Author's response to reviews

Title: The reduction of tuberculosis risks by smoking cessation

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Version: 2 Date: 20 March 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. General Comments

Associate Editor comments #1:
The authors are suggested to break the Methods and Results into subsections with short, informative headings to improve the manuscript readability.

Response:
The methods and results have been reformatted with short headings.

Associate Editor comments #2:
The title should be more concise and clear. The Methods section in the abstract should include a statement of the study purpose and a more clear and concise description of the study design and data analyses methods.

Response:
We have changed the title to “The reduction of tuberculosis risks by smoking cessation” to reflect the practical value of this study.

The purpose of the study has now been added to the method section and revised as: [Page 7, Second paragraph]

“The study attempts to quantify the smoker’s risks on subsequent TB mortality and the change in such risks after smokers quit smoking. In this prospective cohort study, the TB mortality risks of smokers, never smokers and former smokers were compared by using the Cox proportional model to estimate the hazard ratio (HR) of TB.”

Associate Editor comments #3:
The authors are suggested to look at some sample articles from the Journal to improve the organization of information presented in the manuscript. Also, they need to be consistent in line space use throughout their manuscript, including Abstract and references.

Response:
We have checked two sample articles from BMC Infectious Diseases. The
structure of the manuscript has been improved. Line space use was adjusted throughout the manuscript.

Editorial requests #1:
We recommend that you ask a native English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional copyediting service. Examples are those provided by the Manuscript Presentation Service (www.biomedes.co.uk), International Science Editing (http://www.internationalscienceediting.com/) and English Manager Science Editing (http://www.sciencemanager.com/). BioMed Central has no first-hand experience of these companies and can take no responsibility for the quality of their service.

Response:
We have asked an American-born native professional to help edit our manuscript. The modifications have been incorporated into the manuscript.

Editorial requests #2:
Please be sure to include a Conclusion section within your manuscript.

Response:
Conclusion section was included in the revision. [Page 17]

Editorial requests #3:
Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include their source(s) of funding. Please also acknowledge anyone who contributed materials essential for the study. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements.

Response:
We have added the acknowledgement in the revision and obtained their permission to acknowledge. [Page 18]

Editorial requests #4:
Please provide the name of the ethical committee that provided approval, within the manuscript.

Response:
We have added the subtitle named “Ethical issues” in Method section. The name of ethical committee was added. [Page 7]

Editorial requests #5:
Please revise the Background section of the Abstract to include an aim.

Response:
We have added the aim to the background section of the abstract as: “The aim of this study is to assess the benefits of smoking cessation on Tb mortality reduction.”
II. Specific Reviewer Comments:

Reviewer 1’s Comment #0:
The message this paper conveys is simple, but the presentation could be improved by simplifying the results text and tables.

Response:

We have simplified the tables and results by reporting only the variables that are statistically significant.

In Table 1, we excluded the age stratification among different education levels and hypertension, which was insignificant.

In Table 2, we excluded the non-related information on all-cause mortality and the description of the cohort.

In Table 3, we also excluded hypertension and have kept the same variables as those in Table 1.

In Table 4, the national prevalence for smoking was used to calculate population attributable fraction (PAF). The proportion of individuals that smoked in this cohort was not used there. Hence, we also excluded this column. The representativeness of the samples was discussed in the Discussion section.

Reviewer 1’s Comment #1:
I agree with the authors that the relationship and the potential interaction between smoking and TB is generally overlooked. However, I do not think such unawareness (or lack of enthusiasm) is due to the fact that majority of the existing evidence is derived from case-control studies. At least three systematic reviews have been published, suggesting the association between smoking and increased risk of TB infection, active disease and mortality (Slama et al. Int J Tuberc Lung Dis. 2007;11:1049; Lin et al. PLoS Med. 2007;4:e20; Bates et al. Arch Intern Med. 2007;167:335). The authors noted there have been limited cohort studies examining smoking and TB mortality and that information from East Asia was scarce. In fact, three studies from China (Liu et al. BMJ. 1998;317:1411), Taiwan (Lin et al. Am J Respir Crit Care Med. 2009;180:475), and South Korea (Jee et al. Am J Epidemiol. 2009;170:1478) were not cited in the paper. While I could see there are gaps in the existing knowledge, I think the introduction has not adequately presented the picture nor has sufficiently justified the research question.

Response:
We have modified or eliminated the sentence with the word “scarce” and cited the suggested references. [China (Liu et al. BMJ. 1998;317:1411), Taiwan (Lin et al. Am J Respir Crit Care Med. 2009;180:475), and South Korea (Jee et al. Am J Epidemiol. 2009;170:1478)] The latest two papers were published just before or right after the submission of manuscript. Therefore, we were unaware of their existence. The objectives of the research were refined in the last paragraph of the introduction. [Page 4, Second paragraph]

“The objective of this study is to assess the effect of smoking on TB mortality and the benefit of smoking cessation by following a healthy Chinese cohort. Because having TB history (or known TB patient) is a major confounder, we were particularly interested in examining the reduction of TB risks among those without TB history after they quit smoking.”

Reviewer 1’s Comment #2:
I am concerned about the use of the terms “awareness of TB history” (3rd line, 1st paragraph of Results). My understanding from the Methods is that the participants were asked “whether they had a TB history” and not “whether they knew they had ever had TB”. Thus, a participant could be aware he/she had had TB but decided not to report in the questionnaire (possibly because of the heavy stigma associated with the condition). It could hence be argued that the increase of “TB awareness” with age is a mere reflection of increased proportion of under-reporting in younger participants because TB is seen more of a stigma in younger individuals. This “argument” is also supported by the finding that younger participants with lower educational attainment tended to be more likely to report TB. While the authors acknowledged that under-reporting of TB history was “almost a certainty”, without differentiating intentional under-reporting from genuine unawareness, there would not be enough information to determine/compare awareness among smoking/non-smoking subgroups. Some form of objective assessment of TB history would be needed, although this might not be feasible/practical in a setting like the present study.

Response:
It is possible that people could under-report TB history in this society because of stigma, but the evidence is not strong. First, in this study, history of TB was not the only question asked. In fact, it was one of the five sections in the questionnaire, and the TB question was embedded in the 20 diseases asked, such as cancer, mental health and taking psychotropic medications. Some of these questions would seem to be more sensitive than TB. Furthermore, unlike surveying street people, participants in this study were genuinely interested in uncovering medical problems and thus would be
more than willing to provide as much medical information as possible for a more accurate evaluation, because they paid a sizable fee to be screened. In answering a large number of questions, the sensitivity for a single question like TB should have been greatly reduced. As for why older people reported more TB than younger ones, this could be interpreted as a reflection of the cumulative experience in TB exposure among the elderly. A higher number of less educated individuals been exposed to TB also reflected a higher chance of being exposed in that social class. In summary, TB history is valuable for understanding the awareness or the degree of concern about the disease in the general public. Like history of other diseases, certain under-reporting must have existed, but if such under-reporting were similar between smokers and never smokers, then the study results would not be altered.

[Page 16, Line 9]

“While under-reporting of TB history could have existed, most of them should be unintentional, as participants in this study, having paid a sizable fee to be screened, were genuinely interested in uncovering medical problems and thus would volunteer as much medical information as possible for an accurate evaluation. As there is no reason for smokers to have different reporting mechanism from never smokers, our study results showing a low awareness of TB among smokers in this cohort were valid.”

Reviewer 1’s Comment #3:
While the authors did state that “the cohort came from a higher social class, having above average health status”, no further information in the text suggest how this sample is compared with the general population. In Table 4, the proportion of ex-smokers in the sample was 6.18%, while that from the national statistics was 3.65%. The authors should comment on the representativeness of the sample and generalisability of their findings.

Response:
This information was added into the first point of limitation to explain the representativeness of the samples.
[Page 15, Line 9]

“First, the cohort came from a higher social class with the ability to pay for the screening. Therefore, it may not be fully representative of the society. For national prevalence of smoking or TB, the cohort data needs to be standardized by the socioeconomic status as in our previous reports. However, as prevalence was not the focus of this study, and hazard ratios or odds ratios were internally standardized, the
observed increase in smoker’s TB risk can be a reasonable estimate of the general population. In the same vein, we used national smoking rates to calculate TB mortality attributable to smoking, and thus, the resulting estimate should also be valid.”

Reviewer 1’s Comment #4:
The authors referred body mass index (BMI) of <18.5 kg/m\(^2\) as “extreme underweight”. Nevertheless, “extreme underweight” is generally referred to those who have BMI <16 kg/m\(^2\) (WHO. Physical status: the use and interpretation of anthropometry. Geneva: WHO, 1995). The authors need to pay attention to the choice of terminology.

Response:
We eliminated the word “extreme” from our “underweight” definition for a body mass index (BMI) of <18.5 kg/m\(^2\).

Reviewer 1’s Comment #5:
Several inconsistencies in presentation style need to be corrected. For example, on page 14 in the 2nd paragraph 95% CI was presented as “1.53~1.71”, whereas in all tables it is written as “lower limit, upper limit”. There are also extra full stops, e.g. first sentence in the last paragraph on page 3.

Response:
Revision has been made so that the style of the confidence interval is consistent throughout the manuscript.

Reviewer 1’s Comment #6:
In the Methods, it was stated “current smokers were asked to give number of years and number of cigarettes smoked per day.” However, nowhere in the paper does it mention whether the same information was collected from ex-smokers. It needs to be clarified as the definition of ever smoker comprises both current and ex-smokers, and in Table 2 pack-year exposure appeared under the group “Ever smoker”.

Response:
We modified the method section as follows:

[Page 6, Line 2]
“Number of years and number of cigarettes smoked per day were collected from both current smokers and ex-smokers. We used “ever smokers” to represent the combined group of smokers and ex-smokers.”
Reviewer 1’s Comment #7:
The authors should explain their choice of confounders/risk factors in the regression model. BMI, diabetes, and hypertension were described but were not included in the model. This appears to be haphazard.

Response:
Confounders were selected based on those with significant odds ratio in Table 1, including age, gender, education, drinking, BMI, and DM history. Hypertension was not found to be significant.

Reviewer 1’s Comment #8:
It has been demonstrated that exposure to sidestream smoke causes more harm than mainstream smoke (from active smoking) (Schick and Glantz. Tob Control. 2005;14:396). In China (and in other parts of East Asia) in utero and childhood exposure to passive smoking and indoor air pollution has been common. This could potentially have substantial effect on lung growth and increased the susceptibility of infections. Adjustment for these variables is thus necessary in order to determine the exact contribution of smoking to TB mortality.

Response:
Passive smoking or air pollution is a potential confounder, and, in the absence of data, we put it as part of our limitation. Whether side stream smoke causes more harm than mainstream smoke is a matter of the context under which this was compared. In animal studies, with large amount of side stream smoke, the toxicity could be devastating, as shown in the cited study that 10% of animals succumbed to side stream smoke alone. However, the amount of human exposure to second hand smoke is rather limited, and in far less concentration than active smoking. The relative impact of active and passive smoking could not be extrapolated from the cited study. The author of the paper stated that one out of 8 non-smokers was killed by passive smoking, while active smoking killed one out of two smokers.

[Page 13, Line 7 from the bottom]
“Passive smoking is a potential confounder, and in the absence of these data, their impact on susceptibility to TB infection is unknown. However, the concentrations of second-hand smoke to which humans are exposed to are considered to be of far less than that of active smoking.”

Reviewer 1’s Comment #9:
The comparison of participants’ characteristics has been unnecessarily long,
given the detailed Table 1.

**Response:**
We have modified and shortened the description.

Reviewer 1’s Comment #10:
The coexistence of other chronic lung conditions, such as chronic obstructive pulmonary disease (COPD) could complicate the relationship and should be commented on.

**Response:**
We have added the description as follows
[Page 14, Line 8]
“COPD plays an important role in the relationship between smoking and TB. As a large number of smokers develop COPD, which worsens the respiratory system and masks the physical signs of TB, the smokers become less aware of TB. At the same time, in patients with both TB and smoking-related COPD, the severity of disease is aggravated, which accelerates mortality and leads to increased TB mortality among smokers as shown in this study.”

Reviewer 1’s Comment #11:
In the Discussion, the authors stated “This highlights the importance of adjusting educational levels when considering the smoking effect on Tb mortality.” This is not appropriate as educational level was only a proxy for socio-economic status. Educational level per se would have little confounding effect on the relationship.

**Response:**
We agree that educational level was only a proxy for socio-economic status, but it seems to be more representative than other closely related measures such as occupation or income, which often vary from time to time. Income is rarely reported in a consistent way and may not be representative of one’s financial status. However, educational level is considered to be highly correlated to these components of socioeconomic status.

Reviewer 1’s Comment #12:
The presentation of the tables could be improved.
Response:
We tried to make tables more concise.

Reviewer 2’s Comment #1:
The authors all appear to be of Taiwanese origin although two have affiliations in the USA. The quality of the English is not of publication standard and there are numerous grammatical and comprehension errors. The authors would do well to include an English first language speaker with publication experience to rewrite the manuscript as there are excessive grammar and language errors.

Response:
A native English speaker has proofread the entire manuscript, as recommended by the reviewer.

Reviewer 2’s Comment #2:
There is an enormous and excessive amount of data presented in both text and tables. The tables are poorly laid out and several analyses are performed using less than 5 subjects (in a 500,000 patient study). Tables 1,2,3 require extensive revision and simplification.

Response:
We have re-organized the structure of the results, as well as simplifying the tables. Although the sample size was not large enough, the statistical significance was reached in the sub-cohort analysis.

Reviewer 2’s Comment #3:
TB “awareness” is frequently used. This term is confusing and undefined in the manuscript. History of TB is the issue at hand and once defined as “self reported” TB history should be used not “awareness” which has several other connotations. This is especially true when: smokers have less “awareness” of TB history suggesting that they somehow forgot or did not know because they smoked?

Response:
Since the answer to the question on TB history was self-reported by the participants, we defined the “self-reported TB history” in the Method section as “being aware of TB”. [Page 6, Line 10]

Reviewer 2’s Comment #4:
The major finding was that smoking was not associated with TB disease but
was associated with dying from TB. The authors then calculate that 44% of TB was associated with smoking. It is unclear if TB history and TB death were combined to calculate TB incidence in the cohort? I am uncertain how if TB and smoking are not associated that 44% TB can be attributed to smoking?

**Response:**

We were misunderstood. We did not mention smoking was not associated with TB disease. This is because we did not have data on Tb disease. We found that more smokers were less aware of the disease than never smokers (by reporting less TB history). Awareness and having the disease are two different issues. Awareness involved having symptoms or being diagnosed with the disease. Our point was that a majority of TB cases were unaware of the condition.

Reviewer 2’s Comment #5:

Abstract Results section
Line 4 “… were translated into nearly half (44.6%) of Tb being attributable …. “
In this study smoking was associated with TB death but Tb was “25% less” Tb history. If TB and smoking were not associated then is does not seem possible to attribute risk to smoking for TB?

**Response**:

We found more smokers than never smokers were less aware of the disease (less TB history was reported by never smokers). Awareness and having the disease are two different issues. Awareness involved having symptoms or being diagnosed with the disease. Our point was that a majority of TB cases were unaware of the condition. Since the answer to the question on TB history was self-reported by the participants, we defined the “self-reported TB history” in the Method section as “being aware of TB”. [Page 6, Line 10]

Reviewer 2’s Comment #6:

Introduction:
There are numerous grammatical and language errors (throughout the manuscript) that should be rewritten (I strongly recommend asking a first language English speaker to read and correct the manuscript) there are too many to individually indicate but examples are:

“Significance was interpreted with less enthusiasm” : colloquial
“took on an unnoticed importance” poor language
Response:
We have asked a native English speaker to help edit our manuscript. The modifications have been incorporated into the manuscript.

Reviewer 2’s Comment #7:
Methods
The use of the term “awareness” should be avoided unless awareness is specifically meant i.e. awareness n. Synonyms: aware, cognizant, conscious, sensible, awake, alert, watchful, vigilant These adjectives mean mindful or heedful: Aware implies knowledge gained through one's own perceptions or by means of information free dictionary ref. It would be more logical to define TB history as self reported… i.e. the elderly reported more TB (which is logical as the chances of having TB over a life time is higher). “Smoker were less aware of TB history” this sentence implies that somehow smokers had TB but did not know about it – this does not make biological sense. It is unclear if both TB death and TB history are combined to calculate TB incidence? It is important to make this point very clear, as those that died from TB would not necessarily provide a “history of TB” but clearly had TB - but only recorded in the death registry. Statistics - appear to be correctly performed

Response:
We defined the “self-reported TB history” in the Method section as “being aware of TB”.

Reviewer 2’s Comment #8:
Results
The results are presented in a exhaustive manner - It would be better to combine several outcomes together i.e. all smoking related, then associated diseases etc. Some of the variables are reported in a manner that is illogical. i.e. BMI it is well know that malnourishment is a risk for TB therefore reporting high BMI first is illogical unless associated with diabetes… Several associations are reported where the “n” is very small i.e. 2 these are frequently “not significant” and detract from the data that is. In other words report on the significant results and relevant negative ones only. The tables are overly inclusive of data and should be revised and significantly pared down of unnecessary data. The layouts are also confusing with HR$., HR3 etc…

Response:
We reported the significant results only, as suggested by the reviewer. The layouts of
the tables have been changed.

Reviewer 2’s Comment #9:
Discussion
The discussion is over 6 pages and should shortened.
The discussion on the “lack of association” between TB and smoking is poor – lack of awareness of TB or “being less vigilant” is a weak explanation for the finding. The authors are suggesting that if you smoke, you might get TB but don’t know about it or seek help. Again is would be important to note if all TB i.e. history and death without previous history are included in the incidence numbers.
The term “inverse dose response” relationship cannot be attributed to BMI as there is no “dose” – the term inverse relationship between BMI and TB history would be better used.
The final paragraph discusses the limitations of the study and then ends. It would be advisable to provide a summary conclusion at the end of the manuscript.
Response:
Discussion has been shortened. All-cause mortality and TB mortality were calculated for those with and without history of TB. We have deleted the words “dose response”. We also have added the conclusion in the end. [Page 17]

Reviewer 3’s Comment #1:
First, using past history of tuberculosis to evaluate awareness of TB may be problematic. TB history was a past event. The proportion of the study population with such a past event was influenced by several factors that were not investigated by the current study. Patients who had such an event may not be included and Determinants evaluated may change over time, such as smokers may quit smoking because of the diagnosis of tuberculosis. In reference 19, the proportion of non smokers was 46.5%, and that of ex-smokers was 7.1% and that of current smokers was 46.5%; the respective figure in the current cohort was 70.3%, 6.15, and 23.5%. Therefore, the reason that the proportion of smokers with a past history of TB was less than that of ex-smokers could be due to the fact that smokers quitted smoking after the diagnosis of tuberculosis, or smokers with a history of TB were less likely to be enrolled in the program as compared with ex-smokers. Over-interpretation of past history of TB should be avoided. It is not adequate to conclude that smokers were less aware of having TB history than nonsmokers.
Response:
We found more smokers than never smokers were less aware of the disease (by
reporting less TB history). Awareness and having the disease are two different issues. Awareness involved having symptoms or being diagnosed with the disease. Our point was that a majority of TB cases were unaware of the condition. Since the answer to the question on TB history was self-reported by the participants, we defined the “self-reported TB history” in the Method section as “being aware of TB”.

Reviewer 3’s Comment #2:
Second, tuberculosis mortality is not accurate in Taiwan. Wu et al reported substantial under-coding and over-coding in the assignment of TB-related underlying cause of death (Assessing the Quality of Tuberculosis-related Underlying Cause of Death Assignment in Taiwan, 2001–2005. J Formos Med Assoc 2008;107(1):30–36). The main source of over-coding was “old” TB cases. Official coders assigned TB as the underlying cause of death for those who had old TB. This partly explained the finding of current study that those who have a past history of tuberculosis had a high TB mortality. Unless those who had a history of TB developed active tuberculosis since enrollment and subsequently died of tuberculosis, TB should not be assigned as the underlying cause of death. Authors should first of all investigate developing tuberculosis disease in this cohort, then investigate TB mortality among those who develop active tuberculosis. Table 2, it is better to analyze daily consumption, years of smoking and pack-year among current smokers. These may not be relevant among ex-smokers who had stop smoking for several years. Findings reported in second paragraph of page 8 did not make sense.

Response:
In our data, we cannot identify whether they are active TB or not. The prevalence of TB among elderly was higher. If the diagnosis procedure between smoking and non-smoking were not different, then over diagnosis would be a systematic problem, and the relative risk wouldn’t be affected.

Being an ever smoker will increase the risk of TB infection. The quantification of smoking status of ever smokers was based on this assumption.

Reviewer 3’s Comment #3:
As the study last from 1994-2007, smoking status of participants may change. How did author address this issue?

Response:
In general, smokers don’t change their behavior patterns unless there is a pressing medical condition. Some participants may be smokers at the enrollment and later on quit smoking, and vice versa. However, the proportions of people started or quit smoking are relatively low. Moreover, some low-risk participants were misclassified as high-risk participants and thus the relative risk for TB mortality calculated in this study would more likely be over-estimated.

Reviewer 3’s Comment #4:
Introduction: First paragraph, increased risk of relapse may alter clinical practice as well.

Response:
We added the following sentence to Introduction:
[Page 3, Line 8]

As there was limited evidence on TB mortality from cohort studies,[6-8] the clinical significance of reducing smoking on TB mortality was largely unrecognized [9]. **Whether smoking was viewed as a risk factor for TB relapse was also not fully established.**[10] This is due to the fact that since TB is a treatable disease[9], the role of smoking as a risk factor for TB disease was mostly perceived as irrelevant.