Author's response to reviews

Title: Prevalence of the metabolic syndrome and its components in Northwest Russia: the Arkhangelsk study

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Author's response to reviews: see over
Dear Editor,

We highly respect the professional notion of the reviewer and greatly appreciate the constructive criticism and suggestions for improvements. We have addressed thoroughly the comments of the reviewer and changed the manuscript in the following way:

Reviewer David Laaksonen

1. “My original opinion that data on the metabolic syndrome and its components in a Russian province gives some value to the paper, but the purely cross-sectional data focusing only on prevalence limits its value. I would also agree that because the prevalence of the metabolic syndrome is relatively low, it is clear that other risk factors explain the high rate of cardiovascular morbidity and mortality in Arkhangelsk. Nonetheless, since 2000, many papers on the prevalence of the metabolic syndrome from various geographical areas have been published. As time goes on, the international interest in papers on the prevalence of the metabolic syndrome according to various definitions decreases.

As the authors note, the ethnic composition, lifestyles and socioeconomic conditions of Russia and its provinces differ widely. The paper would have been improved dramatically if data on how these factors are associated with the metabolic syndrome were presented. I disagree with the authors that incorporation of determinants of the metabolic syndrome and its components is unrealistic or very complicated.”
The primary purpose of this article is to study MetS epidemiology in adult population of the North-West Russia on the background of unprecedentedly high (for a developed industrial country) cardiovascular mortality. The Arkhangelsk city, a typical regional center, is a capital of the largest region in the Northeast of Russia, is predominantly populated with ethnical Russians (>90%). So we consider that our results can be extrapolated to the whole North-Western part of Russia (area of 1/3 of EU’s size).

Despite of the Russia’s size and large ethnical and cultural heterogeneity, no reliable data are available until now. We hope that a number of studies with a similar topic from other geographical areas of Russia will be published and compared with our results later. Therefore we considered that our paper, the first population-based study from Russia on this actual and important topic, must represent a thorough description and analysis of the MetS and its components with regard to the complex socio-economic and demographic conditions. Under the complex and specific demographic conditions we mean primarily the gap in life-expectancy at birth between genders which exceeds 12 years by the country in average. In the Northern regions like Arkhangelsk this between-gender gap is even wider (men’ average life expectancy is 55 years only). The Russian phenomenon, unfortunately not of that type to be proud of, is that “already old” and frequently aging population quickly decreases in number. The males of working ages contribute most to the observed between-gender gap, constituting a non-proportionately large group among the dying.

This is the main reason to provide sex-specific and age-standardized rates to attempt to compare our results to other Western populations. Even from the descriptive data on MetS and its components’ distribution a reader may take notice of a profound difference between men and women in our study setting. It makes clear that the multifactorial analysis of MetS should be sex-specific.

2.
“The authors missed my point on examining waist cutoffs in this population of Russian men and women. The original cut-offs of 94 and 102 cm in men and corresponding cutoffs in women are based on cross-sectional studies from
Holland, in which those cut-offs corresponded to BMIs of 25 and 30, and were also in turn associated with large increases in the prevalence of various chronic diseases. The authors could carry out ROC or linear regression analyses to see what BMIs the waist cut-offs correspond to in their cohort. In middle-aged eastern Finnish men in the 1980s, these cut-offs corresponded to higher BMIs, suggesting a lower tendency for abdominal obesity at a given body mass index."

To meet this proposal we have added following data:

1. Under the Methods, Statistical analysis, page 9
   “To identify sex-specific cut-offs for waist circumference corresponding to BMI of \( \geq 25 \) kg/m\(^2\) and \( \geq 30 \) kg/m\(^2\) a receiver operating characteristic (ROC) analysis was carried out.”

2. Under the Results, Description of the study sample, page 10
   “The prevalence of obesity (Table 2) strikingly varied depending on definition (WC, BMI or WHR). We performed a ROC analysis to evaluate the applicability of the given WC cut-offs in our study sample. The WC cut-off \( \geq 94 \) cm identified men with BMI \( \geq 25 \) kg/m\(^2\) with sensitivity (Se), 0.35 and specificity (Sp), 0.99. The WC cut-off \( \geq 102 \) cm identified men having BMI \( \geq 30 \) kg/m\(^2\) with Se, 0.41 and Sp, 0.99. In men of our study setting, the BMI cut-offs of \( \geq 25 \) kg/m\(^2\) and \( \geq 30 \) kg/m\(^2\) best corresponded to WC of \( \geq 84 \) cm (Se, 0.82; Sp, 0.85) and 92 cm (Se, 0.88; Sp, 0.86), respectively. The standard WC cutoffs of \( \geq 80 \) cm and \( \geq 88 \) cm applied in women, and corresponding to BMIs of \( \geq 25 \) kg/m\(^2\) and \( \geq 30 \) kg/m\(^2\), respectively, were originally characterized with good test properties, i.e. Se, 0.79; Sp, 0.91 and Se, 0.87; Sp, 0.88, respectively.”

3. Under the Discussion, page 15-16 text was rewritten accordingly:
   “The method used to define obesity (BMI, WC or WHR) strikingly affected the reported prevalence of this condition in both genders. The variation was particularly striking among men, ranging from 6% to 26% using the WC and WHR definitions, respectively. Among women, in contrast, the frequency was highest for WC. The original sex-specific thresholds for WC were originally, at least partly, established in cross-sectional studies
from the Holland and the UK, using the correlation between WC and BMI in subjects with BMI $\geq 25$ kg/m$^2$ and 30 kg/m$^2$. The cut-off levels for obesity using WC depend on ethnicity. According to the ROC analysis the optimal cut-offs for WCs corresponding to BMIs of $\geq 25$ kg/m$^2$ and $\geq 30$ kg/m$^2$ were about 10 cm lower ($\geq 84$ cm and $\geq 92$ cm, respectively) than the original one ($\geq 94$ cm and $\geq 102$ cm, respectively) suggesting a lower tendency for central adiposity at a given BMI among the men of our study setting. Similar results were reported from the study of middle-aged eastern Finnish men in the late 80$^{th}$. On the contrary, the standard cut-offs of WCs for women ($\geq 80$ cm and $\geq 88$ cm) originally corresponded well to BMIs of 25 kg/m$^2$ and 30 kg/m$^2$. Therefore, the original cut-offs used for WC, being too high, could be inappropriate for men living at the North-West of Russia. This is an important finding that might largely explain unequal MetS distribution by sex and it needs further verification.

4. The authors use HbA1c as a substitute for fasting plasma glucose in the definition of the metabolic syndrome. These additional analyses are useful, but the authors should note that the HbA1c cut-off mainly identifies those with diabetes, whereas IFG is a more subtle finding. There may be published studies suggesting cut-offs for HbA1c corresponding to IFG, but they are certainly not clinically used. At any rate, that HbA1c identifies mainly those with diabetes rather than IFG should be noted in the discussion.

Search in PubMed revealed no large meta-analyses, literature reviews or recommendations provided by expert groups regarding application of HBA1c in detection of Impaired Fasting Glucose. Use of glycated hemoglobin as a diagnostic test for diabetes or intermediate hyperglycemia, is currently not recommended according to the reports of The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus and World Health Organization (WHO) [1,2], primarily because of difficulties with standardization of HBA1c measurements. But an active work is ongoing on this direction.
From the beginning we were aware that the reported MetS rates were influenced by the methods used to define the glycemia but decided to avoid this space-consuming discussions since we thought that our motivations would become clear for a reader. The MetS rates based on cut-offs recommended for plasma glucose were characterized with slight over-reporting as a result of effect of the non-fasting group, and higher sensitivity vs. HBA1c in detection of the IFG. Whereas, the rates based on HBA1c provided us with a “dense ground” and were somewhat conservative because of lower sensitivity of HBA1c in IFG detection. The rates based on cut-offs for serum glucose (0.2 mmol/l higher than for plasma glucose) were somewhere in the middle. The difference in MetS prevalence estimated on the base of these three criteria of hyperglycemia did not exceed 1.5% between any used definition (IDF, AHA, NCEP). The true prevalence is somewhere in the middle. A relatively large sample size provided us with narrow confidence intervals.

Accordingly we have corrected the article’s content:

Page 12, the lowest 1/5th, Discussion, in the paragraph starting as “There was a potential for clinical-chemical measurement error…”

“The rates of the MetS based on the HBA1c were the most conservative since on the chosen cut-off point of >6.1 % the test identifies subjects with Impaired Fasting Glucose (IFG) with lower sensitivity than those with the diabetes. Thus, some participants having IFG were falsely labelled as having normoglycemia. Second, the cut-offs for serum glucose were raised from 5.6 to 5.8 mmol/l (IDF and AHA/NHLBI), and from 6.1 to 6.3 mmol/l (NCEP), according to the local standards at the UNN laboratory. Although agreement between the two eccentric definitions of hyperglycemia was relatively fair (kappa=0.68), corresponding agreement for MetS diagnosed according to the NCEP criteria based on these two definitions of hyperglycemia was very good (kappa=0.97). Similar results were seen for other definitions. It could be explained by the cluster nature of the MetS and by the fact that hyperglycemia was the least prevalent metabolic abnormality in both genders and its impact on the probability to have the MetS was minimal in our study setting.”
Reference List

   Ref Type: Electronic Citation