Author’s response to reviews

Title: Interaction of nutritional status and diabetes on active and latent tuberculosis: A cross-sectional analysis

Authors:

Rachel Kubiak (rwkubiak@uw.edu)
Sonali Sarkar (sarkarsonaligh@gmail.com)
Charles Horsburgh (rhorsbu@bu.edu)
Guatam Roy (gautam.r@jipmer.edu.in)
Mario Kratz (mkratz@fredhutch.org)
Ayiraveetil Reshma (dr.reshma04amrita@gmail.com)
Selby Knudsen (Selby.Knudsen@bmc.org)
Padmini Salgame (salgampa@njms.rutgers.edu)
Jerrold Ellner (jerrold.ellner@bmc.org)
Paul Drain (pkdrain@uw.edu)
Natasha Hochberg (nhoch@bu.edu)

Version: 1 Date: 05 May 2019

Author’s response to reviews:

May 5, 2019

Manuscript ID: INFD-D-19-00453

Title: “Interaction of nutritional status and diabetes on active and latent tuberculosis: A cross-sectional analysis”

Dear BMC Infectious Diseases,
Thank you for providing comments and inviting us to resubmit a revised version of our paper. We provide a point-by-point response to the editorial review below. We have also resubmitted two versions of the revised paper, one version with the changes highlighted by Track Changes.

All authors have contributed significantly to the work, have seen and approved of this manuscript, and can attest to the validity and honesty of the results. The contents of this article have not been published and the paper is not under review elsewhere for publication. Thank you for your consideration.

Please direct all correspondence to:

Rachel W. Kubiak, MPH, University of Washington, Department of Epidemiology,
1959 NE Pacific Street, Health Sciences Building, Box 357236, Seattle, WA 98195 USA.
phone: (907) 382-3267 email: rwkubiak@uw.edu

Sincerely,

Rachel Kubiak, MPH
University of Washington

Reviewer #1 - Kavitha Saravu, MBBS, MD, DNB, DTM&H

The authors have addressed a very important aspect of Interaction of Nutritional status with TB & DM. Authors also have explored this association among LTBI which is commendable.

My specific comments are:

1. Table 1: How is that predominant Gender differences in TB patients and household contacts? It means, for household contact tracing, not all eligible male members were not available.
How was the TB contacts screened? Is it by a house visit or the house hold contacts who were available? Is there a possibility that the gender bias could have affected the comparison? Especially age, hazardous alcohol use (more commonly in males)

Response: The male predominance of TB cases is in keeping with what is found internationally, hence we have a larger proportion of female household contacts. For example, male index cases are likely to live with female spouses; therefore the gender distribution is not surprising. TB contacts were screened at their homes and were enrolled if they were present and agreed to participate. It is possible that gender may have affected alcohol use, but it is unlikely that this greatly affected diabetes and nutrition as the prevalence of these is quite similar between genders. Additionally, we controlled for gender in all analyses.

Manuscript Revisions: We edited the following sentences (bold = new): “At household contact enrolment, which occurred primarily at the household, the study nurse injected. . . .” and “All household contacts were followed for one year; symptom screens (and sputum testing if indicated) were performed to identify incident active TB disease.” (Methods section; study procedures)

2. Table 1: Other Comorbidities; the numbers for individuals with renal failure and HIV are too low; It may be that all individuals are not tested for this. In that case the number of individuals tested can be mentioned.

Response: All individuals were asked about renal failure, but this was not tested using a laboratory assay. All index cases were screened for HIV and the prevalence is <1%, therefore we don’t anticipate higher rates in household contacts.

Manuscript Revisions: We added the following sentence. “Individuals were questioned regarding a history of renal failure or HIV infection.” (Methods section; study procedures)

3. Under study procedure: Page 6, line 34. All household contacts were followed for one year to identify incident active TB disease. This is not clear. How often the household contacts were followed over 1 year and what was the follow up like? Were they followed up with symptom
screen for TB? The result of this follow up is not mentioned anywhere. If it is not required, then the follow up need not be mentioned in this manuscript.

Response: Household contacts were followed up at 12 months with a symptom screen. We think this information is useful for the reader to understand that these individuals didn’t have active TB, so we have edited the manuscript to reflect this.

Manuscript Revisions: As stated above, we edited the following sentence: “All household contacts were followed for one year; symptom screens (and sputum testing if indicated) were performed to identify incident active TB disease.” (Methods section; study procedures).

4. Statistical analysis section: Page 7, Line 4; Exclusions have been mentioned; Authors could better depict the enrollment, exclusions and main results as a flow diagram. This is clearly, sub analysis of the data from the RePORT India Consortium. The sample size was not calculated prior to the study for the given objectives. What is the power of the conclusions?

Response: The data presented in this manuscript represent the available data from a household contact survey from the RePORT India Consortium. Since this was a secondary analyses if existing data, a sample size and power calculation was not performed prior to starting this analysis. The full cohort of RePORT-India has been presented in another paper (Hochberg NS, Sarkar S, Horsburgh CR, et al. PLoS One 2017;12(8):e0183195.) the power of the conclusions for these analyses were strong, as evidenced by the 95% confidence intervals presented in the tables.

Manuscript Revisions: We edited/added the following sentences: “Our findings consistently support the inverse association of BMI with active TB risk and increased risk of TB from diabetes.4,7 Our observation of highly significant multiplicative and additive BMI-diabetes interaction on active TB…” (Discussion, page 11)

“Similarly, in both unadjusted and adjusted models, we found no statistically or clinically significant association of LTBI with prior diabetes diagnosis, or in sensitivity analyses with elevated RBG. These findings add to the evidence that diabetes is not a significant risk factor for LTBI in India where exposure to MTB is common.” (Discussion, page 12)
5. Results section, Page No 8: The proportion of underweight, normal weight, and overweight or obese participants with diabetes was 11%, 25%, and 20% respectively. - This is not clear; esp. the numerator and denominator.

Response: We have added the numerator and denominator in parentheses for each of these percentages.

Manuscript Revisions: We edited/added the following sentence. (e.g. Results section, page 9): “The proportion of underweight, normal weight, and overweight or obese participants with diabetes was 11% (82/746), 25% (157/653), and 20% (126/633), respectively.”

6. Discussion: Page 10, Page 36: "Our findings provide support for current Indian national guidelines recommending bi-directional screening of all diabetes patients for active TB and all TB patients for diabetes". This study findings only tested and provide support that all TB patients should be tested for diabetes. Where is the evidence to support that all DM patients should be tested for TB?

Response: The results for this conclusion can be inferred from the cross-sectional nature of the study design. A high proportion of these symptomatic, smear-positive active TB cases were attributable to diabetes and hence could be identified at a diabetes clinic. Importantly, the excess risk (adjusted prevalence difference) of active TB due to diabetes was significantly heightened within each BMI category, indicating BMI should not be used to restrict screening of diabetes patients for TB in India. Therefore, our results also indicate that all DM patients should be screened for active TB disease irrespective of BMI.

Manuscript Revisions: We edited/added the following sentence: “Our findings provide support for current Indian national guidelines recommending bi-directional screening of all diabetes patients for active TB and all TB patients for diabetes irrespective of BMI.” (Discussion, page 10).
7. Page 11, Line 53-58: "Our finding that prior diabetes diagnosis alone or in combination with elevated RBG is not associated with LTBI adds to the evidence that diabetes is not a significant risk factor for LTBI in India" The selection of a house hold contact cohort for LTBI seems biased in view of the strong gender bias. Hence could this be an inappropriate conclusion? Logically if DM is not associated with LTBI, then how is TB diseases associated with DM?

Response: The presence of latent TB infection (LTBI) signifies exposure to TB bacilli, and does not represent active TB disease. India is a high-TB endemic country and TB exposure is common. Our results suggest that acquisition of MTB is not meaningfully influenced by DM, which makes sense in a setting where exposure is to TB is common and may often occur prior to type 2 diabetes development, but that the progression to active TB disease (once exposed) is strongly associated with presence of DM (given alterations in immunological function and systems).

Manuscript Revisions: We edited/addled the following sentence: “These findings add to the evidence that diabetes is not a significant risk factor for LTBI in India and instead suggest diabetes increases the risk of TB activation.” (Discussion, page 11)

Reviewer #2 - Anna Odone

Kubiak et al. conducted a cross-sectional study to assess the interaction between nutritional status and diabetes on active and latent TB. The paper is well structured and clear; the methodology is sound. Authors report BMI and diabetes to be associated with newly diagnosed active TB, but not LTBI in regional India and Diabetes to confer greatest risk of active TB in overweight and obese adults.

The topic of the dual TB-Diabetes epidemics and their control is of great interest, especially in low and middle-income countries and this report contributes to add evidence from the Indian setting and to highlight the importance of bi-directional diabetes-active TB screening.

Part of the findings - i.e. the diabetes and low increasing the risk of TB - are already well known and do not add much. More interesting, although not conclusive, are data on LTBI. Although
data interpretation is well conducted and nicely put into context, the main limit is the cross-sectional design of the study.

I have some other general and specific comments.

1. I believe authors should expand a bit more both - in the introduction and in the discussion when interpreting results - on the pathogenetic mechanisms around the reported interaction between diabetes, undernutrition and TB. This can be, for instance, done including a visual representation (a graph or additional figure)

Response: We agree that this information is important. We have added information to the manuscript regarding the impact of malnutrition. We refrained from adding a graphic, as these have been done in other manuscripts, so we have referred the reader to these including a reference to our recent review paper on the mechanism of the interaction between malnutrition and TB (Sinha P, et al. J Infect Dis 2019;219;1356-63).

Manuscript Revisions: We edited/added the following sentence. (Discussion, p.12): “Similarly, malnutrition affects a range of immune responses from macrophage phagocytosis and activation to T cell response and IFNγ production that results in increased TB risk.”

2. Authors might consider stressing more the importance of the bi-directional screening and the evaluation of cost-effectiveness of these intervention (cost effectiveness of TB screening in DM patients and DM screening in TB control programmes) in order to focus on the need to allocate the limited resources

Response: This an excellent point. While this is far from being a formal cost-effectiveness paper, we have added a sentence to the Discussion stressing the importance of the bi-directional screening and potential cost-effectiveness of these interventions.

Manuscript Revisions: We edited/added the following sentences: “Bi-directional screening could lead to earlier diagnosis of both conditions and improved disease management, but
additional research is needed to optimize integrated care and identify the most cost-effective screening methods.” (Discussion, page 11)

“Additional research is needed to better understand the biological mechanisms involved, optimize timing of diabetes testing and clinical care for diabetic or hyperglycemic TB patients, assess the cost-effectiveness of bi-directional screening, and estimate the public health impact of diabetes and obesity on active TB in other regions.” (Discussion, page 14)

3. Authors should take into consideration and comment on other relevant literature published on the specific topic of TB-BMI and diabetes interaction (i.e. Lancet Diabetes Endocrinol. 2014 Sep;2(9):754-64 and PLoS One. 2011;6(6):e21161.).

Response: Thank you. We have added sentences to comment on these papers and have incorporated these publications in the references.

Manuscript Revisions: We edited/added the following sentences: “Diabetes and malnutrition, known risk factors for active TB, have been recognized as two important factors that could prevent achieving the global target of reducing TB incidence by 2035.” (Introduction, page 3)

“The rising prevalence of diabetes may be contributing to persistently high TB incidence in high TB burden countries, outweighing the protective effect of high BMI.” (Introduction, page 3)

We added the following references: Odone A, Houben RM, White RG, Lonnroth K. The effect of diabetes and undernutrition trends on reaching 2035 global tuberculosis targets. Lancet Diabetes Endocrinol. 2014 Sep;2(9):754-64.

4. Please check age range of included participants as misleading info is provided in the methods and results section (older than 6 or 18?)

Response: The inclusion criteria for RePORT is 6 but this study analyzed only those 18 and older. This information is shown in the methods section. We are open to further edits to this section if that would be of use.