Author's response to reviews

Title: Longitudinal study of respiratory function and symptoms in a non-smoking group of long-term officially-acknowledged victims of pollution-related illness

Authors:

Takako Tanaka (tanakataka@nagasaki-u.ac.jp)
Masaharu Asai (asaichan@bc.mbn.or.jp)
Yorihide Yanagida (dependonhero@yahoo.co.jp)
Tsuyoshi Nishinakagawa (nisituyo0217@yahoo.co.jp)
Naomi Miyamoto (naomi0102us@ybb.ne.jp)
Kenji Koutaki (koutaki@kokoro.ac.jp)
Yudai Yano (yudai_yano_121@yahoo.co.jp)
Ryo Kozu (ryokozu@nagasaki-u.ac.jp)
Sumihisa Honda (honda@nagasaki-u.ac.jp)
Hideaki Senju (senju@nagasaki-u.ac.jp)

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Author's response to reviews: see over
21 June 2013

Dear Jimmar Dizon

Re: MS: 2040406270932461
Title: Longitudinal study of respiratory function and symptoms in a non-smoking group of long-term officially-acknowledged victims of pollution-related illness

Thank you for the opportunity to submit our revised manuscript. We thank the reviewers for their helpful comments and have revised the manuscript to address the points raised. The revisions to the manuscript are shown by red font. Our point-by-point responses to the comments are given below.

Please address all correspondence to:
Takako Tanaka
Course of Health Science
Nagasaki University Graduate School of Biomedical Science
1-7-1 Sakamoto, Nagasaki 852-8520, Japan
Tel: +81 95-819-7967
Fax: +81 95-819-7967
E-mail: tanakataka@nagasaki-u.ac.jp

Thank you for your assistance.

Yours sincerely,
Takako Tanaka
**Responses to the comments of Reviewer #1**

**Major comments:** It is hard to establish causal relationships in epidemiology, and the authors should be more careful on the pages 13 - 17.

We have reworded the relevant parts of the Discussion to clarify the difficulty of establishing causal relationships.

**Minor points:**

1. I think that the columns with total numbers should be skipped in all tables because in most of them the two sexes are compared, and that is enough. Then, only one point will be missed, on page 13 para 1 is stated one important result in the total population which are not statistically significant for men and women separately, but that result can be placed in the text.

   We have deleted the columns with total numbers in all the tables. We have described the results according to the two sexes in the text, and have also described the important results for the total population in the text (Page 13, Line 13-15).

2. On page 11 para 2 is stated that SO2 were above the accepted level in 1965 to 1974 but on figure 2, I find this level in the years 1968 to 1974.

   The text has been corrected to “1968 to 1974”.

3. On page 12 para 3, I wonder if the results in table 4 are statistically significant?

   We tested the significance of the differences between males and females, and the results are shown in the revised Table 4. The significant result is also described in the text (Respiratory function over time, Page 13, Paragraph 1).

**Responses to the comments of Reviewer #2**

**Major comments:**

1. If the authors have the data of the relationship between the level of air pollution and the change in respiratory function and symptoms during more polluted era (around 1970), it might be more interesting.
Unfortunately, we do not have these data.

2. Were the data of 2000 and 2009 compared, or were the yearly consecutive data from 2000 to 2009 analyzed?
We compared the data of 2000 and 2009 (Table 3 and Table 5), and calculated the annual mean changes in FEV\textsubscript{1}, FEV\textsubscript{1} % predicted, FVC, VC, VC % predicted, and FEV\textsubscript{1}/FVC using the yearly consecutive data from 2000 to 2009 (Table 4 and Table 6). The captions of Table 4 and Table 6 have been revised to clarify this.

3. Treatment status in these patients may affect respiratory symptoms and pulmonary function during the study duration. If the authors have the data of the content of the treatments, please add the data and describe it.
We agree that treatment status may affect the symptoms. As the treating doctors indicated only that they treated patients according to their clinical condition, we do not have detailed treatment data such as information about the medications administered. We have indicated this in the revised manuscript (Discussion, Page 16 Line 18- Page 17, Line 1-2).

4. Please discuss the relationship between the results of concentrations of air pollution (Figure 2) and the changes of pulmonary function from 2000 to 2009. Do the authors want to describe that temporal exposure to high concentration of air pollution before 1975 does not influence the decline of pulmonary function from 2000 to 2009, even though worsening or sustention of respiratory symptoms?
The high concentrations of air pollutants around 1970 affected respiratory function and symptoms, resulting in registration of the subjects as officially-acknowledged victims of pollution-related illness. However, the mean annual changes in respiratory function from 2000 to 2009 were within the normal ranges of individuals not exposed to these high concentrations of air pollutants, even though the severity of dyspnea worsened. These results suggest that the changes in respiratory function from 2000 to 2009 were limited to the effects of aging. We have revised the Discussion and Conclusion sections to clarify this.
Minor comments:

1. It might be more interesting if the authors could show the causes of deaths among these victims with stratified analysis in each era or pollution level. Unfortunately, we do not have enough data to perform these analyses.

2. FEV1 /FVC should be expressed as % or ratio throughout this article. We have expressed FEV1/FVC as a % throughout the revised manuscript.

3. If you use the data from previous reports as shown in discussion, it is necessary to show the air pollution levels of each previous paper. We have added information about the air pollution levels referred to in the previous papers (Page 14, Line 8).

4. Page 3, line 12
We have corrected this sentence in the revised manuscript.

5. Page 8, Line 2;
The majority of these patients were diagnosed with chronic bronchitis (n = 528, 68.2 %), asthma (n = 242, 31.3 %), or emphysema (n = 4, 0.5%), and complete spirometry data for the preceding 10 years were available for most.
->What were diagnostic criteria of chronic bronchitis, asthma and emphysema used in this study?
The criteria for victims of pollution-related illness were those specified by the Pollution-Related Health Damage Compensation Law. All victims resided or spent time on activities in an area specified as having significant air pollution as shown in Table 1, and were diagnosed based on their symptoms as described in interviews by authorized doctors. This has been clarified in the revised manuscript (Page 8, Lines 3-7).

6. Page 8, Line 6;
A further 167 patients were excluded because they were former or current smokers.
If the authors have additional data of pulmonary function tests in smoking patients, it may be interesting to see combined effect of smoking and air pollution exposure.

Smokers were excluded from the current study so that we could focus on the effects of air pollution only. We intend to analyze and report on the effects combined exposure to smoking and air pollution in a separate study.

7. Page 8, Line 8;
These patients included 156 males and 407 females who had been certified for 25.9 ± 4.6 years (males: 26.0 ± 4.6 years, females: 25.9 ± 4.6 years).

What is the reason of gender difference (more female patients)? Are they more smoking male patients?
There are two main reasons for the gender difference: the proportion of smokers was higher in males than in females, and the death rate was higher in males than in females. We have added these numbers to Figure 1 and to the text ((Page 5, Line 15, and Page 8, Line 10) and have clarified the description in the limitations section (Page 18, lines 13-14).

8. Page 12, Line 4-8;
“However, 99.8% of patients ~ cough and sputum production” Category 4 symptoms seem not to be severe, and “severe” symptoms in each category should be defined.
We have revised the text to specifically describe the severity of symptoms, and have changed the percentage values accordingly (Page 12, Paragraph 2).

9. Page 13, line 5~line 9 and Table 2
“In males, the mean~ worsening “dyspnea” In contrast to larger annual decrease of pulmonary function in male than female patients, intensities of worsening of dyspnea were not different. Please add the discussion of the reasons of this.
Table 2 shows that there were significant differences in respiratory function between males and females at the time of certification. We have discussed this in the text (Page
We have also added discussion about the different relationships between worsening dyspnea and mean annual changes in spirometry findings in males and females (Page 17 Lines 9-Page 18, Line 1 and Table 6).