Author's response to reviews

Title: Indoor solid fuel use and tuberculosis in China: a matched case-control study

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Author's response to reviews: see over
We thank the reviewers for their comments. We provide below a point-by-point response to the reviewers’ comments.

First Reviewer's report
Title: Indoor solid fuel use and tuberculosis in China: a matched case-control study
Version: 1 Date: 23 March 2011
Reviewer: Rogelio Perez-Padilla
Reviewer's report:
GENERAL: Question was the risk of tuberculosis in those exposed to solid fuel smoke, with well described and appropriate methods and sound data, with a good manuscript, clear and concise. Previous work is acknowledged and abstract and writing is good. Strengths of the study are clearly stated and some of the limitations, for example the presence of missing data, but with clear strategy to analyze the database taking into account the missing data.
It is also clearly stated that exposure in the studied community is likely much lower than in communities cooking with open fires and higher levels of indoor pollution as happens in many developing countries, also having high tuberculosis problem. This is an important issue.

1- Other limitation is that exposure is not measured but categorized by cooking fuel and type of stove and ventilation. Categories used in the study correlate with overall measured levels of indoor particles and other pollutants but each group has a wide dispersion of mean levels and also peak levels during cooking. This may lead to some misclassification of exposure by indoor particulate matter levels or any other pollutant considered relevant.

Answer: We agree there is a limitation of this approach and have discussed the limitation extensively in Discussion.

2- What exposure the authors considered the most relevant? Current? That would have to do with enhancing recent transmission and disease progression but can also be previous at the moment of primary infection. A model of impact of exposure to solid fuel smoke in relation to tuberculosis infection and disease is relevant for the study model. People non exposed to solid fuel smoke in the study, may have been exposed in the past in the right moment for the infection or for developing of disease. Past exposure is important for past development of disease (before diagnosis)

Answer: We agree with the reviewer that this is an important issue. To investigate
whether exposure to combustion of solid fuels is associated with either the transition from exposure to tuberculous infection or the transition from infection to disease requires differing study designs. The former requires tuberculin skin test or interferon-\(\gamma\) release assay to detect latent tuberculous infection in the absence of disease, and the latter requires a population with positive tuberculin skin test or interferon-\(\gamma\) release assay followed prospectively toward development of disease. As a first step, we have investigated whether exposure to combustion of solid fuels is associated with tuberculosis, without separating the transition from exposure to tuberculous infection, and the transition from infection to tuberculosis disease.

3- Case control studies have been used to assess indoor pollution as a risk factor or cause of tuberculosis. Case control studies have limitations, even those population based, with possible biases that have to be acknowledged. One is the quantification of exposure, done in retrospect. Other is the association between use of solid fuel and poverty with many derived risk factors. Community matching by neighbors tends to match SE level and in this sense exposures: difficult or impossible to separate low SES and solid fuel use.

Answer: we agree with the reviewer that the case-control study design has limitations. We have added this to the discussion.

4- Better designs are needed in this field. Cohort studies are lacking to address the issue of tuberculosis and indoor pollution, and those studies are welcome and needed. Other very powerful design is the intervention study, where stoves are improved in a community or part of it, with the great advantage that the permanent link between poverty and use of solid fuels is broken. Some of those studies are now reported but not for tuberculosis. Interesting, improved stoves, with chimney are associated with high level of pollutants in the kitchen, although much lower than with open fires.

Answer: we fully agree with the reviewer that the cohort and experimental study designs on this subject are needed. However, even in high burden countries, tuberculosis is a relatively infrequent disease (one case in a thousand in a year) making such designs expensive and complex.

5- Population studied: may be typical for China but is peculiar for other parts of the world in terms of exposures. Smoking is very high, and in general smoking is a very powerful driving force for lung diseases, more powerful than indoor pollution. Smoking requires more than yes or not, something semi quantitative at least. About
half of the studied population smokes what is much higher than in other rural areas of developing countries. Also coexist several fuels used for cooking, including coal, charcoal, wood, crop residues, gas, what is also uncommon in other parts of the world. Risk for several diseases differs from coal, especially smoky coal and biomass and it may be the same for tuberculosis. Putting together all solid fuels may be questionable. WHO speaks of solid fuel effects in fact, and for example finds an increased risk for lung cancer, but it is due mainly of exposure to coal (in China), and not to biomass.

Answer: We have conducted a systematic review to investigate the association between smoking and tuberculosis and reported that a positive association between smoking and tuberculosis has been convincingly demonstrated by a substantial number of studies; a clear dose-response relationship between smoking and tuberculosis has been highlighted in several studies as well. The association between smoking and tuberculosis is not the focus of this study. Therefore, we did not go into the detail to quantify amount of daily consumption of cigarettes. We agree with the reviewer that a strong risk factor may mask the effect of other risk factors; the association between smoking and TB may not be easily demonstrated among the HIV infected with a low CD4 counts. However, smoking as a risk factor is not as strong as HIV. Further, in this study population, smoking was not associated with use of solid fuel; higher levels of smoking were also not associated with greater use of biomass fuel (thus causing a confounded relationship). The association between use of solid fuel and TB remained not significant in a multivariate model that includes all possible risk factors regardless of p value in univariate analysis. We have added this to the discussion.

Concerning different types of fuels used for cooking, we used the approach recommended by Kirk Smith and colleagues in classification of solid fuel. This study is not powered to differentiate associations of different types of fuel and tuberculosis.

6- Indoor pollution affects mainly women and small children, unless used also as a heating source and if a cause of tuberculosis it is expected to increase tuberculosis mainly in women and children. Others only by contact with tuberculous patients. The studied population is mostly men. Possible impacts of this situation should be commented.

Answer: we agree with the review and have added this in Discussion. Tuberculosis is primarily reported amongst men in China, much higher than amongst women. Thus, the number of cases in women (and particularly in children) was very small.
In summary information provided is useful and welcome but not necessarily applicable to the situation in many poor countries with higher levels of indoor pollution. Indoor pollution was not measured and in the design exposure to solid fuel pollution cannot be separated from other effects of poverty. Smoking is a leading risk factor for lung diseases, and may be leading risk of diseases in the studied population. China has advanced a lot in eliminating the most pollutant indoor stoves, and as the results of this study can not necessarily be extrapolated to most regions of the world with high indoor levels of pollutants, if phrased poorly, the results of this study may reduce interest to improve stoves in poor countries.

Answer: we fully agree with the reviewer and have emphasized in the Discussion that the results of this study may not be generalized to other countries. Further studies are needed.

Second Reviewer's report
The authors present a study on the topic of indoor solid fuel use and the risk of disease progression to tuberculosis in China. In a setting with predominantly proper ventilation in cooking places the authors find no association of solid fuel use with tuberculosis. The study is well written and adds new information to this field.

Major Comments:
1-Almost 20% of the cases had a history of TB contact within the previous 5 years, but only 1% of controls. Do the results change, when including only cases and controls without known prior TB contact?

A: We understand the reason why the reviewer raised this point. However, excluding tuberculosis contact from analysis would break the match and is not consistent with our study design. We prefer not to do so, as we are concerned that this would result in ‘data dredging’.

2-No association of use of solid fuels with sex was observed by using stratified univariate analysis. However, no information is given about the sex distribution of prior TB contact among the cases that might lead to negative confounding. Did the authors perform a stratified analysis by prior TB contact among women, only? Was there a correlation between sex and prior TB contact supporting the hypothesis of potential negative confounding? In addition, only 27% of cases and
28% of controls were female. Based on the power calculation presented, an association with sex would only have been found at markedly higher ORs than 2.

A: We thank the reviewer for this comment but prefer not to perform further analysis stratified by TB contact because this is not our study design and would break the match (as we noted in response to the first comment). There was no association between sex and prior TB contact. We have indicated in the Discussion that less than 30% of participants were female, which limits the power in detecting the association between exposure to combustion of solid fuels and tuberculosis because female are more likely to be affected by such exposure. We think it is better to stratify case enrollment by sex in future studies.

3-The authors state that they matched for age (+-15 years), as the results show, however, age (being a proxy for TB prevalence) showed a significant association. The authors should mention as a limitation that the cases were “undermatched” for age.

Answer: The range of age used for matching in this study design was wide. Therefore, we included age in multivariate analysis. We performed matching to increase the study efficiency and included age in the multivariate analysis to control for age as a potential confounder. We believe this approach addresses the potential ‘undermatching’ for age.

Minor Comments:
3-Results on page 9 are redundant to Table 1 and should be shortened.

Answer: we shortened page 9 as recommended.

4-Please give median age rather than the average

Answer: we present the median age as recommended.

Once again, we thank the reviewers for their comments on this manuscript.