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:

We thank Editors’ comments. We provide point-by-point response to Editors’ comments.

Editors comment:

"The authors have provided detailed responses to the points raised by the first reviewer and myself, however before accepting the manuscript for publication, I would like to follow-up the central issue of pre-existing TB infection for the study of the risk of progression to active disease after exposure to indoor air pollution caused by use of solid fuels for cooking.

As known prior TB contact represents the main risk factor for developing active disease and given the distribution among cases (20%) and controls (1%), the source population of cases and controls differ with respect to risk of infection. As infection and progression to disease are two separate events, including known prior TB contact into the conditional logistic regression model can only partially address this problem. It was suggested to include only cases and their matched controls that did not have a known history of prior TB contact to ensure that the source population did not differ with respect to TB infection rates.

In response to my Major Comment 1, the authors point out that excluding cases and controls from the analysis would break the match and therefore no additional analysis for cases and controls without known prior TB contact could be performed. Breaking the match will not occur, if cases and corresponding controls are excluded from the analysis. It is clear that this would lead to the loss of up to 21% of cases (and their controls, worst case scenario) reducing the power of the analysis.

Answer: Following Editors’ advice, we performed analysis restricted to triplets of cases and controls who had no prior family TB contact. If any case or control of a triplet had prior family TB contact, the triplet was dropped. This created a subset..."
of study population with 159 cases and 318 controls (total 477). In this subset, using solid fuel for cooking (OR 1.2, 95% CI 0.8 -1.8) was not significantly associated with tuberculosis; using solid fuel for heating (OR 1.0, 95% CI 0.8 -1.3) was also not significantly associated with tuberculosis.

Of course all cases are results of prior infection therefore the study design chosen by the authors requires that all cases and controls were infected. Is there any additional information to confirm this? Otherwise previously infected cases of TB are compared with controls that might not be infected at all. Please comment and include into the discussion.

Answer: To investigate whether exposure to combustion of solid fuels is associated with the transition from infection to disease will require controls who are infected, either with positive tuberculin skin test or positive interferon-γ release assay. 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 and our conclusions are only valid for the full transition and not its components. In this approach, it has not been possible to separate the two components of the transition and is not possible (or relevant to the analysis of the total, rather than specific, transitions) to ensure that controls are infected. This is unfortunate but cannot be addresses post hoc. In spite of this limitation, the same study design has been used in many of the studies on the association between smoking and tuberculosis and all published studies on the association between exposure to combustion of solid fuels and tuberculosis. We recognize this limitation, thank the editor and have added this to the discussion.

Additional Comments:

The changes made in response to the comments by the reviewers result in some inconsistencies in the manuscript that need to be resolved.

1. p12, the authors state " The association between the use of solid...in a multivariate (conditional?) model that includes all possible risk factors REGARDLESS of p value in the univariate analysis". However in the methods section (p9) the write "ALL significant variables were entered into a multivariate conditional logistic regression model...".

Answer: Initially we undertook a conventional analytic approach, and only significant variables were entered into a multivariate conditional logistic regression model. In response to reviewers’ comments, we re-analyzed and included all possible risk factors in a multivariate conditional logistic regression model regardless of p value in univariate analysis under the consideration that the association between exposure to combustion of solid fuel and tuberculosis may become significant in multivariate analysis if it was negatively confounded by other determinants in univariate analysis. We accept this and have revised the manuscript.
2. p18, "Further we used predetermined procedures in selecting neighbours as controls to reduce selection bias". However, the authors point out (p19) "...neighbourhood controls automatically entails matching and may introduce selection bias".

Answer: Thanks. We revised the first sentence as the following: "Further we used predetermined procedures in selecting controls to reduce selection bias".

Other Editorial requirements:

Title page: Please include a title page in the manuscript file. This should contain; Title, Author list, Affiliations (department names, institution name, street name, city, zip code, country), email addresses. The author list and email addresses must be identical in the manuscript file and on the submission system, and it must be clear which affiliation pertains to each author.

Answer: we have included a title page containing required information.

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