Author's response to reviews

Title: The metabolic syndrome in different age groups as defined by the International Diabetes Federation: prevalence data from the Norwegian HUNT 2 Study

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Author's response to reviews: see over
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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 Makri,

Thank you for your response dated Nov 10, 2006. We hereby send you a detailed point-by-point response to the original reviewers’ comments:

Reviewer: Vasilios G Athyros

This reviewer emphasized our findings of relatively high prevalence of the metabolic syndrome among elderly people by using the IDF criteria and recommended accepting our manuscript without revisions.

Reviewer: Charles M Alexander

Quote:
“General comments
Metabolic syndrome by any definition increases in prevalence with age. That fact has been known since the first definition of metabolic syndrome (i.e. WHO) in 1998.”

- It is correct that several population studies have reported an increase in prevalence with age regardless of definition. Some studies, however, have reported a peak in the sixth decade and then a decline. To our knowledge, our study is the first to show that this increase in prevalence with age continued into the eighties (see “Discussion”). In the “Discussion”, we highlight the challenge of managing this high prevalence among elderly people.

Quote:
“Specific comments
Abstract
Background: The IDF definition was certainly designed to be useful in any population, but whether it will be useful in any population remains to be determined.”
- We agree with the reviewer and the text has been changed to “The 2005 International Diabetes Federation (IDF) definition of the metabolic syndrome was designed to be useful worldwide.”

Quote:
“Conclusions:
1st sentence: “Prevalence of metabolic syndrome increases with age and this occurs regardless of sex, ethnicity, etc.””

- Our population were predominantly (97%) Caucasians so the reviewer’s term “regardless of ethnicity” was not applicable. We have changed the sentence to: “According to all three definitions, the prevalence of the metabolic syndrome increased strongly with age.”

Quote:
“2nd sentence: “IDF cutoff values are not implemented. They are either used in a given individual or population or not. Also, metabolic syndrome does not put an individual at high risk for cardiovascular disease. It is not comparable with diabetes, coronary heart disease or Framingham Risk Score greater than 2% per year.””

- In 2005, the IDF and the American Heart Association / National Heart, Lung and Blood Institute (AHA/NHLBI) published guidelines on clinical management of metabolic syndrome. In our resubmitted manuscript (Oct 31, 2006), we have referred to these guidelines in “Background” and more thoroughly in “Discussion”. We have changed the 2nd sentence in the abstract to: “The IDF and AHA/NHLBI guidelines for clinical management of the metabolic syndrome would classify a high proportion of elderly Norwegian as in need of overall risk assessment for cardiovascular disease.”

The reviewer states that, “the metabolic syndrome does not put an individual at high risk for cardiovascular disease.” To the best of our understanding, the reviewer’s position is here in conflict with influential guidelines: The IDF Epidemiology Task Force Consensus Group recently wrote, “The ultimate importance of metabolic syndrome is that it helps identify individuals at high risk of both type 2 diabetes and cardiovascular disease” (Alberti et al, Lancet 2005;366:1059-1062). But as the association between metabolic syndrome and risk of cardiovascular disease, particularly among elderly, still is uncertain, we have changed the 2nd sentence as described above.

Quote:
“Background
1st paragraph, 1st sentence: I would discourage the authors from categorizing metabolic syndrome as a “potent” risk factor. It has also not just emerged. It has been recognized for many years. It is true that the prevalence is slowly increasing.”

- When we used the term “has emerged as a global epidemic”, we referred to a recent review (Eckel et al: The metabolic syndrome. Lancet 2005, 365:1415-1428). According to the reviewer’s comment, we have changed the sentence to “The metabolic syndrome has been identified as a clustering of risk factors for atherosclerotic cardiovascular disease and type 2 diabetes, and is described as a global epidemic.”

Quote:
“1st paragraph, 2nd sentence: I would discourage the authors from using the term “malignancy.” Metabolic syndrome is not a malignant condition.”
• In accordance with the reviewer’s comment, we have changed the sentence to: “In the past few years, increased attention to the syndrome has led to several attempts to develop a definition accepted worldwide.”

Quote:
“2nd paragraph, 1st sentence: It would be better to just state that the IDF definition requires that abdominal or visceral obesity be present.”

• We have changed the sentence and referred to the IDF: “IDF considered that visceral obesity is highly correlated with insulin resistance and thus essential for diagnosis of the metabolic syndrome.”

Quote:
“2nd paragraph, last sentence: There are increasing number of studies published using the IDF definition and the results have been consistently similar to results using the NCEP ATP III definition.”

• The sentence has been removed. In “Discussion”, we have referred to several prevalence studies, particularly studies in samples with a wide age span.

Quote:
“Methods
1st paragraph, next-to-last sentence: Four hours has been shown not to be sufficient to normalize triglyceride levels after eating. The issue is whether triglyceride levels are any different after four or eight hours of fasting, not just glucose.”

• We agree this problem of too short fasting (>= 4 hours) is a limitation of our original analysis. We have re-analysed our results with the aim of accounting for this problem. Please see our response to “General comments”, reviewer Heinz Drexel, for details.

Quote:
“Results
1st paragraph, last sentence – Were triglyceride levels any different after four vs. eight hours of fasting?”

• Yes, they were different. Our resubmission includes detailed analyses of this. Please see our response to “General comments”, reviewer Heinz Drexel.

Quote:
“Conclusions
1st paragraph, 3rd and 4th sentences: The authors have misinterpreted the objective of the metabolic syndrome definition. The Framingham Risk Score is highly influenced by age. Prevalence of diabetes, coronary heart disease, hypertension, dyslipidemia, metabolic syndrome all increase with age. The intent of the metabolic syndrome is to identify individuals that might otherwise be labeled as healthy and try to implement lifestyle intervention to reduce their risk for diabetes and cardiovascular disease. Presence of the metabolic syndrome, per se, does not require drug therapy.”

• We agree that presence of metabolic syndrome, per se, does not require drug therapy. We also agree with the reviewer in that the intent of metabolic syndrome is to identify individuals that might otherwise be labelled as healthy and try to implement lifestyle changes. However, the guidelines from the IDF and from AHA/NHLBI recommend a full
cardiovascular risk assessment (like the Framingham Risk Score) in all individuals with metabolic syndrome. Our findings of increasing prevalence rates right up to the eighties question whether the metabolic syndrome is a clinically useful diagnosis in elderly people. At the best of our knowledge, it is not yet established if the risks associated with metabolic syndrome are the same in elderly people as what have been found in younger people.

**Reviewer: Heinz Drexel**

Quote:
“General comments:

The work of the authors suffers two important shortcomings. First, they used non-fasting blood samples which is especially flaking the triglycerides results and therefore one of the five traits of the metabolic syndrome. Because the normal limit of triglycerides is 1.7 mmol/l it is mandatory to stick on overnight fast for an exact classification of patients. Using wrong criteria can render the conclusion wrong.

As is known from glucose and fat tolerance studies, the four-hour fasting period is usually long enough for a return of postprandial glucose levels to a postabsorptive value. However, the peak of the postprandial triglyceride increase occurs between four and six hours, therefore triglyceride values at four hours are not valid for diagnosing fasting hypertriglycerideamia."

- We agree that assessing triglyceride levels after a four-hour fasting period is a shortcoming. To overcome this problem, we have made adjustments of both glucose and triglyceride levels in the resubmitted manuscript (Oct 31, 2006). Based on data from the fourth of the included sample that reported ≥9 hours fast, triglycerides and glucose levels for individuals fasting 4-8 hours were adjusted before further analyses were performed. This procedure is described under Methods (Sample characteristics and Statistical analyses) and discussed under Strengths and limitations. Totally, these adjustments gave a minimal increase in prevalence (IDF metabolic syndrome increased from 28.6% to 29.0% among men and from 29.3% to 30.3% among women)

Second, as the authors state correctly, the Norwegian population is one of the healthiest ones in the world. The prevalence of around 90 percent of a syndrome in an age stratum of such a population may be meaningless, unless there are prospective data on the outcome of the patients.

- We cannot see how our main result (the relatively high prevalence of about 60 (not 90) percent with metabolic syndrome in elderly in a fairly healthy general population) can be a shortcoming of our study.

Quote:
“Specific comments:

1) Page 3 line 17: there “are” no adjustment for age.”
   - The sentence is removed in the resubmitted manuscript (31 Oct 2006)

2) “Page 6 line 5: fasting blood glucose: Venous or capillary specimens?”
• We used venous specimens. This is not specified in the resubmitted manuscript (31 Oct 2006) as venous specimens are used for assessing C-peptide and anti-GAD antibodies (which were other purposes of the blood sampling). We can, on request, add information on this to the manuscript.

3) “Page 6: paragraph 3, line 6: in the original ATP-III definition, which the authors quote in the introduction (JAMA 2001;285:2486-2497), the cut-off for fasting glucose is 6.1, not 5.7 mmol/l.”

• We have corrected this. In the resubmitted manuscript, we have compared the IDF definition with the original ATP III definition and the 2005 modification of ATP III published by AHA/NHLBI, all with references.

4) “Page 8, line 3, data shown is not acceptable. The authors have to show these data, both for glucose and for triglyceride levels.”

• We agree, and the complete data are described (in methods section) in the resubmitted manuscript. See also our response to “General comments”.

5) “Page 9, line 4: the authors state that hypertriglyceridemia was the second most prevalent metabolic syndrome component. Taking into account the methodological flaw outlined under general comments, this is very unfortunate for the study.”

• We agree. The paragraph is rewritten, based on the adjustments described under “General comments”.

6) “Page 12, line 6: as mentioned above it is not acceptable that data are not shown on postprandial triglyceride levels.”

• This addresses the same problem of fasting, which is addressed in detail in the resubmitted manuscript, also in the discussion section. This relates to our response under “General comments”.

7) “Page 12, last line: this underscore the importance of prospective studies: The authors should add to their reference list a very recent paper by Saely et al (Diabetes Care 2006 Apr;29(4):901-7) which used a prospective design to compare the IDF and ATP-III criteria.”

• The paper (by Saely et al, where the reviewer is last author) is a study of coronary patients, and not based on the general population. These patients were referred for coronary angiography due to symptoms of coronary disease. Thus, many of them have already developed a condition metabolic syndrome is a risk factor for. The preferred alternative over following such a clinical sample is prospective studies of the general population. In the resubmitted manuscript, we have referenced three recent prospective studies based on community samples.
To the editor:

Obviously, it was a mistake to submit our manuscript as a technical advance. It should of course have been submitted as a research article and I agree to have our manuscript considered as such.

Best regards (on behalf of the authors)

Bjørn Hildrum