Author's response to reviews

Title: Non-Hispanic Whites have higher risk for pulmonary impairment from pulmonary tuberculosis.

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Author's response to reviews: see over
Response to the reviewers

Title: Non-Hispanic Whites have higher risk for pulmonary impairment from pulmonary tuberculosis.

Version: 1 Date: 29 July 2011

Reviewer: Gerald H. Mazurek

Reviewer’s report:

Minor essential revisions are preceded by “*”. Discretionary revisions are listed without additional designation.

1. *Line 82: “… treatment for culture-confirmed pulmonary M. Tuberculosis at …” should be “… treatment for culture-confirmed pulmonary tuberculosis at …”

2. Line 83-84: To clarify consider changing “The population includes all persons with culture-confirmed tuberculosis in Tarrant County” to “The population includes all persons with culture-confirmed tuberculosis in Tarrant County, some of whom also had extra-pulmonary tuberculosis”.

3. Line 85: “TCH is health authority for …” should be “TCH is the health authority for …”

Line 90: In place of “...were asked to participate in a study of ...” consider “...were asked to participate in this study of ...”

Response: Items 1 through 3. Corrections made.

4. *Line 95 -7: The statement “Spirometry was conducted according to ATS guidelines for maneuver, techniques and quality control using the Spirotouch device (Spirotouch Spirometry System 086578; Spacelabs Burdick; Deerfield, WI)” and references are somewhat contradictory. Reference 19 states that “ATS recommendations for diagnostic spirometry must be followed for office spirometry, except for the following seven factors”. If all ATS guidelines for maneuver, technique, and quality control were followed, the authors may wish to delete reference 19. Alternatively, they may wish to indicate which ATS guidelines were not followed. Additionally, they may wish to include the following reference: Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J (2005) Standardisation of spirometry. Eur Respir J 26: 319-338. Of concern is the use of FEV6 in place of FVC by many office sprimoters. The FEV6 is an acceptable surrogate measurement for FVC in most situations when appropriate reference values are used and applied to all populations being compared (which is the case in this study).

Response. We agree with the review that a reference that standardizes spirometry, would be more appropriate. We have taken the reviewers’ suggestion. With regards to the methods, we
used the maneuvers’ and procedures recommended by both ATS and ETS. Since we did not use FEV6, we did not adjust our methods. However, we replaced ref 11 with the one suggested by the reviewer.

5. Line 98 – 99: A more typical approach is to perform at least 3 tests, with additional tests (up to 5 or 8) as tolerated until 3 give consistent results (with variation of 5% or less between measurements). Were results of subjects without 3 consistent results excluded?

Response: Since there were very few subjects with inconsistent measurements, they were included in the analysis.

6. Line 102-104: “Forced Expiratory Volume in 1 minute (FEV1) >=80%, Forced Vital Capacity (FVC) >=80% and FEV1/FVC>70% of predicted were considered normal.” If correct, consider adding: “Other results defined pulmonary impairment.” Based on the results presented, it appears that both restrictive and obstructive patterns of impairment were considered.

Response: Done, as suggested.

7. Line 104-106: “Impairment was categorized as none, mild (FEV1 values >60% but <80%), moderate (41% to 59%) or severe (FEV1 values <40%) using an interpretive algorithm from the AMA 19; 20.” This suggests that pulmonary impairment was defined and graded by the extent of obstruction as measured by FEV1 and ignores impairment due to restrictive patterns of impairment. Clearly this was not how the data was interpreted based on information in lines 255 to 256: “we identified some PIAT in over half (52%) of patients and severe PIAT, in which less than 50% of personal lung function remains, in almost 1 in 10 patients (9%).” Additionally, based on results presented in Table 1, the majority of subjects with pulmonary impairment had a restrictive pattern or a mixed (restrictive & obstructive) pattern.

Response: We agree with the reviewer, that indeed the AMA grading is biased towards impairment that is obstructive in nature. We stated that limitation in our discussion. However, to be consistent we have changed line 256 to say: “we identified some PIAT in over half (52%) of patients and severe PIAT, in which less than 50% of personal lung function remains, in almost 1 in 10 patients (9%).” The following statement was added; “Additionally, AMA grading is biased towards impairment that is obstructive in nature; hence patients with restrictive patterns might be under-represented in these estimates (8, 11).”

8. Line 113-114: Consider revising to include all the items used to assess socioeconomic status. For example: “Socioeconomic status was assessed according to established methods,22;23 and included (1) highest level of education attained, (2) employment status at diagnosis, (3) self-identified occupation, and (4) estimate of household income.” In addition to disclosing how education and income was categorized, consider indicating that “occupational status was ranked according to prestige” and explain or reference method used.

Response: We have changed the methods to describe how socioeconomic status was assessed.
“Socioeconomic status was assessed according to established methods (6,9) and included (1) highest level of education attained, (2) employment status at diagnosis, (3) self-identified occupation, and (4) estimate of household income. Occupational status was ranked according to prestige (6,9,35).”

9. Line 115-116: Consider changing “Similarly, household income derived from census-tract ZIP codes of the patient’s home address was ...” to “Area-median household income, derived from census-tract ZIP codes of the patient’s home address, was ...” to match subsequent use in tables. Was income of homeless persons set to “0”?

Response: We corrected the syntax, including data on homeless patients. It now reads as: “Homeless person who did not report income were treated as missing data.”

10. Line 117: Change “ranges comparable published data” to “ranges comparable with published data”.

11. Line 121: “Time-to-TB-diagnosis” is referred to as “Time-to-TB diagnosis and treatment” in other places in the document. Using the same designation throughout the document, setting it off with quotation marks, and shortening it a bit (e.g. “days to begin TB Treatment”) may improve clarity.

12. Line 126: Consider revising for clarity to “TB disease type was classified as “cavitary” when patients had single or multiple cavities visible on regular posterior-anterior chest radiographs.” If correct consider adding “TB Disease site was classified as “pulmonary only” or “both pulmonary and extra pulmonary”.

Response: to items 10 through 12, Syntax was corrected as suggested by reviewer.

13. *Line 134-135: The sentence “Impairment, the primary outcome variable, was dichotomized by combining mild, moderate and severe impairment versus no impairment” suggests that restrictive pulmonary impairment was not considered since (as stated in lines 104-105) only those with FEV1 < 80% of predicted had mild, moderate, or severe impairment. Based on the results presented, it appears that both restrictive and obstructive patterns of impairment were considered. Thus this sentence should be deleted. (Please also see comments for lines 102-104 and 104-106.)

Response: Line 134-135 was deleted.

14. *Line 138: Please indicate what statistical tests were used to assess statistical significance. Line 156-157: To what “pattern” is the author referring to? Consider revising to “TB disease type and site, and patients’ access to TB care (as estimated from “Time-To-TB-Diagnosis-and-Treatment”) was similar between races (Table 1).”

Response: The following sentence was added; “Comparison between groups was performed using Chi-Square or Fisher’s exact tests and/or analysis of variance (ANOVA) plus the Kruskal-Wallis tests when appropriate.”
11. *Line 164: Should it read “… Figures 2 to 4”?* Line 165: Did the authors compare PIAT frequent and severity among Whites versus non-Whites, or Whites compared to each or the other racial groups? The accompany figure is interesting but does not clarify this issue. *Line 166: Should it read “… Figures 2”?* Line 167-169: Should it read “… Figures 4”? Base on Figure 4, among ever-smokers the p-value for the comparison of proportions with impairment among racial groups was 0.006, and among never-smokers it was 0.001.

**Response:** We have clarified the title of figure 2 to demonstrate the comparisons made. It now reads: “Figure 2 demonstrates that proportions impaired and the severity of impairment significantly varies between racial/ethnic groups; specifically both impairment frequency and severity was significantly higher among Whites compared to non-Whites.”

15. Line 176 - 179: “(inter-quartile range [IQR])” appears in an unusual position in the sentence. Consider revising to “The median “time to beginning TB treatment” for non-impaired persons was 62 days (interquartile range [IQR] was 12 - 110); 93 days for mildly impaired persons (IQR 61 - 110), 138 days for moderately impaired subjects (IQR 32 - 271), and 37 days for severely impaired subjects (IQR 12 -60).”

**Response:** Done

16. *Line 186-187: “Socioeconomic status, (table 2) occupation, and employment status (data not shown) were not associated with PIAT.” This is confusing since prior statements indicate that “education was used as a proxy for socioeconomic status” and that “education, employment status, and occupation were used to assess socioeconomic status.

**Response:** The statement was supposed to highlight and confirm the results shown in figure 3. We have since removed the confusing statement.

17. *Line 190-191: Considered adding a sentence indicating that racial group and foreign birth were correlated and indicate the correlation coefficient. Consider indicating the benefit of using 2 models. Avoid using “country of birth” when referring to “foreign birth”. For example “Since racial group and foreign birth were correlated, and to avoid confounding, separate multivariate regression models ...”

**Response:** The following sentence was added to the univariate section of the results: “Racial groups and foreign birth were correlated: Spearman’s rho=0.69, p<0.001.”

14. *Line 199-200: “Onset of age-related lung function decline starts is variable (19 -21); however, for this study cohort onset of impairment was related to time of acquiring tuberculosis.” The word “starts” should probably be deleted. It is not apparent how data presented in this study supports the first or second part of this sentence.
The data supports that notion that PIAT influences age-related pulmonary function declines, possibly via the age at which TB occurs among the different racial groups. We have changed the sentence to: “Onset of age-related lung function decline is variable (19 - 21); however, for this study cohort onset of impairment was related to the age at which the different racial groups acquired tuberculosis. Consequently, the risk for moderate or severe pulmonary impairment is significantly higher among older Whites compared with non Whites. As an example, the median age was 51 years for Blacks, 59 for Whites, 56 for Asians and 71 years for Hispanics (Figure 5).”

15. *Line 224 – 225: Correct typographical error by changing “… access, medical …” to “… access to medical …”. Avoid using “country of birth” when referring to “foreign birth”.
**Response:**

16. *Line 223: Correct typographical error by changing “…for each additional increase in age …” to “…for each additional year increase in age …”
**Response:** We corrected the typographical error. It now reads: “These differences persist despite control for the effects of age, body mass index, smoking, access to medical treatment, foreign birth and socio-economic status.”

17. Line 262: If “SES” is to be used for “socioeconomic status” it should be defined with the first use of the term.
**Response:** We have changed SES in text to socio-economic status.

18. *Table 1: The title should probably be “Table 1. Demographic and clinical characteristics of 317 patients with pulmonary tuberculosis included in analysis”. Three others were enrolled but not included in the analysis. “%(%)” in the second row should probably be deleted. The row labels can include “, n (%)” for rows indicating counts. Others should be “Mean Age (SD)”, “Mean FVC % of Predicted (SD)”, “Mean FEV1 % of Predicted (SD)”, “Mean FEV1/FVC % (SD)”, “Mean BMI (SD)”, “Mean Years of Biomass Some Exposure (SD)”, “Mean Pack-years Smoking Volume (SD)” and “Median Days to Begin TB Treatment (IQR)” Consider deleting rows with “Clinical Impairment” and it subcategories. These were not defined in Methods section and can be confused with pulmonary impairment.

19. *“Years of Biomass Smoke Exposure (SD)” should follow immediately after “Biomass Smoke Exposure, n (%).” “Pack-years Smoking Volume (SD)” should follow immediately after “Never-Smokers”. Either “Ever-Smokers” or “Never-Smokers” can be deleted to conserve space (if needed). Add a row for “Pulmonary Impairment, n (%)” and indicate the number and percent for each racial/ethnic group. Indent “Restrictive”, “Obstructive”, and “Mixed” to indicate the percentages listed are of those with impairment.
**Response to 18 & 19:** Corrections to the table were made as suggested by the reviewers.

20. *Table 2: Consider changing “Access-to-TB-diagnosis and treatment time to diagnosis and treatment (days)” to “Days to Begin TB Treatment”
**Response:** Corrections to the table were made as suggested by the reviewers.
21. Table 3: Consider changing title to “Predictors for pulmonary impairment in 69 White, 85 Black, 82 Asian and 81 Hispanic patients with pulmonary tuberculosis”

Response: The title of the table was changed to: “Predictors for pulmonary impairment in 69 White, 85 Black, 82 Asian and 81 Hispanic patients with pulmonary tuberculosis”

22. *Inclusion of the “Omnibus Tests of Model Coefficients” adds more confusion than clarity, and could be deleted. Alternatively, the table could be simplified by: (1) adding 2 rows labeled “Cox & Snell R-Square” and what presumably is the “Chi-square Statistics Significance”, and (2) moving the “R2” and “p” values to these rows at the end of the table. *“^”, “OR”, and “CI” are in footnotes but not in table title or table. Apparently “^” should be “a”. *Replace the second row of the table with “OR (95%CI)” below each race/ethnic group.

Response: We removed the confusing text

23. Table 4: Consider changing the title to “Predictors for pulmonary impairment in 144 US-born patients with pulmonary tuberculosis” Figure 1: Consider adding a footnote to indicate that “3 other” were not included in analysis.

Response: Title of the table was changed to: “Predictors for pulmonary impairment in 144 US-born patients with pulmonary tuberculosis”. Additionally, the footnote “3 patients were not included in analysis” was added to figure 2.

24. *Figure 2: Consider removing the label “Non-White” and associated bar to avoid suggestion that “Whites” group was compared to “Non-Whites” as a whole.

Response: The bar and label was removed, figure 2 is now moved to ‘Figure 3’.

25. *Figure 3: The figure and title do not match. Consider changing the title to “Comparisons of the frequency and severity of pulmonary impairment among patient with different socioeconomic status.” Define categories according to educational level attained. Consider removing space between first and second group. Change “…does not varies with increase …” to “…does not vary with increase …”

Response: Corrected the syntax. Title now reads: “Comparisons of the frequency and severity of pulmonary impairment among patient with different socioeconomic status.” Figure 3 has been moved to Figure 4

26. *Figure 5: The figure title should be revised to do match the figure. For the Panel B, x-axis label, change “… moderate/severe…” to “… moderate or severe…”

Response: The title for ‘figure 5’ now renamed to ‘figure 7’ in revised manuscript was changed to: “Hazard ratios for different racial groups in developing some pulmonary impairment (Panel A.) and moderate or severe pulmonary impairment (Panel B) with increase in age.” A new figure 5 has been added.
Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.
Reviewer’s report

Title: Non-Hispanic Whites have higher risk for pulmonary impairment from pulmonary tuberculosis.

Version: 1 Date: 1 August 2011

Reviewer: Tom Schaberg

Reviewer’s report:

1. The manuscript investigated "post TB impairment" in 320 TB-pts by measuring pulmonary function at least 20 weeks standard antituberculous treatment. They authors found post TB impairment significantly increased in non hispanic White pts. Surprisingly the most common type of post TB impairment was a restrictive pattern of impairment in all groups of pts. This is difficult to interpret, because no data are given about the extent of lung involvement by the TB-pts. A restriction in pulmonary function measured only by spirometry could be caused by lung destruction due to pulmonary TB or by hyperinflation eg a high residual volume (RV) and/or a high intrathoracic gas volume (ITGV). RV and ITGV could not be measured by spirometry. For this a bodyplethysmographic pulmonary function test is necessary. Since smoking was significantly more common in Whites (81%) compared to 43-52% in the control groups) one can speculate that the restriction pattern in Whites is caused by hyperinflation rather than by lung destruction due to TB. Another interpretation of the restrictive pattern might be lung destruction by TB. If this is the case, the data could be interpreted in the way that Whites have more advanced forms of pulmonary TB. In summary, I can not go along with the authors conclusion, because no data are given about the extent of lung destruction (x-ray) and about hyperinflation.

Response. We have included chest x-ray data for study patients for the reviewer. These are depicted in Figure 5. Additionally we also added this text presented in the 6th paragraph of the results section.

2. Although the statistic investigation found the main finding not related to the smoking history, it seems not explained why a much longer smoking history in the Whites (32,6 pack years compared to 4.6-8.1 in the control groups) does not have an impact on pulmonary function.

Response. We appreciate the reviewers’ concern with regards to smoking possibly confounding these findings. It is for these reasons that we used statistical methods to control for smoking variables including running separate several multiple regression models to tease out the association between smoking, race and PIAT. These results are presented in Figure 5. We have included the following text in the results: “Since racial group and foreign birth were significantly correlated, and to avoid confounding, separate multivariate regression models were constructed and are shown in Tables 3 and 4.” Indeed, as is suggested by the reviewer further data are required to fully characterize the PIAT phenotypes.
Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'