Author's response to reviews

Title: The reduction of tuberculosis risks by smoking cessation

Authors:

Chi-Pang Wen (cwengood@nhri.org.tw)
Ta-Chien Chan (dachianpig@gmail.com)
Hui-Ting Chan (hueiting@nhri.org.tw)
Min-Kuang Tsai (minlight@nhri.org.tw)
Ting-Yuang Cheng (chengty.tw@gmail.com)
Shan-Pou Tsai (Shan.Tsai@shell.com)

Version: 3 Date: 7 May 2010

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

Thank you very much for your consideration of our manuscript (MS: 1148603078313132). We have carefully reviewed and revised according to the comments by the three reviewers. As a result, we have made point-by-point responses to the reviewers’ comments as follows.

I. Specific Reviewer Comments:

Reviewer 1’s Comment #1:

My fellow reviewer and myself have pointed out, “aware of TB” is different from a report of a previously diagnosed/treated TB”. In this revised manuscript, the authors defined self-reported TB history as “being aware of TB infection when the participants were first enrolled in this study”. This is not valid unless the original question in the questionnaire was “Are you aware of (ever) having a TB infection?” Such question is substantially different from “Have you ever had TB” or “Have you ever been diagnosed of TB?” Throughout the manuscript and the cover letter, the authors suggested (or implied) smokers were less aware of TB and hence they “report(ed) less TB history”. I see this as a fundamental error.

Response:

In order to avoid the misunderstanding on the “awareness”, we re-defined the self reported TB history as the participants knew/remembered their TB history. (Page 6, Line 12-13)

Reviewer 1’s Comment #2:

“One surprising finding…This paradoxical phenomenon, however, confirmed our fear that smokers were less vigilant regarding the potential onset of TB.” (Page 13 2nd paragraph) I am not convinced that one could draw such conclusion based on the information available in this study. Interestingly, the authors stated in the cover letter “if such under-reporting were similar between smokers and never smokers, then the study results would not be altered” (response to reviewer 1’s comment #2), which is contradictory to the statement in the discussion, which implies there exists differential reporting of TB history between smokers and non-smokers.

Response:
The under-reporting refers to participants answering questionnaires as best as they can, but memory fades as time lapses and they could miss certain medical history. In this regard, this under-reporting was similar between smokers and never smokers. However, smokers did not report Tb history because they were not told as explained in the text: “Partly because of fewer contacts with medical professionals, and partly because TB and smoking shared many clinical symptoms, smokers were less informed of the TB risk.” (Page 13, 2nd paragraph, Line 12-14)

Reviewer 1’s Comment #3:
Could the authors clarify how the N numbers in Table 2 could be reconciled?
Total TB deaths=77, but never smokers (n=8)+current smokers (n=21)+ex-smokers (n=6)=35. Where are the remaining individuals?

Response:
We relied on the 77 Tb deaths to assess the mortality risks (hazard ratios) between those with self-reported Tb history and those without. In addition, similar analysis was done for HR from a subset with smoking history (35 Tb deaths). In the former, those with Tb history had 5.9-fold risk of dying from Tb, and in the latter, those never smokers with Tb history had 29.47-fold risk when compared with never smokers without Tb history. The difference in the HRs reflected the need for identifying the smoking status in assessing the mortality risk of Tb history.

Reviewer 1’s Comment #4:
The HR in Table 4 has been adjusted for age, gender, education, drinking, BMI and DM history, but the latter two variables were not included in the legend.

Response:
We have updated the legend of Table 4.

Reviewer 1’s Comment #5:
The presentation is still not consistent. For example, TB was sometimes written as Tb. The way 95% CI was presented was not consistent too. In the 2nd paragraph on page 9, it was “0.26 (0.1, 0.9)”, while a few lines further on it became “HR=2.02, 95% CI: 0.7~ 6.0”.

Response:
We have revised accordingly and made the presentation consistent. For example: 95% CI was expressed as “0.26 (95% CI: 0.1 ~ 0.9)”. 
Reviewer 2’s Comment #1:
Abstract
Page 2 “conclusions” line 2 “ became close to” this could be better phrased as: “was similar to…”
Response:
We have so revised.

Reviewer 2’s Comment #2:
Methods
Page 5 Paragraph 3 line 3 “ diabetes” should be “ diabetics”
Response:
We have so revised.

Reviewer 2’s Comment #3:
Results:
Page 8 Paragraph 2 “ there was a reversed relationship …. ” This sentence could be better written: suggest “A lower BMI was associated with higher reported TB history”.
Response:
We have so revised.

Reviewer 2’s Comment #4:
Discussion
Page 10 line 1 sentence “ smokers had a very high TB mortality as many…” ”as many "should be replaced with “as much” . As in the abstract suggest replacing “and became close to” with “was similar with”. Note: same in final conclusion paragraph.
Response:
We have so revised.

Reviewer 2’s Comment #5:
Page 14 paragraph 2
The discussion about the reasons for the increased mortality should be written as hypotheses as they are not proven: for example “ COPD plays an important role” rephrase as “COPD may play an important role”… same for rest of paragraph...
Mid paragraph the sentence beginning with “ As a large… “ change “worsens” to “impairs”. Sentence “ at the same time…” mid sentence change to “the severity of
disease may be aggravated and lead to increased mortality…”

**Response:**

We have so revised.

Reviewer 2’s Comment #6:

Ref 31,32 these references are for previously published data to which you are comparing your data – either make this comparison clear by adding a sentence or two, such as “Similar observations have been previously reported” or remove the references as they are out of place after your data.

**Response:**

We modified the sentence as “as previously reported from India [31]”. (Page 14, Line 9-10)

Reviewer 2’s Comment #7:

Page 15 second paragraph

This section is confusing – the authors indicate that they are the first to report an association between TB and diabetes then report a systematic review on the subject? Please clarify.

**Response:**

Our study was the first study to link diabetes with TB mortality and not active TB. We revised as “This study was the first to associate diabetes with increased TB mortality (HR=1.89), although the relationship with active TB was well known[35]. A review of 13 observation studies found the positive relationship between diabetes and the risk of getting active TB…”(Page 15, Line 11-14)

Reviewer 2’s Comment #8:

Conclusions page 17

As indicated earlier – change “as many as” to “as much as” and “became close to” with “was similar to”

**Response:**

We have so revised.

Reviewer 2’s Comment #9:

It might be worth referencing the paper by Lin and colleagues Lancet 2008. They computer modelled the impact of smoking cessation and solid fuel usage on COPD, TB etc – They showed a reduced mortality for COPD and Lung cancer and reduced incidence of TB – they however did not report on TB mortality – this
data that the authors now present fills in this gap and has major relevance to public health interventions as they suggest.

**Response:**

We have added the reference in page 11 as “Smoking cessation has been demonstrated for reducing TB incidence [27], but this study extended the benefit of smoking cessation on reducing TB mortality.” (Page 11, Line 12-14)

Reviewer 3’s Comment #1:

Table 1, Education, middle school or below had a higher proportion (1.49% vs 1.15%) of self-reported TB history, but a lower OR – is this correct?

**Response:**

Yes, the lower educated had higher proportion of self-reported TB history, but because this relationship was reversed in the middle and old age group as shown below.

<table>
<thead>
<tr>
<th></th>
<th>Middle school or below</th>
<th>High school or above</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N of Total</td>
<td>n of Self-report TB history (+)</td>
</tr>
<tr>
<td>Overall</td>
<td>107,424</td>
<td>1,605</td>
</tr>
<tr>
<td>Age 20-39</td>
<td>11,817</td>
<td>102</td>
</tr>
<tr>
<td>Age 40-59</td>
<td>58,403</td>
<td>684</td>
</tr>
<tr>
<td>Age ≥60</td>
<td>37,204</td>
<td>819</td>
</tr>
</tbody>
</table>

We revised as “Lower education appeared to have more self-reported TB history, reflecting the large number of younger people in the lower educated group having higher self-reported TB history. However, the rates were reversed in middle age and older age, where self-reported rates were higher among the higher educated group. The conflicting result made this relationship difficult to conclude.” (Page 8, Line 7-12)

Reviewer 3’s Comment #2:

Page 9, “The group that reported smoking the least, those smoking less than half a pack a day (HR=2.60), those smoking less than 10 years (HR=3.77), or those smoking less than 15 packs per year (HR=2.89) showed substantially increased TB mortality risks.” As most papers on smoking and TB reported a dose-response relationship on amount of smoking and TB, a negative
dose-response relationship reported by this study is very strange and difficult to understand. As the reviewer indicated previously, daily consumption, years of smoking and pack-year among current smokers may not be relevant among ex-smokers who had stop smoking before enrollment. Authors should restrict the analysis of dose-response relationship among current smokers.

Response:

All the hazard ratios listed were intended to show they were statistically significant, but not necessarily different from each other, and therefore the results, without clearly showing dose response relationship, were due to limited sample size. We noted this and included this in one of our limitations.

“.....significance was found after statistical treatment, even though limited sample size failed to show dose response relationship between smoking quantity or intensity and TB mortality risks in Table 2.” (Page 16, Line 18-19)

Reviewer 3’s Comment #3:
Page 13, the paragraph beginning with one surprising finding …. needs revision. The reviewer repeats the comment that the proportion of ex-smokers who reported a history of TB was higher than smoker, which was possible that they quitted smoking because of tuberculosis. Authors assumed that smokers had a higher risk of tuberculosis but reported less, therefore, they were less aware of tuberculosis. This assumption may not hold. If smokers had tuberculosis but were less aware of tuberculosis, they should be diagnosed with tuberculosis at enrollment. Shouldn’t they? Authors should recognize that those who had tuberculosis have a higher risk of new episode of tuberculosis than those who had not. A higher proportion of ex-smoker reported a history of tuberculosis prior to enrollment in the program but had a lower TB mortality than smokers after enrollment, which provides evidence that quitting reduce the risk of subsequent development of tuberculosis.

Response:

In Taiwan, everyone had BCG vaccination, and TB skin test was not very useful in detecting or diagnosing TB. So the enrollment exam could not determine the high risk group or make new TB diagnosis. Ex-smokers had more TB history, but because of their nonsmoking status, they died less from TB than smokers.
Reviewer 3’s Comment #4:
Page 6, Self-reported TB history was defined as being aware of TB infection. Is it TB infection or disease?
Page 12, Third, … those who reported a history of TB

Response:

We have so revised as TB history.