Author's response to reviews

Title: Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: the Norwegian HUNT 2 study

Authors:

Bjorn Hildrum (bjorn.hildrum@hnt.no)
Arnstein Mykletun (arnstein.mykletun@psyhp.uib.no)
Torstein Hole (torstein.hole@helse-sunnmore.no)
Kristian Midthjell (kristian.midthjell@ntnu.no)
Alv A Dahl (alvd@ulrik.uio.no)

Version: 3 Date: 13 April 2007

Author's response to reviews: see over
Assistant Editor Anita Makri,
BMC Public Health
The BioMed Central Editorial Team
Middlesex House
34-42 Cleveland Street
London W1T 4LB

Object: MS: 1001909799120644 - The metabolic syndrome in different age groups as defined by the International Diabetes Federation: prevalence data from the Norwegian HUNT 2 Study. Bjorn Hildrum, Arnstein Mykletun, Torstein Hole, Kristian Midthjell and Alv A Dahl
BMC Public Health

Dear Editor,

Thank you for your response dated Mars15, 2007. We hereby send you a detailed point-by-point response to the reviewers’ comments.

Best regards (on behalf of the authors)

Bjørn Hildrum
Reviewer: Rod Jackson

This reviewer found that our paper highlights some of the implications of metabolic syndrome and recommended acceptance without revisions.

Reviewer: Charles M Alexander

“General comments
The increasing prevalence of metabolic syndrome with age is well known. The authors seem to be very alarming regarding the high prevalence of metabolic syndrome in the elderly – difficult to understand given the wealth of data on the subject. Whether elderly individuals with metabolic syndrome need additional evaluation or specific intervention should be determined by their health care providers.”

- We agree that increasing prevalence of metabolic syndrome with age is well known. However, 1) This has been incompletely studied in European populations, 2) Only one study worldwide has assessed prevalence separately for those aged ≥80 years, and 3) Our study is the first one to show that increase in prevalence continued into the ninth decade.
- We agree that health care providers should determine whether elderly individuals need evaluation or specific intervention. For clinicians, however, there is a dilemma when the current recommendations by the IDF and AHA/NHLBI indicate that all individuals found to have the metabolic syndrome should receive long-term management and follow-up, including a full cardiovascular risk assessment. When the majority of elderly in one of the world’s healthiest populations are classified as at high risk and in need of a full cardiovascular risk assessment, it is reason to expect limited adherence among clinicians to such guidelines. A comparable dilemma linked to very high prevalence has recently been described for The European risk scoring system for cardiovascular disease (SCORE project), by Getz et al, BMJ 2005;331:551-4. Furthermore, as risk studies in the elderly have given conflicting results, this fact increases the dilemma of defining the majority of elderly as in need of interventions. We therefore think the reviewer’s suggestion of leaving the problem to the health care providers, is in need of further discussion and consideration. We think that our paper makes a contribution here.

“Major compulsory Revisions
Title – The current title is misleading since the authors evaluated participants with regards to both the IDF and the revised ATP III definitions of metabolic syndrome.”

- We have revised the title and included both the IDF and the NCEP:ATP III definitions.

“Abstract
Background – The intent of the ATP authors including Scott Grundy and Jim Cleeman was to revise the original definition by incorporating the revised ADA definition for IFG and adding drug treatment as part of the components. The ATP III and AHA/NHLBI are not separate definitions. There is the original and the revised ATP III definitions. The authors should use and refer to it as the revised ATP III definition. Please revise here and throughout the manuscript.”
We have followed the recommendations of the referee. However, there are two important reasons to use both the original and the revised ATP III definitions in our study. First, using the original definition will help comparing prevalence in this Norwegian population with that found in other populations, using that definition. Second, the original definition is still used in many risk studies (ex: ref 33, 36, 37 in the manuscript).

We refer to the original ATP III definition as “2001 ATP III” and the 2005 revision by AHA/NHLBI as “2005 ATP III”.

“Methods – The representativeness or lack thereof of the 10,206 participants is a result and should be in the Results and not the Methods section of the abstract.”

- We have revised the text in the Methods section.

“Results – Authors should use the revised ATP III definition.”

- See our comment above.

“Conclusions – It is not surprising that metabolic syndrome prevalence increases with age and that many elderly people are categorized as having the syndrome. Prevalence of all components increases with age. Further, any risk model will classify elderly individuals as having high risk. Those statements are neither novel nor surprising.”

- We agree that increasing prevalence with age is not surprising. However, several studies have reported a peak in the seventh decade and then a decline. Furthermore, there has been a lack of age-specific prevalence data in European populations, particularly among the elderly. We therefore consider our findings worthwhile to report.
- The second part of our conclusion concerns the dilemma of implementation of the current guidelines for clinical management of metabolic syndrome in elderly individuals, as described in our response to the referee in the “General comments” above.

“Background

1st paragraph – The intent of the ATP III authors including Scott Grundy and Jim Cleeman was to revise the original definition by incorporating the revised ADA definition for IFG and adding drug treatment as part of the components. The ATP III and AHA/NHLBI are not separate definitions. There are not separate definitions. Authors should use the revised ATP III definition. Please revise.”

- See our comment above.

“2nd paragraph – The authors might want to acknowledge that the IDF definition evolved from the earlier WHO definitions.”

- We have revised the text according to recommendations of the referee. In the revised manuscript, we have described that the focus on central obesity in the IDF definition carry on the focus on insulin resistance in the WHO definition.
“4th paragraph – There are just 2 definitions (IDF and revised ATP III definitions).”

- See our comment above.

“Methods
Sample characteristics
1st paragraph – It needs to be explicit stated that this was a cross-sectional study with all of the inherent limitations of such studies. It is assumed that the time from last meal is self-reported data and that it may be inaccurate. This needs to be acknowledged as a limitation of the study.”

In the revised manuscript, we have stated that our data are cross-sectional. Regarding the self-report of time since last meal, the participants answered question about this at the screening site. We have no reason to believe that there is more uncertainty of these data than of self-reported data obtained from questionnaires in health studies like HUNT. In fact, we consider that these answers are at least as accurate as data obtained from questionnaires.

“Definitions of the metabolic syndrome
2nd paragraph – Delete paragraph focused on the original ATP III definition.
3rd paragraph – Authors should just use the term “revised ATP III definition”.”

- See our comment above.

“Results
1st paragraph – Non-fasting individuals are older (95% confidence intervals do not overlap). Non-fasting men had lower HDL-C levels (95% confidence intervals do not overlap). Not surprisingly, fasting individuals have lower glucose and triglyceride levels (95% confidence intervals do not overlap). It is hard to understand how the authors can ignore such important differences and claim that the sample is representative of the entire study population without additional evidence.”

- We understand the reviewer’s comment. In the revised manuscript (the last paragraph in “Statistical analysis” and in “Results”), we have given additional evidence indicating that the included sample is fairly representative of the entire HUNT 2 population. There are some statistical significant differences between the fasting and non-fasting samples, but most effect sizes (except for glucose and triglycerides) are generally low (Table 3 in the revised manuscript). Our large sample sizes may easily lead to statistical significant differences, even though this differences are clinically unimportant and not affecting our main findings and conclusions.

“2nd paragraph – Isn’t it obvious that those with metabolic syndrome should have the stated differences? Is this text necessary?”

- We agree with the reviewer, and the text has been revised.
“3rd – 5th paragraph – Much of the text is redundant with table 3 and adds little, if anything.”

- We agree with the reviewer, and the text has been revised.

“6th – 9th paragraph – The intent of the ATP III authors including Scott Grundy and Jim Cleeman was to revise the original definition by incorporating the revised ADA definition for IFG and adding drug treatment as part of the components. The ATP III and AHA/NHLBI are not separate definitions. There is the original and the revised ATP III definitions. The authors should use and refer to it as the revised ATP III definition.”

- See our comment above.

“Discussion
1st paragraph – It needs to be explicitly stated that this was a cross-sectional study with all of the inherent limitations of such studies. The finding that the prevalence of the metabolic syndrome and its components increase with age is neither novel nor surprising.”

- See our comment above.

“4th paragraph – Since this is a cross-sectional study, survivor bias is always an issue in the older age groups. Survivor bias is the most common explanation for the failure of metabolic syndrome prevalence and component prevalence to continue to rise with increasing age in cross-sectional studies. Not observing that phenomenon in their data confirms that this is a very healthy population.”

- We agree with the reviewer that our population is very healthy. In the paper, we have described that the WHO regards the Norwegian population as very healthy by international comparisons (ref 11). A potential survivor bias in the older age group should mean that more individuals with than without metabolic syndrome were dead or did not attend the health study. If so, this should indicate that we have underestimated prevalence of risk factors for mortality, underlining the problem of classifying the majority of elderly participants in the health study as in need of additional risk evaluation and intervention.

“9th paragraph, 3rd sentence – I’m not sure why the authors find it surprisingly that elderly individuals are at high risk of morbidity and mortality from common disease of aging. The value of identifying younger individuals is that aggressive intervention (especially lifestyle) may prevent their early demise. Obviously, that benefit diminishes with age. Whether elderly individuals with metabolic syndrome need additional evaluation or specific intervention should be determined by their health care providers.”

- We commented on this objection of the reviewer at the start under General comments. We do agree that it is not surprisingly that elderly individuals are at high risk of morbidity and mortality from common diseases of aging. However, in this paragraph we discuss the dilemma of using a diagnosis of metabolic syndrome to identify a very large part of elderly individuals as having increased risks compared to elderly without the syndrome, given the conflicting results from risk studies in elderly populations.
“9th paragraph, 5th sentence – Most studies have not shown that risk from metabolic syndrome is independent of its components. In one study, HDL-C and systolic blood pressure were found to be independent predictors of risk. However, the clinical value of metabolic syndrome does not depend on its independence as a predictor of risk.”

- We agree with the reviewer that many studies have not shown that risk from metabolic syndrome is independent of its components. In the mentioned sentence, we referred to a recent paper (ref 35 in the article) discussing several aspects of the clinical value of metabolic syndrome, including independence of its components and independence of other conventional risk factors. In the revised manuscript, we have more precisely described independence as independence of other conventional risk factors.

“9th paragraph, 6th sentence – It is commonly observed that the relative risk diminishes with age as absolute risk increases. It would not be surprising if this was also true with regards to metabolic syndrome.”

- We agree with the reviewer.

“9th paragraph, last sentence – The risk from metabolic syndrome is from cardiovascular and diabetes. Why is there any concern as long as any given study shows increased cardiovascular risk?”

- We agree with the reviewer that the risk from metabolic syndrome is from cardiovascular disease and diabetes. However, as the majority of studies estimating risks of death include both cardiovascular and total mortality, we have discussed the findings from such studies.

“10th paragraph, 2nd sentence – As stated above, why does there need to be data showing increased all-cause mortality? Isn’t increased CV mortality sufficient?”

- We have revised the sentence to include both cardiovascular and total mortality, commonly used as end-points in studies estimating risks of death associated with metabolic syndrome.

“10th paragraph –, 3rd sentence – Many studies have shown that metabolic syndrome is useful for identifying individuals at risk for CV events and diabetes. Isn’t that sufficient to make it clinically useful?”

- The 3rd sentence is not a separate statement, but part of a discussion where we refer to important perspectives on metabolic syndrome in recent papers by Scott M Grundy (ref 34) and Richard Kahn et al (ref 35).

“10th paragraph, last sentence – I’m not sure why authors find it surprising that elderly individuals are at high risk of morbidity and mortality from common diseases of aging. Whether elderly individuals need evaluation or intervention should be determined by their health care providers.”
• See our responses above to other comments.

“Conclusions
Disagree with the authors’ conclusions as stated above.”

• See our responses above to other comments.

“Figure 3
The authors should use and refer to it as the revised ATP III definition. Please revise figure.”

• We have revised the figure, according to our comments above.