Author’s response to reviews

Title: The association between tuberculin skin test result and active tuberculosis risk of college students in Beijing, China: a retrospective cohort study

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Author’s response to reviews:

Point-to-point response to reviewers’ concerns

Thank you for the valuable suggestions to improve this article. All concerns have been addressed in the revised version. We also made corrections to meet the journal's requirements referring to the journal's Submission Guidelines. All changes have been underlined in the new version to facilitate easy evaluation. The responses are summarized below.
Concern of Editor:

This is a really large-scale cohort study and provides some relevant information to optimize public health policy. However, per the requirement of the STROBE guidelines, clearly describing the participants selecting process is necessary. For example, how many college students were screening? How many refused to participate? Were there any significant differences between those who agreed to participate and those who didn't? Furthermore, as pointed out by the reviewers, the authors should consider to include some well-known risk factors for developing active TB in their analysis, such as BMI, smoking status, comorbidity...

Answer: In response to this concern, we rechecked the raw records included in this study. As shown in table 1, a total of 68288 individuals were included in the enrollment TB screening project of college students during 2013-2016, and 67428 of them actually participated. There were no significant differences in age, sex and region between those who agreed to participate and those who didn't. After excluding 88 individuals diagnosed as active TB and 48 ones who had active TB history, 67292 (98.54%) individuals were included in the final follow-up cohort (lines 57-61). Unfortunately, the BMI, comorbidity and other risk factors were not recorded in the raw records. The above information has been added in the revised manuscript.

Reviewer reports:

Sheng-Wei Pan (Reviewer 1): This large-scale retrospective cohort study investigated the predictive value of TST on the risk of active TB in college students in China (n=67,428, aged 17-21 years). The study disclosed that active TB risk significantly increased by about 3 times per 5 mm increasing in TST size compared with reaction size ≤5-10 mm, up to 9.8-fold with reaction size ≥20 mm. In addition, the adjusted HR of active TB was 3.6 (1.4~9.5) of males compared to females. The authors provided explanation on this gender difference in this specific population going through puberty. The authors also clearly stated the limitations of this study which included uncontrolled potential confounders (smoking status, TB contact history). In general, this study is well conducted and may provide important information on the value of TST for predicting high TB-risk college students before providing IGRA tests in less developed areas.

Concerns of reviewer 1.

Concern #1. Title: may change "a retrospective study" to "a retrospective cohort study".
Answer: As suggested, "a retrospective study" in the title has been changed to "a retrospective cohort study". Furthermore, in order to make the title more clearly expressed, it has been rewritten as “The association between tuberculin skin test result and active tuberculosis risk of college students in Beijing, China: a retrospective cohort study”.

Concern #2. In Abstract, last 3 lines, and Conclusions (first 2 lines): the authors stated that "the risk of active TB increased rapidly in college students when the TST reaction size was ≥10 mm, particularly in males". However, there is no data on dose-response relationship between TST size and TB risk for male and female population, respectively. I suggest the authors to perform a subgroup subgroups analysis and to present the results before making this conclusion.

Answer: Thanks for your reminding. Our original writing does cause ambiguity, so it has been rewritten as “This study indicated that the risk of active TB increased in college students when the TST reaction size was ≥10 mm, and males had a higher risk compared to females”. The males and females have been compared in Table 2 (Adjusted HR [95% CI]: 3.593 [1.354~9.537]). Moreover, as suggested, subgroups analyses of males and females were performed. The results showed that HR of cohort with TST reaction size ≥ 10mm was 5.41 (95% CI: 2.28~12.84, P < 0.001) compared to those with reaction size < 10mm for males, and 5.08 (95% CI: 0.85~30.37, P > 0.05) for females. This suggested that in males, the risk of active TB was higher in college students with the TST reaction size ≥10 mm, but the difference was not significant for females. The above information has been added in the revised manuscript (lines 210-215).

Concern #3. Methods, statistical analysis: I suggest the author to delete "with a backward selection process" if this was not used in this study.

Answer: In the study, a backward stepwise selection method based on likelihood ratio test was used to select the variables. However, after selected candidates with the P value cutoff 0.10 of univariate analysis, all of them, sex and TST response, were entered into the final analysis.

Concern #4. Results, first 2-3 lines: In order to better understand the demographic background of this study, I suggest the authors to remove "(excluded the records of Hong Kong, Macao,
Taiwan and overseas)" and replaced it by "including A province (N1, %), B province (N2, %), C province (N3, %), …(the major 3-5 contributing provinces or areas).

Answer: As suggested, this sentence has been rewritten as “They came from 31 provincial divisions of China, including Beijing (16234, 24.12%), Hebei (3922, 5.83%), Shandong (3125, 4.64%), He’nan (2889, 4.30%), Xinjiang (2086, 3.10%) and so on” (lines 161-165).

Concern #5. Results, page 5: should correct three typos, including (1) However, "No" significant, (2) per "10000persons-years", (3) P = "9.451e-07".

Answer: As suggested, we have modified those errors in the revised manuscript.

Concern #6. Results, Table1: I suggest the authors to change the item from "PR (active TB)" to "number of active TB at screening" to simplify the presentation since prevalence rate of active TB is not the key issue of this study.

Answer: In order to avoid misleading and make the structure of paper well-delivered, the item "PR (active TB)" of Table 1 was removed and the number of active TB was reported in the results section.

Concern #7. Results, Figure 1: Regarding the hazard of active TB between subgroups, I think the information shown in Fig 1 have been clearly presented in Table 2. Hence, the author may consider to change Fig 1’s demonstration from "cumulative hazard" to "cumulative incidence" by using Kaplan-Meier method.

Answer: In response to this concern, Figure 1 has been changed as "cumulative incidence" curve by using the Kaplan-Meier method. The log-rank test was used to compare the curves. The methods and results associated with this change were added in the revised manuscript.
Concern #8. Results, Table 2: I suggest the authors to delete the "Follow-up" item and replace it by (n=xx) for each subgroup. More importantly, for this cohort study, the author should add data on "TB events/follow-up person-years" in this table before presenting the corresponding incidence rates. In addition, why not age, BMI and comorbidity be included in the models? Those are risk factors for active TB disease and should be adjusted in analysis.

Answer: As suggested, in Table 2, "Follow-up" item has been replaced by the number of individuals of each subgroup. Besides, the data on "TB events/follow-up person-years" has been added in the revised manuscript.

Because all the students were college freshman, the distribution of age (mean ± standard deviation: 19.52±1.26) of this cohort was relatively concentrated. About 96% of individuals were ranged from 18 to 21 (Table S3). We consider it is feasible to regard them as one age group. As mentioned in the last paragraph of discussion in the revised manuscript, the BMI, comorbidity and other risk factors were not recorded in the raw records.

Concern #9. Finally, it would be interesting to compare the characteristic of students with TST positive versus TST negative. Are the two groups different in their sex percentage, BMI, BCG status, ethnicity, region or comorbidity? Furthermore, is there a synergistic effect of male sex, low BMI and TST positive on the risk of active TB in the college students? That information may be helpful if we want to construct a further TST-base TB screening strategy for college student in areas where IGRA is not feasible.

Answer: As suggested, we have compared the characteristics of students with TST positive versus TST negative (Table S2). There were significant differences between the two groups in sex percentage, ethnicity, and region. Specifically, males had a higher percentage of TST positive (12.18% vs. 11.61%) compared to females; non-Han cohort had a higher percentage of TST positive (15.86% vs. 11.45%) compared to Han cohort; the distribution trends of regions of TST positive was high in the west and low in the east (west: 14.22%, middle: 12.39%, east: 10.55%) (lines 173-178). Unfortunately, for other potential risk factors, the BMI, comorbidity and so on were not recorded in the raw records.

Sheng-Yuan Ruan, MD, PhD (Reviewer 2): This is a retrospective study based on the data of a TB screening program in China. The study aimed to evaluate the risk of active tuberculosis
among college students with different cutoffs of tuberculin skin test (TST). This study question is important and is relevant to the audience of BMC Infectious Diseases. I have some comments for the authors.

Concerns of reviewer 2:

Major comments:

Concern #1. Please provide the details about the follow-up plan for each individual receiving TST. Did the subjects with strong TST reaction receive more intensive follow-up? The information is important to understand whether there was detection bias. In addition, the number of lost to follow-up should be reported.

Answer: Beijing Changping institute for tuberculosis prevention and treatment (BCITPT) is the public health institution mainly responsible for TB prevention and control in Changping district. Moreover, it is the only organization to handle, compile and report the active TB cases in this district. The subjects with strong TST reaction did not receive more intensive follow-up. Few students who dropped out of college and left from Changping district would be lost to follow-up. Yet the number of them did not been retrieved.

Concern #2. Please address your policy about the preventive therapy for latent TB infection (LTBI) during the study period. Was there any subject excluded from the analysis due to receiving LTBI treatment? If LTBI treatment was not suggested, what was the TST screening program for?

Answer: Though preventive therapy is recommended for people with LTBI by WHO, it is not mandatory in China at present. Furthermore, the main purpose of TST is to find active TB cases in freshmen enrolment physical examinations (FEPE). According to “Standard for tuberculosis prevention and treatment (Beijing, 2013)”, TB screening was necessary for FEPE. On the one hand, TST result was used as an index to determine whether did further examination to diagnose active TB, such as X-ray, Mtb culture of sputum and microscopy examination of sputum smears. On the other hand, the students, TST reaction size ≥ 20mm (886 individuals in this study) were advised to receive preventive therapy. However, it was non-obligatory, a few students received preventive therapy, and because it needs three months of treatment, few ones successfully
complete treatment. In this study, no one was excluded from the analysis due to receiving LTBI treatment.

Concern #3. The information about the distribution of TST results should be provided, either in a table or a figure.

Answer: As suggested, the information about the distribution of TST results was provided in Table S1 in the revised manuscript.

Concern #4. I suggest generating a graph to illustrate the relationship between the absolute risk of active tuberculosis and induration of TST (Y-axis: absolute risk or proportion of TB; X-axis: TST induration).

Answer: As suggested, Figure 2 has been added in the revised manuscript to illustrate the relationship between the proportion of active tuberculosis and induration of TST. The information of Figure 2 also has been added in the revised manuscript (lines 208-210).

Minor comments:

Concern #1. I think the article title is a bit confusing. The authors could come up with a better one.

Answer: In response to this concern, the title has been rewritten as “The association between tuberculin skin test result and active tuberculosis risk of college students in Beijing, China: a retrospective cohort study”.

Concern #2. Abstract: The case number should be 67340 but not 67428 because active TB identified during screening should be excluded. Additionally, the number and incidence rate of incident TB during the follow-up period should be reported in the abstract. Hazard ratio alone does not provide sufficient information for decision making.
Answer: As suggested, the case number has been modified as 67292 (excluded 48 individuals who had active TB history) in the abstract. Moreover, the number and incidence rate of incident TB during the follow-up period have been added in the abstract (lines 59-61).

Concern #3. Abstract (the last two sentences): I have no idea about the meaning of "increased rapidly". Is there any statistics supporting this conclusion?

Answer: Thanks for your reminding. Our original writing does cause ambiguity, so this sentence has been rewritten as “This study indicated that the risk of active TB increased in college students when the TST reaction size was ≥10 mm, and males had a higher risk compared to females”. Moreover, subgroups analyses of males and females were performed. The results showed that in males, the risk of active TB was higher in college students when the TST reaction size was ≥10 mm, but the difference was not significant for females. The above information has been added in the revised manuscript.

Concern #4. Table 1: I suggest removing the right second column to prevent misleading. The number listed in this column is prevalent case of TB during the screening but the right first column is the person-time of follow-up.

Answer: As suggested, in order to avoid misleading and make the structure of paper well-delivered, the item "PR (active TB)” of Table 1 was removed and the number of active TB was reported in the results section. And in table 1, items sex, age, TST positive (%) and strong TST positive (%) were based on follow-up population.

Concern #5. The reporting of statistical analysis requires some improvement. In general, P values larger than 0.01 should be reported to two decimal places, and those between 0.01 and 0.001 to three decimal places; P values smaller than 0.001 should be reported as P<0.001.

Answer: As suggested, the P values of statistical analysis have been formatted in the revised manuscript.