Author's response to reviews

Title: Population Attributable Fraction of Smoking and Metabolic Syndrome on Cardiovascular Disease Mortality in Japan: a 15-Year Follow Up of NIPPON DATA90.

Authors:

Naoyuki Takashima (takasima@belle.shiga-med.ac.jp)
Katsuyuki Miura (miura@belle.shiga-med.ac.jp)
Atsushi Hozawa (ahozawa@m.tains.tohoku.ac.jp)
Aya Kadota (ayakd@belle.shiga-med.ac.jp)
Tomonori Okamura (okamurat@hsp.ncvc.go.jp)
Yasuyuki Nakamura (nakamura@kyoto-wu.ac.jp)
Takehito Hayakawa (thayaka@fmu.ac.jp)
Nagako Okuda (okuda@belle.shiga-med.ac.jp)
Akira Fujiyoshi (afujiy@belle.shiga-med.ac.jp)
Shin-ya Nagasawa (nagasawa@belle.shiga-med.ac.jp)
Takashi Kadowaki (kadowaki@belle.shiga-med.ac.jp)
Yoshitaka Murakami (ymura@belle.shiga-med.ac.jp)
Yoshikuni Kita (kita@belle.shiga-med.ac.jp)
Akira Okayama (aokayama@jatahq.org)
Hirotsugu Ueshima (hueshima@belle.shiga-med.ac.jp)

Version: 2 Date: 23 March 2010

Author's response to reviews: see over
To the Editor:

The reviewers’ comments were very useful for us to revise the manuscript. We hope that the revised manuscript is now suitable for publication in “BMC Public Health”. We would be willing to make additional changes if they are needed. Points of the revisions and responses to the reviewers’ suggestions are summarized as follows:

**Response to the reviewer #1:**

Takashima and colleagues have examined an interesting topic of public health importance in an Asian-Pacific population. The findings are intriguing but the underlying message is loud and clear. The methodology has been adequately described, statistical techniques are appropriate and discussion is logical. Minor editorial assistance is essential. The study has both strengths and limitations. The strength of this study is its longitudinal nature. The authors have highlighted the study limitations and the main limitation is the non-availability of socio-economic data. However, I have the following main concerns to offer.

We thank the reviewer for his/her positive evaluation of our work.

**All Major Compulsory Revisions:**

1. First, it is not clear why the authors did not use the Asia-Pacific Region cut-off for the BMI- this might have misclassified obese individuals as non-obese and thereof the probability of introducing a systematic bias in the effect estimates.

The definition of obesity for Japanese was proposed as BMI 25kg/m² or more by the Examination Committee of Criteria for Obesity Disease in Japan (ref. No. 22). A number of previous reports on the metabolic syndrome in Japanese also used this definition when waist circumstance was not available. We appreciate the reviewer’s understanding to use this definition for Japanese in the present study. We have added a statement on this limitation in the Discussion section (page 12, last paragraph – page 13, first paragraph).
2. Second, it is also not quite clear which international definition for Metabolic Syndrome was employed.

We used the criteria of metabolic syndrome by the Japanese Committee to Evaluate Diagnostic Standards for Metabolic Syndrome (ref. No. 23); unfortunately, this is not published in English. This criteria is based on the criteria by IDF and is modified for Japanese. The criteria is as follows:

1. Abdominal obesity (waist $\geq$ 85cm in men and $\geq$ 90cm in women) is essential. (Or body mass index $\geq$ 25 kg/m$^2$ if waist is not available.)

2. Plus two or more following metabolic factors:

   Blood pressure $\geq$ 130/85 mm Hg
   Blood glucose $\geq$ 110 mg/dl
   Serum triglyceride $\geq$ 150 mg/dl
   Serum HDL cholesterol $<$ 40 mg/dl

We have revised the statements on this definition clearly in the Methods section (page 8, second paragraph).

3. Third, the operational definitions of smoking status were not clearly spelled out. This limitation has to be discussed in the context of the adjusted HRs that were statistically significant in both sexes only among the smokers.

We have added detailed methods to ask smoking status in the Methods section (page 7, second paragraph). We could not exactly understand the meaning of the second sentence of this comment.

4. Fourth, it is not clear whether data on the duration and intensity of smoking history were available. If available, then the reasons for not factoring them into the models are to be discussed as well.
We have information about the duration of smoking and the average number of cigarettes smoked. Because most of Japanese smokers start smoking at around age 20, there is a strong correlation between age and smoking duration in smokers (r=0.88 for men and r=0.52 for women in our study participants). Therefore, we did not include smoking duration into the models where age was included as a covariate.

On the other hand, the number of participants and CVD events were not enough to do analyses using the number of cigarettes. Because most of Japanese smokers consume one package (20 cigarettes)/day or more, only 25% of current smokers in our study participants were classified as light smokers (less than one package/day). We have added a discussion on this limitation in the Discussion section as follows (page 13, first paragraph): “The numbers of participants or CVD events were not enough to analyze according to the number of cigarettes per day; therefore, we did not consider the intensity of smoking in this paper.”

5. Self-reporting smoking history introduces recall and information biases that need to be discussed.

We would agree with the reviewer that self-reporting smoking history could introduce recall and information biases. However, in 1990 in Japan, more than half of adult men were smokers and Japanese society have much tolerance for smoking. Therefore, there would be little possibility that smokers hide their smoking habit. We have added a statement on this limitation in the Discussion section (page 13, first paragraph).

6. It could be interesting to see the results with an interaction term.

In the present study, we showed hazard ratios according to categories cross-classified by smoking status and the presence of metabolic syndrome (or obesity) (Tables 2-4). Our understanding is that an interaction of two factors can be observed by looking at these hazard ratios and that any apparent interaction was not likely to exist in both sexes.
7. Finally, the results of table 4 are less counter-intuitive and more convincing from a public health policy perspective. Therefore, such findings need to be reinforced in the discussion section as well.

We would agree with the reviewer that the results in Table 4 are important, because, when obesity was dealt with one of metabolic risk factors (not an essential factor), the PAF in smokers with metabolic risk factor clustering got larger in men (34.3%). We have added a discussion that a public health policy for this part of people is also important for CVD prevention (page 12, second paragraph).

Response to the reviewer #2:

Examining CVD deaths in an important Japanese cohort, The authors quantify the contributions from smoking [large] and metabolic syndrome MS[ small] OK. But the definitions of MS used are arbitrary, over-inclusive and do not agree with standard international definitions.

We thank the reviewer for his/her positive evaluation of our manuscript. We used the criteria of metabolic syndrome by the Japanese Committee to Evaluate Diagnostic Standards for Metabolic Syndrome (ref. No. 23). This criteria is based on the IDF criteria and is modified for Japanese, as we mentioned above for the reviewer #1. We have revised the statements on this definition clearly in the Methods section (page 8, second paragraph).

It might be more useful and informative if they exploited the uniqueness of this cohort, and did a more conventional multiple linear regression analysis, making use of the continuous variables. That would tease out the relative contributions from the "major" risk factors such as cholesterol, systolic BP etc.

By all means, they could add a table later in the paper, forcing their data into the [rather artificial] metabolic syndrome categories.
The below table (Table A) shows hazard ratios of CVD death for each component of metabolic risk factors including all factors simultaneously in a model. It shows that current smoking, past-smoking, systolic blood pressure and glucose were significant risk factors of CVD mortality. Because the focus of the present report was to investigate the attribution of the combination of smoking and metabolic syndrome (or obesity) to excess CVD deaths, we would not like to show this table in the paper. If the reviewer strongly recommends to include this table in the paper, we will consider again.
Table A. Adjusted HR for 1 standard deviation increasing in the continuous variables and sex, smoking and drinking habits for mortality from cardiovascular diseases.

<table>
<thead>
<tr>
<th></th>
<th>Adjusted hazard ration (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current –smoker</td>
<td>3.45 (2.12-5.60)</td>
</tr>
<tr>
<td>Past-smoker</td>
<td>2.04 (1.11-3.75)</td>
</tr>
<tr>
<td>Body mass index (1 SD increasing)</td>
<td>0.99 (0.83-1.18)</td>
</tr>
<tr>
<td>Systolic blood pressure (1 SD increasing)</td>
<td>1.32 (1.13-1.54)</td>
</tr>
<tr>
<td>Triglyceride (1 SD increasing)*</td>
<td>0.85 (0.69-1.04)</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol</td>
<td>0.93 (0.76-1.11)</td>
</tr>
<tr>
<td>(1 SD increasing)</td>
<td></td>
</tr>
<tr>
<td>Glucose (1 SD increasing)</td>
<td>1.10 (1.00-1.24)</td>
</tr>
<tr>
<td>Sex (Female/male)</td>
<td>1.00 (0.61-1.64)</td>
</tr>
</tbody>
</table>

This Cox model also includes age, and drinking habit, simultaneously.

* The variable was tested after log-transferred.