PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of tuberculosis among people with diabetes mellitus: An Australian nationwide cohort study
AUTHORS	Claudia C Dobler, Jeffrey R Flack and Guy B Marks

VERSION 1 - REVIEW

REVIEWER	Blanca I. Restrepo, Ph.D. Associate Professor, Division of Epidemiology Univ of Texas Health Science Center Houston School of Public Health, Brownsville Regional Campus USA No Conflicts of interest declared
REVIEW RETURNED	05/12/2011

THE STUDY	Regarding the study design: In the current times it is clear that the re-emerging importance of DM to TB is due to the growning number of type 2 DM cases. While it is understandable that they do not know who has type 1 or 2, the best way to enrich for this population is to include individuals who are at least 20 years or older. In fact, mostly 30 years or older, as shown by most studies (see recent by Restrepo et al., Bull WHO; studies by Stevenson et al; Ponce de Leon et al, etc). This is probably why their relative risk calculations are below those shown in other studies. In order of this study to be comparable, the analysis in adults only should be conducted. Table 2 shows a higher incidence in the 35-54, or 55-74 age groups. Along these lines, and even though they control for age, the authors should also consider presenting the data with age stratification given that those in their 40s have the highest risk studies addressing the role of DM on TB (see Restrepo et all, Bull WHO for an example).
RESULTS & CONCLUSIONS	The conclusion in the abstract is not clear in itself- it is only evident when the rest of the manuscript is read. The goal of screening for LTBI in the abstract should be made clear
GENERAL COMMENTS	Additional suggestions/comments: In the Introduction I would definitely mention that the relative risk of DM due to TB, at least from the meta-analysis, but also from other studies. The findings are very similar (about 3-fold). This should set the stage for what will be found in the current study. In the conclusion I would specify that in the study by Leung et al, the observation of a significant risk for TB among the subset of patients with chronic hyperglycemia (there is only mention that there is no significant risk among those with DM when controlled for hyperglycemia). This will support their hypothesis for the stronger association between TB and insulin-dependent diabetes due to poor DM control.

REVIEWER	Christie Jeon Post-doctoral Research Scientist Columbia University U.S.A.
REVIEW RETURNED	12/12/2011

GENERAL COMMENTS	The authors present the result of an observational study of how diabetes affects the risk of tuberculosis in Australia. While there has been growing evidence that diabetes affects tuberculosis to varying degrees in the West and in East Asia, there has been a lack of study in Australia, which represents an important piece in understanding the how diabetes may affect global TB control. The strengths of the study are that there was enough power to detect a relatively risk of 1.16, that interactions were tested for, that only diabetes preceding tuberculosis were counted (thereby establishing temporal order), and that it employed nation-wide registries. The paper was written very clearly and was easy to read. Some limitations include a lack of adjustment of socioeconomic status that may influence glucose control, access to insulin and vulnerability to tuberculosis. Another limitation is the potential misclassification of both diabetes and tuberculosis, diseases that are often underdiagnosed without active screening. Adult diabetes prevalence in Australia was estimated at 8% for men and 6.8% for women in 2000 (Dunstan et al. 2002). I presume the prevalence has increased from year 2000 to 2006. The lower diabetes prevalence of 3.6% in the current study likely reflects the inclusion of children who have lower prevalence of diabetes, but also lack of data to account for undiagnosed individuals. Further, tuberculosis may have been underdiagnosed especially among those with low access to care who experience delays in diagnosis. The potential bias that misclassification of the primary exposure of and outcome of interest could have caused should be further expounded on in the discussion. Also, given the fact that prospectively collected data with time of DM diagnosis and TB diagnosis were available I would recomend survival analysis or poisson regression with time rather than a log-binomial model to account for the amount of person-time observed in people with and without diabetes. If the method of analysis does not influence the result, it would be fine to leave the current analysis as is and state the robustness of the results to method of analysis in the discussion. For the lay readers, it would helfpul to include a sentence on why correction for overdispersion was needed, and also if there was any issues of convergence when using the log-binomial model.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Blanca I. Restrepo

#1. Regarding the study design: In the current times it is clear that the re-emerging importance of DM to TB is due to the growning number of type 2 DM cases. While it is understandable that they do not know who has type 1 or 2, the best way to enrich for this population is to include individuals who are at least 20 years or older. In fact, mostly 30 years or older, as shown by most studies (see recent by Restrepo et al., Bull WHO; studies by Stevenson et al; Ponce de Leon et al, etc). This is probably why their relative risk calculations are below those shown in other studies. In order of this study to be comparable, the analysis in adults only should be conducted. Table 2 shows a higher incidence in the

35-54, or 55-74 age groups. Along these lines, and even though they control for age, the authors should also consider presenting the data with age stratification given that those in their 40s have the highest risk studies addressing the role of DM on TB (see Restrepo et all, Bull WHO for an example).

Response: We have shown that age was not an effect modifier of the relation between DM and TB (second last paragraph in the results). Schulz and Grimes have argued that it is not advisable to do sub-group (ie stratified) analyses in this setting because of the increased risk of both Type 1 and Type 2 errors (1).

#2. The conclusion in the abstract is not clear in itself- it is only evident when the rest of the manuscript is read. The goal of screening for LTBI in the abstract should be made clear

Response: We have added the study goal of obtaining information for making a decision about LTBI screening under objectives in the abstract.

Additional suggestions/comments:

#4. In the Introduction I would definitely mention that the relative risk of DM due to TB, at least from the meta-analysis, but also from other studies. The findings are very similar (about 3-fold). This should set the stage for what will be found in the current study.

Response: We have included information on the relative risk of DM due to TB from the meta-analysis and other studies.

#5.In the conclusion I would specify that in the study by Leung et al, the observation of a significant risk for TB among the subset of patients with chronic hyperglycemia (there is only mention that there is no significant risk among those with DM when controlled for hyperglycemia). This will support their hypothesis for the stronger association between TB and insulin-dependent diabetes due to poor DM control.

Response: We have added the suggested observation from the study by Leung at al. in the discussion.

Reviewer: Christie Jeon
#1. Some limitations include a lack of adjustment of socioeconomic status that may influence glucose control, access to insulin and vulnerability to tuberculosis.

Response: We have added the lack of adjustment of socioeconomic status as a study limitation in the discussion.

#2. Another limitation is the potential misclassification of both diabetes and tuberculosis, diseases that are often underdiagnosed without active screening. Adult diabetes prevalence in Australia was estimated at 8% for men and 6.8% for women in 2000 (Dunstan et al. 2002). I presume the prevalence has increased from year 2000 to 2006. The lower diabetes prevalence of 3.6% in the current study likely reflects the inclusion of children who have lower prevalence of diabetes, but also lack of data to account for undiagnosed individuals. Further, tuberculosis may have been underdiagnosed especially among those with low access to care who experience delays in diagnosis. The potential bias that misclassification of the primary exposure of and outcome of interest could have caused should be further expounded on in the discussion.

Response:

We acknowledge that the findings do not extend to patients with undiagnosed DM and have clarified this in the manuscript. We have also added in the discussion why the rate of undiagnosed TB in Australia is assumed to be very low.

#3. Also, given the fact that prospectively collected data with time of DM diagnosis and TB diagnosis were available I would recommend survival analysis or poisson regression with time rather than a log-binomial model to account for the amount of person-time observed in people with and without diabetes. If the method of analysis does not influence the result, it would be fine to leave the current analysis as is and state the robustness of the results to method of analysis in the discussion. For the lay readers, it would helfpul to include a sentence on why correction for overdispersion was needed, and also if there was any issues of convergence when using the log-binomial model.

Response: We have inserted a statement in the statistical methods to explain the rationale for correction for overdispersion.

As this is a cohort study with a binary outcome, known number of at risk subjects and duration of follow-up for each combination of covariates, we believe the log-binomial model is the preferred model for estimating relative risk (2). The major problem, in practice, with this model is that it often does not converge. When this is the case many authors recommend alternative models (including the Poisson and proportional hazards) (3). However, in this case, the log binomial models did converge in each case, probably because of relatively little variation in the duration of follow-up. Hence, there was no need to resort to these less direct methods of estimating relative risk.

References:
1. Schulz KF, Grimes DA. Multiplicity in randomised trials II: subgroup and interim analyses. Lancet. 2005 May 7-13;365(9471):1657-61.
2. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol. 2003 May 15;157(10):940-3.
3. Deddens JA, Petersen MR. re: “Estimating the relative risk in cohort studies and clinical trials of common outcomes". Am J Epidemiol. 2004 January 15, 2004;159(2):213-4.

Yours sincerely,

Claudia Dobler, Jeffrey Flack, Guy Marks

VERSION 2 – REVIEW

REVIEWER	Christie Jeon Post-doctoral Research Scientist Columbia University U.S.A.
REVIEW RETURNED	16/01/2012

GENERAL COMMENTS	On page 18, line 36-37, the words 'a lesser' is confusing. I suggest deleting, because we can't measure the extent to which an unmeasured confounder may bias the results. On page 17, line 32, I would add to the last sentence, 'undiagnosed DM, who may have an elevated risk of TB compared to those truly without diabetes.'