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: 2 Date: 20 Jun 2019

Author’s response to reviews:

June 19, 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 this feedback 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 improvised the paper. My specific comments on this revision are:

1. 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.

The authors in the revision have reported that it is the history of renal failure and history of HIV positive that was captured. Manuscript Revisions: We added the following sentence. "Individuals
were questioned regarding a history of renal failure or HIV infection." (Methods section; study procedures)

Reviewer: The same has to be reflected in the table 1; History of renal failure/ and history (self-reported status) of HIV

Response: Thank you for this suggestion. We have clarified that HIV testing was performed for TB cases and revised renal disease in Table 1 accordingly. We have chosen not to include self-reported HIV status for household contacts in Table 1.

Manuscript revisions: The clinics performed HIV testing as part of the standard of care. (Methods, Study Procedures Section)

Table 1 now lists Self-reported history of renal failure.

2. "To determine LTBI status, the study nurse measured induration within five days and the majority within three days."

Reviewer: Usually TST has to be read within 48-72 hours. Would it be possible that the delay of 5 days might have resulted in negative test for LTBI in some patients. Would this have altered the association of DM and LTBI?

Response: Data indicate the potency of the TST reaction persists for at least five days (Snider DE. The tuberculin skin test. Am Rev Respir Dis. 1982;125:108-18.; (Division of TB Elimination, CDC, 2016 www.cdc.gov/tb/education/corecurr/pdf/chapter3.pdf).). A study of 417 subjects with repeated readings on days two, three, four, and five, found only 18 readings resulted in classifications that differed from day three (WHO Tuberculosis Research Office. Tuberculin reaction size on five consecutive days. Bull WHO 1955;12:189-96.). Additionally, in our study, 54% of household contacts were TST-positive, which is similar to the proportion observed in other studies of household contacts in India (e.g. 55% Shivakumar et al. Int J Tuber Lung Dis 2018; 52% Sharma SK et al. PLoS ONE 2017) and in a systematic review of LTBI globally (52%, 95% CI 47-56%; Fox GJ et al. Euro Resp J 2014). Therefore, we do not believe our study underestimated the prevalence of LTBI.
3. Discussion, Page 17, Line 4: Prior studies suggest diabetes may increase the risk of LTBI.\textsuperscript{(18 19 35)}. As the present study shows a different result from few previous studies with respect to LTBI and DM, what may be the reasons for the difference? Any difference in method of testing for LTBI?

Response: Prior studies suggest there may be a modest association, but results are mixed. We site a meta-analysis that found a small increase in the odds of LTBI (OR 1.18, 95\% CI 1.06–1.30) but no association was observed in the one cohort study identified (RR 4.40; 95\% CI 0.50–38.55) \textsuperscript{(Lee M-R et al. Clin Infect Dis 2017)}. As we state in the discussion, another recent study in India found no association \textsuperscript{(Shivakumar et al. Int J Tuber Lung Dis 2018)}. We have tempered our language to reflect the uncertainty around this relationship. It is also possible that the effect of diabetes on LTBI is so small that in places with high LTBI prevalence and other stronger risk factors, no diabetes has no meaningful effect on LTBI risk.

Manuscript revisions: Prior studies suggest diabetes may modestly increase the risk of LTBI but the evidence is mixed.\textsuperscript{(18 19 35)} A recent meta-analysis found the odds of LTBI was higher among diabetic patients although the effect size was small (1.18, 95\% CI 1.06, 1.30).\textsuperscript{18} However, LTBI was not associated with diabetes in a prospective cohort study or recent cross-sectional analyses of another Indian cohort.\textsuperscript{18, 20} (Discussion, page 12)