PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Household food insecurity among pulmonary tuberculosis patients and its associated factors in south India: A cross-sectional analysis
AUTHORS	Ayiraveetil, Reshma; Sarkar, Sonali; Chinnakali, Palanivel; Jeyashree, Kathiresan; Vijayageetha, Mathavaswami; Thekkur, Pruthu; Lakshminarayanan, Subitha; Knudsen, Selby; Hochberg, Natasha; Horsburgh, C; Ellner, Jerrold; Roy, Gautam

VERSION 1 – REVIEW

REVIEWER	Chandrashekhar t sreeramareddy International Medical University Kuala Lumpur Malaysia
REVIEW RETURNED	22-Sep-2019

GENERAL COMMENTS	This is an interesting manuscript based on an ongoing/completed international collaborative cohort study. A new distal determinant/driver of tuberculosis is tested using cross-sectional data from larger Cohort study. The presentation of the paper is clear and written English is comprehensible. Even as i commend this paper for its novelty, i have some reservations about the structure and approach to the analyses of data, which if done differently would throw light on more/new results. 1) title does not convery clearly that prevalence of HFAI among TB patients only. Perhaps they should write HFAI among TB patients (pulmonary?). 2) Not clear from the paper, how patients were recruited into the study. Likely from the DOTS clinics. Hence, we cannot called this as prevalence as it was not population-based, representative sample of patient. I would call this as just a proportion of patients with HFAI. Based pn the TWO point listed above i suggest "household food access insecurity among pulmonary TB patients and its associated factors- cross-sectional study. Abstract should mention patient recruitment. Please check the results on level of HFAI. Its rather unusual to have severe as highest %. Background should make deeper presentation of complex inter-relationships between HFAI, undernutrition, TB and its outcomes. This is the essence of this paper. Hence, i am a bit surprised on lack of association of HFAI with BMI and few other variables.

	Authors seemed to have used rigorous and statistical analyses for factors associated with HFAIS (outcome variable), they did not consider complex interactions between the variables that are associated with them. In this respect, when HFAI was measured when BMI was measured, the stage of the TB patient when interviews were done are all important information to interpret the association. Employment status, income associated are too simplistic results, as its well know the patients would not have been able to work as a result of TB, hence, they could not earn money. The findings are no-brainer. I suggest the following: 1) do not use prevalence as it was not population based sample 2) it was not a secondary data as the authors are all, owners of this data (data comes from their own ongoing study) 3) too many details on the RePORT International are not needed, please provide reference to main publication or study protocol if it has been published. 4) Authors rather focus on literature on associated factors than citing piblications from RePORT International. Factors associated with HFAI among PTB patients is essence of this paper. 5) to achive the above analyses be done to test interactions, effect modifiers, or mediation analyses. As i said before its a no-brainer the factors that were found significant. 6) the HFAI score is a different distribution needing a different regression approach, in addition to complex interactions with associated factors i highlighted above. See our paper https://www.ncbi.nlm.nih.gov/pubmed/28738826 7) stucture the MS according to STROBE cross-sectional study, not as secondary data analyses. I suggest that the authors do not dichotomise or polytomies the continous variables. They should treat them as they are for example BMI, age, Karnofsky score

REVIEWER	Bareng A.S. Nonyane Johns Hopkins Bloomberg School of Public Health, USA
REVIEW RETURNED	30-Sep-2019

GENERAL COMMENTS	Prevalence of household food insecurity and its associated factors in tuberculosis patients in south India: A cross sectional analysis The aim of the paper was to assess prevalence of food insecurity and its associated factors among people with TB Study design: Cross –sectional cohort, National TB Program in India through the RePORT international cohorts, Data from October 2015 –October 2018were used Smear /culture positive participants were included The HFIAS tool used – this is a well- known and validated scale. Reduced to 4 categories of severity. AUDIT alcohol use questionnaire was used GLM models were used to test for associations Methods for data extraction and management, as well as statistical analyses were clearly described Comments 1. What were the reasons for not assessing the 462 cohort enrollees for food insecurity? Can this lead to potentially biased findings in this study?

	2. Related to the above (1), how does the 80% male composition of the cohort compare to the composition of people with TB in India? 3. Were there multiple members of the same household diagnosed? If so what proportion of households. Was (or should) this clustering accounted for? 4. 77% of the participants were employed, any information on what types of employment? Could the type of employment be the risk factor for TB in the first place? Likewise, could the type of employment be related to ability to purchase food and thus TB risk – a nutritional pathway mentioned in the discussion?

VERSION 1 – AUTHOR RESPONSE

GENERAL COMMENTS:
This is an interesting manuscript based on an ongoing/completed international collaborative cohort study. A new distal determinant/driver of tuberculosis is tested using cross-sectional data from larger Cohort study.
The presentation of the paper is clear and written English is comprehensible. Even as i commend this paper for its novelty, i have some reservations about the structure and approach to the analyses of data, which if done differently would throw light on more/new results.

Author's response:
We thank you for appreciating our work and words of encouragement. We have tried our best to address the comments and provide a point-by-point response below in detailed comments section of the reviewer.

1) title does not convey clearly that prevalence of HFAI among TB patients only. Perhaps they should write HFAI among TB patients (pulmonary?).
Author's response:
We thank the reviewer for the suggestion. We have included pulmonary patients in the title and the revised title is 'Household food insecurity among pulmonary tuberculosis patients and its associated factors in south India: A cross sectional analysis'. We have removed the word 'prevalence' from the title (Page number:1 Line number: 2-4).
Comment 2) Not clear from the paper, how patients were recruited into the study. Likely from the DOTS clinics. Hence, we cannot call this as prevalence as it was not population-based, representative sample of patient. I would call this as just a proportion of patients with HFAI.
Based on the TWO point listed above i suggest "household food access insecurity among pulmonary TB patients and its associated factors- cross-sectional study.

Author's response:
Thank you for the comment. We have included the details on patient recruitment in the cohort in the methods section (Page number: 9 Line number:195-196). The details of the cohort are already described in the below published articles.
1. Van Ness SE, Chandra A, Sarkar S et al. Predictors of delayed care seeking for tuberculosis in southern India: An observational study. BMC Infect Dis. 2017;17(1):1–9.
2. N.S. Hochberg, S. Sarkar, C.R. Horsburgh et al. Comorbidities in pulmonary tuberculosis cases in Puducherry and Tamil Nadu, India: Opportunities for intervention. PLoS One. 2017;12(8):e0183195.
3. Hoyt KJ, Sarkar S, White L et al. Effect of malnutrition on radiographic findings and mycobacterial burden in pulmonary tuberculosis. PLoS One. 2019;14(3):1–11.

4. Leong S, Zhao Y, Joseph NM et al. Existing blood transcriptional classifiers accurately discriminate active tuberculosis from latent infection in individuals from south India. Tuberculosis . 2018;109(August 2017):41–51. https://doi.org/10.1016/j.tube.2018.01.002

We agree with the reviewer on using the term 'prevalence'. Hence, we have replaced 'prevalence' with 'proportion' in the revised manuscript.

Comment: Abstract should mention patient recruitment.
Author's response:
We have included the details on patient recruitment in the abstract in the revised version (Page number: 3 Line number: 65-67).

Comment: Please check the results on level of HFAI. Its rather unusual to have severe as highest %.
Author's response:
We checked the program file and ran the analysis again; the results are same. Yes, it is surprising to note that 'severe level of food insecurity' is higher.

Comment: Background should make deeper presentation of complex inter-relationships between HFAI, undernutrition, TB and its outcomes. This is the essence of this paper. Hence, i am a bit surprised on lack of association of HFAI with BMI and few other variables.
Authors seemed to have used rigorous and statistical analyses for factors associated with HFAIS (outcome variable), they did not consider complex interactions between the variables that are associated with them. In this respect, when HFAI was measured when BMI was measured, the stage of the TB patient when interviews were done are all important information to interpret the association. Employment status, income associated are too simplistic results, as its well know the patients would not have been able to work as a result of TB, hence, they could not earn money. The findings are no-brainer.

I suggest the following:
1) do not use prevalence as it was not population-based sample
Author's response: We have removed the term 'prevalence' and reported it as 'proportion'
2) it was not a secondary data as the authors are all, owners of this data (data comes from their own ongoing study)
Author's response: We thank the reviewer for the suggestion. We have made the modification in the revised manuscript (Page number: 3 Line number: 60, Page number:8 Line number:168)

3) too many details on the RePORT International are not needed, please provide reference to main publication or study protocol if it has been published.
Author's response:
Thank you for the suggestion. We have modified the information on RePORT International (Page number:9 Line number:184-199)

4) Authors rather focus on literature on associated factors than citing publications from RePORT International. Factors associated with HFAI among PTB patients is essence of this paper.
Author's response:
We cited previous publications from the cohort where the methodology is described in detail. The essence of the paper is about reporting the levels of Household Food Insecurity Access (HFIA) in a cohort of PTB patients registered for care in national TB program. Since, we could not find many studies on associated factors, we tried to look for the factors associated with HFIA. However, being a cross sectional design for examining the association between Household Food Insecurity Access Scale (HFIAS) and other variables, we do not emphasize much on 'association'. The findings on 'level of HFIA' will act as baseline for future comparison.

5) to achieve the above analyses be done to test interactions, effect modifiers, or mediation analyses. As i said before its a no-brainer the factors that were found significant.

Author's response: We thank the reviewer for the suggestions. Being a cross sectional data on exposure variables and outcome (HFIA), our intention to build the model was to identify the target groups where the proportion of HFIA is higher. Also, as mentioned by the learned reviewer, the variables like BMI, income and education status may not have good discriminatory power due to cross sectional nature of data. Thus, we did not try to look for interaction.

6) the HFAI score is a different distribution needing a different regression approach, in addition to complex interactions with associated factors i highlighted above. See our paper
https://www.ncbi.nlm.nih.gov/pubmed/28738826

Author's response:

We would like to treat the HFIA as a categorical variable as we have already mentioned that we want to report as level of HFIA. For, we would like to use the categorical -Household Food Insecurity Access Prevalence (HFIAP) Status indicator rather than using the HFIAS score indicator (continuous variable) as HFIAP is recommended to report for program monitoring and evaluation by the Household Food Insecurity Access Scale Indicator Guide, v.3,
(https://www.fantaproject.org/sites/default/files/resources/HFIAS_ENG_v3_Aug07.pdf, page number 18).

7) structure the MS according to STROBE cross-sectional study, not as secondary data analyses.

Author's response:

Thank you for the suggestion. We have modified the manuscript accordingly and we used STROBE guidelines for reporting.

Reviewer: 2
Reviewer Name: Bareng A.S. Nonyane
Institution and Country: Johns Hopkins Bloomberg School of Public Health, USA
The aim of the paper was to assess prevalence of food insecurity and its associated factors among people with TB
Study design: Cross –sectional cohort, National TB Program in India through the RePORT international cohorts, Data from October 2015 –October 2018were used
Smear /culture positive participants were included
The HFIAS tool used – this is a well- known and validated scale. Reduced to 4 categories of severity.
AUDIT alcohol use questionnaire was used
GLM models were used to test for associations
Methods for data extraction and management, as well as statistical analyses were clearly described
Comments
1. What were the reasons for not assessing the 462 cohort enrolees for food insecurity? Can this lead to potentially biased findings in this study?
Author's response:
Thank you for the comment. Complete food insecurity assessment questions were not included in the case report forms when the study started, so the food insecurity was not assessed for the first enrolled 462 participants. The case report forms were modified to include Household Food Insecurity Access Scale (HFIAS). We have taken all the consecutive cases further recruited into the cohort for the analysis of food insecurity. The exclusion of 462 patients was based on time of enrolment rather than patient characteristics and hence, we believe it will not affect the study findings.

2. Related to the above (1), how does the 80% male composition of the cohort compare to the composition of people with TB in India?

Author's response:
As per National Family Health Survey (NFHS)-4 conducted during 2014-15, prevalence of TB among male population is almost double in Indian households (http://rchiips.org/nfhs/NFHS-4Reports/India.pdf) when compared to females. The study setting had higher prevalence of alcoholism in males (risk factor for TB), we expect higher proportion of males in our sample. However, we agree with the reviewer that 80% is on higher side and we don't have any other explanation for this.

3. Were there multiple members of the same household diagnosed? If so what proportion of households. Was (or should) this clustering accounted for?
Author's response:
It happened in only one of the households. We included only the first member diagnosed in the analysis and excluded the other one.

4. 77% of the participants were employed, any information on what types of employment? Could the type of employment be the risk factor for TB in the first place? Likewise, could the type of employment be related to ability to purchase food and thus TB risk – a nutritional pathway mentioned in the discussion?
Author's response:
Thank you for the comment. The employed participants were involved in any kind of income generating work like daily wages, coolie etc. Type of employment was not explored in detail for the cohort. We have included this as a limitation in the study (Page number:14 Line number: 322-325). We too agree with the reviewer on this, employment could be a risk factor and type of employment be related to ability to purchase food which in turn causes malnutrition and increases TB risk.

VERSION 2 – REVIEW

REVIEWER	chandrashekhar sreeramareddy International Medical University
REVIEW RETURNED	13-Nov-2019

GENERAL COMMENTS	The authors have addressed most of the comments; however, there remain a few outstanding issues which they have not satisfactorily addressed. They mention associated factors in the title, however, they do not take rigorous approach to the analyse citing that they used the model to identify those target groups who had higher food insecurity levels. Often these are limitations of publications arising from larger studies. The required power or variables were not available to perform rational statistical analyses. The authors should at the least agree more on these as their limitations. I would like highlight that they categorised age, BMI, income, TB score, etc. into categories which is wrong approach to multivariate analyses. Authors refer to https://www.sciencedirect.com/science/article/pii/S0895435608003223 I suggest that they also admit that time at HFAI was measured and time BMI was measured, the stage of the TB patient when interviews were done could not be considered during analyses. They are important information to be interpret association as food insecurity, weight loss at the time of diagnoses, weight improvement during course of treatment are all interlinked.

	Higher Karnofsky score cannot be associated with food insecurity that arises from poverty arising from unemployment which again arises among mostly daily wage earners who were debilitated by illness and hence could earn their livelihood. In abstart authors write "...had higher prevalence proportion of HFI". Univariate analyses not multivariate analyses is needed for above results. There are a lot confounders that were not addressed during analyses.

REVIEWER	Bareng A.S. Nonyane Johns Hopkins Bloomberg School of Public Health
REVIEW RETURNED	18-Dec-2019

GENERAL COMMENTS	Revised Manuscript review • With respect to the point-by-point response to the questions raised by me in the first submission, the question on type of employment was addressed as a limitation in the discussion. The rest of the questions were not addressed and they are critical to strengthening this manuscript o What were the reasons for not assessing the 462 cohort enrollees for food insecurity? Can this lead to potentially biased findings in this study? o Related to the above (1), how does the 80% male composition of the cohort compare to the composition of people with TB in India? o Were there multiple members of the same household diagnosed? If so what proportion of households. Was (or should) this clustering accounted for?

VERSION 2 – AUTHOR RESPONSE

RESPONSES TO COMMENTS

Comment 1:

The authors have addressed most of the comments; however, there remain a few outstanding issues which they have not satisfactorily addressed. They mention associated factors in the title, however, they do not take rigorous approach to the analyse citing that they used the model to identify those target groups who had higher food insecurity levels. Often these are limitations of publications arising from larger studies. The required power or variables were not available to perform rational statistical analyses. The authors should at the least agree more on these as there limitations. I would like highlight that they categorised age, BMI, income, TB score, etc. into categories which is wrong approach to multivariate analyses. Authors refer to
https://www.sciencedirect.com/science/article/pii/S0895435608003223

Response: Thank you for this suggestion. We completely acknowledge the highlighted deficiencies in the model. We have carefully discussed these suggestions for improving the model and also the interpretaion of the findings. As suggested, we have more explicitly mentioned the lack of confounding variables and low sample size (power) as a major limitation under the discussion section. Changes made in line number 370-374. We have also mentioned this as a deficiency in line number 105 to 107 under article summary section.

Regarding considering age, BMI, income, TB score as catergorical instead of continuous data in multivariate model, we agree the association might differ based on the cut-offs on conversion and ideal is to use the independent variables as it is. With our data, we did try to model with age, BMI and TB score as continuous variables (income was collected as categorical vaiable). However, there was no change in the observed significant associations and also did not improve the AIC and BIC of the model. Thus, we wish to present the existing table in the manuscript.

Comment: I suggest that they also admit that time at HFAI was measured and time BMI was measured, the stage of the TB patient when interviews were done could not be considered during analyses. They are important information to be interpret association as food insecurity, weight loss at the time of diagnoses, weight improvement during course of treatment are all interlinked.

Response: We agree that the temporality of the BMI, HFI and weight loss could not be established due to lack of information and thus, not accounted during analysis. We have mentioned this as a limitation in the manuscript now. Changes made in line number 345 to 350.

Comment: Higher Karnofsky score cannot be associated with food insecurity that arises from poverty arising from unemployment which again arises among mostly daily wage earners who were debilitated by illness and hence could earn there livelihood.

Response: We agree on the limitation of our anlysis to suggest the pathways for high HFAI among those with high Karnofsky score. Thus, we have not made any attempt to speculate much on the possible pathways.

Comment : In abstarct authors write "..had higher prevalence proportion of HFI". Univariate analyses not multivariate analyses is needed for above results. There are alot confounders that were not addressed during analyses.

Response: Thank you for the vaild suggestion. We have made the necessary changes. Changes made in line number 79 to 80

Reviewer 2:

Comment: With respect to the point-by-point response to the questions raised by me in the first submission, the question on type of employment was addressed as a limitation in the discussion. The rest of the questions were not addressed and they are critical to strengthening this manuscript

Response: Thank you for the comment. We have made prompt attempt to address all the comments.

Comment: What were the reasons for not assessing the 462 cohort enrollees for food insecurity? Can this lead to potentially biased findings in this study?

Response: Thank you for the comment. The 462 enrolless were not assessed for food insecurity because of not having HFAI scale in the study proforma during initial phase of the project. The HFAI scale was introduced in the revised study proforma after the 462 patient were already enrolled into the

project. The baseline demographic and clinical characteristics did not differ between these two groups and, thus, there might not have been any selection bias affecting the estimate of food insecurity. Changes made in line 225 to 229.

Comment: Related to the above (1), how does the 80% male composition of the cohort compare to the composition of people with TB in India?

Response: Thank you for the comment. According to India Annual TB report-2019, the proportion of male among all TB patients notified (including pulmonary and extrapulmonary) is about 64%. In the state of Tamil Nadu and Puducharry where the study was conducted, the proportion of male among all notified is about 68% and 70%, respectively. However, as we included only sputum positive non-severe pulmonary TB patients, we would have ended up with 80% male patients. However, this was not because of any selection bias among the eligible patients, as we included all the patients who met the inclusion crietria.

Comment: Were there multiple members of the same household diagnosed? If so what proportion of households. Was (or should) this clustering accounted for?

Response: Thank you for this comment. We did not have multiple patients from the same house during our study period. If at all there were multile patients from the same house, we would have definitely adjusted for clustering and also would have interpreted our results considering such clustering.