).

7) Much of novel knowledge generated in the past decade in the fields of MetS and cardiometabolic risk has been provided by A. Onat, none of whose publications have been referred to (a few examples:
Exp Opin Pharmacother 2011; 12;1887, Metabolic syndrome: nature, therapeutic solutions and options.
Metabolism 2009; 58:963, Smoking inhibits visceral fat accumulation in Turkish women: relation of visceral fat and body fat mass to atherogenic dyslipidemia, inflammatory markers, insulin resistance, and blood pressure.
Curr Pharma Design 2013 Apr 2 [Epub], Enhanced Proinflammatory State and Autoimmune Activation: a Breakthrough to Understanding Chronic Diseases.
Int J Cardiol 2010; 142:72, The paradox of high apolipoprotein A-I levels independently predicting incident type-2 diabetes among Turks.
Nutrition 2010; 26:382, Visceral adipose tissue and body fat mass: predictive values for and role of gender in cardiometabolic risk among Turks.
This makes the Discussion little fruitful although the need to identify the underlying factors for MHO is stressed by authors.

We thank the reviewer for adding this information, and appreciate his extensive experience in this research area. We have adapted parts of the manuscript accordingly, and included reference to the Atherosclerosis 2002 paper and the Exp Opin Pharmacother 2011 paper. However, several of the mentioned publications (i.e. rheumatic disease, gGT, creatinine, apoA1, autoimmune activation) are outside the scope of the current manuscript.

8) The request to revise one-size-fits-all approach and to re-evaluate the concept that all obesity is bad is to be commended.

Thank you for supporting this important conclusion.

9) Reference 30 is not yet published. Please, refer to it in the text, removing from the reference list.

We have adapted this, as the paper has in the meantime been accepted for publication.

Referee 2:
Reviewer’s report
Title: The prevalence of Metabolic Syndrome and Metabolically Healthy Obesity in Europe: a collaborative analysis of ten large cohort studies
Version: 1 Date: 12 September 2013
Reviewer’s report:
This paper describes the characteristics of metabolically health obese subjects in 10 different cohorts from 7 different European countries, comprising 163,517 individuals. Prevalence of MOH seems to vary across cohorts, although in general women have higher rates and they decline with age. No standardizations or adjustment of data (for age and sex) have been carried out.
Comments:
Results:
1. Page 13, Fig 4AB description should start as new paragraph.

We have adapted this.

2. My main concern is that the cohorts are being described, while the obese subjects are aged 44 (NCDS) to 60 (KORA). It would be very useful (compulsory to my opinion) to standardize (or adjust) the results for age (and sex).

We fully agree with the reviewer. We now have Figure 3 so that it includes age-standardized prevalence of metabolic syndrome and healthy obesity, separately for men and women. This has also been clarified in the
methodology section. Thus, age and sex effects are illustrated by the information graphed in both Figures 3A and 3B, and Figures 4A and 4B.

Discussion:
1. For good interpretation of the prevalence data it is important to discuss the sampling of the different cohorts, were they population-based, can they be seen as representative for their part of the country? This is discussed more on page 17, but would be more appropriate in the first part of the discussion.

In the appendix, the sampling strategy of each cohort has been described. There is some variation in the degree to which the cohorts represent the background population of its respective country. As an example, the LifeLines study recruited participants in the northern part of The Netherlands, and is not a country-wide population. We have added to the first part of the discussion:

However, although our data are obtained from large population-based cohort studies or biobanks, we have to realize that our results cannot always be generalized to the overall prevalence in the specific countries, as some cohorts have only collected data from a specific region of that country (CHRIS/MICROS/HUNT), or from a specific age group (NCDS).

2. MHO lower in women, is this because of their generally lower waist, do the authors have data on this? Or is it because they differ in age perhaps?

As discussed in the text and depicted in Table 4, the trend towards a higher percentage of MHO in women compared with men was evident in all studies. We have added these details in Figure 3.

3. Is there any explanation for the extraordinary low MOH in Finnish cohorts?

Apparently, the participants in the Finnish cohorts are more unhealthy than in the other cohorts. As mentioned in Table 2, this is driven by both higher percentages of high blood pressure and higher percentages of participants with low HDL and elevated triglycerides. We have modified the discussion to provide some suggestions for an explanation of this finding.

4. The discussion contains some repetitions; probably the part on strengths and weaknesses can be integrated in the first part (see 1st remark).

We agree with the reviewer and tried to adapt the text, so that repetitions are minimized. We think that the paragraphs describing strengths and weaknesses are well integrated into the text and have therefore opted not to alter the order in which this is presented in the paper.

In the paper, several spelling errors have been corrected and small parts of the text updated.