**Diabetes and poor tuberculosis treatment outcomes: issues and implications in data interpretation** **and analysis**

Peijue Huangfu1, Fiona Pearson1, Cesar Ugarte-Gil2,3, Julia Critchley1

1 Population Health Research Institute, St George’s University of London, London, UK

2 Facultad de Medicina Alberto Hurtado and Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru

3 TB Centre, London School of Hygiene and Tropical Medicine, London, UK

Corresponding author: Peijue Huangfu, Population Health Research Institute, St George’s University of London, Cranmer Terrace, London SW17 0RE, phuangfu@sgul.ac.uk

Word counts: summary—146; main text— 2,368;

Number of references: 26

Number of tables and figures: 6

Running head: issues in diabetes and TB research

**Summary**

Tuberculosis remains one of the top ten causes of death globally, especially in low and middle income countries. We conducted a systematic review and meta-analysis including 88 studies examining the association between diabetes and tuberculosis treatment outcomes. However, we found a number of common methodological problems among them, including inappropriate adjustments for confounding factors, not using the most optimal statistical methods, misclassification in exposure (diabetes) and outcomes (tuberculosis treatment outcomes) due to study design and confusion of the definitions, misunderstanding of basic study design concept, standardisation of tuberculosis treatment outcomes, and publication quality control. Many of these problems would apply more broadly to other “risk factors” for a poor tuberculosis treatment outcomes. These issues need to be addressed and solved, in order to improve the quality of the studies and provide more accurate results for policy makers in the future to tackle the burden of tuberculosis.

**Key words** tuberculosis, diabetes, risk factors, data analysis, confounding

**Background**

There is recognition by international bodies and the scientific community that substantial reductions in tuberculosis (TB) may be difficult to achieve without focusing on the high-level determinants and risk factors for TB. This is emphasised by the first two pillars of the WHO post 2015 TB strategy which call for: screening and prevention of TB amongst high risk individuals and addressing the major social determinants of the disease.1 In order to appropriately respond to these calls, TB programme managers and researchers need to ‘know their epidemic’ by staying informed of contemporaneous high level social determinants of TB, the evolving national and local risk factors for disease, and risk factors for poor treatment outcomes.

With TB outcome knowledge a mainstay of TB control programmes, there is great need to improve and expand expertise to enable the production of high quality studies for monitoring and evaluation using national programme data. In this perspectives article, we describe analytical pitfalls and potential biases noted in published research on TB treatment outcomes. We indicate potential design solutions to such short-comings not requiring advanced statistical knowledge; and recommend free online learning resources and free or inexpensive software that researchers can use to improve the quality of their research design and analyses.

The analytical problems discussed in this article were identified as part of a large systematic review and meta-analysis including 88 studies to investigate the association between diabetes and TB treatment outcomes. We found TB-DM patients had twice the odds of death (Odds ratio(OR)=2.11, 95%CI: 1.76-2.51) and an increased odds of relapse (1.80, 1.40-2.30) compared to TB patients. However, we also found a number of continuing problems with the conduct and analysis of TB outcome studies that limited the robustness of conclusions we could make. Most issues were not due to a lack of advanced statistical knowledge and could be improved if authors had limited additional epidemiological training. In this article, we will discuss these issues and suggest potential solutions to them.

**Confounding factors**

The gravest design issues identified were related to the appropriate control of confounding factors. Confounding factors or ‘confounders’ are typically defined as variables associated with both the exposure and outcome of a study, but which are not on the causal pathway between the exposure and outcome (see Figure 1). For example, HIV treatment is a potential confounder of the association between diabetes and TB treatment outcomes; this is because some HIV drugs can increase blood glucose levels,2 and the impaired immune system in HIV patients makes them more vulnerable to poor TB outcomes. Important confounding factors in the association between diabetes and TB treatment outcomes are likely to be age, sex, HIV status, and Body Mass Index (BMI) or other weight related measures. However, control for such key confounders (particularly BMI) were often entirely missing, usually because data on them had not been collected.3-7 We considered studies that adjusted for age, sex, HIV status, and not adjusting for any variable thought to be on the causal pathway between diabetes and treatment outcomes to be “appropriately adjusted”; but only a few studies was found to be in this subgroup in the systematic review.8-13

In some studies, over-adjustment14 occurred when adjusting for an intermediate variable/ a proxy of the outcome (such as culture conversion at two/three months) likely to be on the causal pathway to a poor TB outcome amongst those with DM.15, 16 Such inappropriate control of confounding can suppress as well as inflate overall risk estimates. Culture conversion at two/three months, however, is a known proxy variable for TB treatment outcomes (because a positive culture at two/three months increase the risk of a poor TB treatment outcome due treatment failure) so adjusting for it in multivariate analyses could potentially “adjust out” the true association between DM and poor TB outcomes, biasing estimates towards the null.

Causal diagrams, also known as directed acyclic graphs (DAGs) are increasingly used tools in epidemiology to better formalise the causal pathways operating.17 They help researchers identify potential confounders visually during early planning and thus improve study design (e.g., planning data collection and statistical analysis). In these diagrams, a single headed arrow represents the direct causal relationship between X and Y. Figure 2 shows an example of a causal diagram for the association between diabetes and TB treatment outcomes. Age and sex are identified in the diagram as two common factors to be adjusted in studies as confounders as well as BMI (higher BMI increases the risk of having diabetes) and HIV (explained in the previous paragraph). Culture conversion at two/three months is marked on the causal pathway between diabetes and poor TB treatment outcomes. DAGs can be generated using free online software (http://dagitty.net/).18

**Regression and survival analyses**

When looking at some longer-term outcomes, such as relapse and development of multi-drug resistant TB (MDR-TB), it is important to consider patients who did not have these outcomes within the study period (i.e., those who were censored).19 Among the studies we reviewed, logistic regression was largely used to investigate such outcomes; however, survival analysis techniques are normally more appropriate.

In longer term studies “competing risk” between conventional outcomes and longer term outcomes can occur. For example, relapse cannot “compete” with early death in the course of TB treatment (i.e., the relapse case would not occur if a patient dies early in their treatment). Therefore, when examining these longer-term outcomes, it is important to take into account the time period between the start of the treatment and outcome occurring to avoid potentially underestimating the outcome rate.

Survival analysis takes into account time-to-event (e.g., time to death) as well as the outcome itself and as such is a more appropriate analysis technique to use. For example, a study was designed to investigate TB relapse among TB patients with a two-year follow-up (see Figure 3); however, some patients died during year one, and these patients “lost the chance” to be diagnosed with relapse; this would potentially underestimate the relapse cases, and could potentially attenuate the association of interest. In the schematic example of Figure 3, if we use logistic regression, four relapse cases would be found; however, patient 1 and 5 have died before developing any longer-term outcomes and don’t contribute data to the analysis; if survival analysis is used, the time to develop relapse would be considered and patients 1 and 5 would contribute some information to the analysis.

Cox proportional hazard regression is a specific type of survival analyses. It examines a rate (the number of events per population at risk per unit time), while logistic regression examines the proportion of the events occurring within a certain time period. Example 1 shows the difference in the findings when using these two different techniques.

Example 1: A study was designed to investigate whether TB patients with diabetes have a higher risk of TB relapse. New culture positive TB patients were recruited through a local hospital registry, and had been followed up for one year. The sample characteristics are shown in Table 1 and 2. Whilst this example is illustrative, the rate of losses to follow-up are consistent with some studies identified in the systematic review.20

In this example, results from a typical regression model (logistic regression) showed that the odds ratio was 1.80 (95%CI: 0.73, 4.47); while using Cox’s regression showed that the hazard ratio was 4.53 (95%CI: 1.85, 11.14). In this example, using logistic regression substantially underestimated the impact of diabetes on TB relapse as this method fails to consider the patients who left the cohort without experiencing the outcome (relapse) (censoring). Table 2 shows that 30 patients were transferred out before the end of the study and 11 patients were lost to follow-up. These 41 patients potentially could have experienced TB relapse if they had remained. Therefore, Cox regression analysis is more appropriate in this context, as it takes into account the amount of time each patient has remained in the study for and thus the opportunity they had to develop the outcome.

Among the studies we reviewed, only 8% of them considered survival analysis to investigate the association between diabetes and TB treatment outcomes.9, 11, 16, 21-25 One explanation for this may be less familiarity with the methods and statistical software availability. Apart from licence-based statistical software (e.g. Stata, SAS), there are several well-established free or inexpensive online packages that allow for survival analysis, some of them are listed in Table 3.

**Misclassification**

Our review suggested that the association between diabetes and poor TB treatment outcomes was considerably stronger among studies which screened individuals for diabetes using blood glucose tests (or related measurements), compared to those that classified diabetes status only on self-reported and / or medical records. Studies that do not actively screen for diabetes may result in substantial misclassification of diabetes status, as in low and middle income countries a high proportion of diabetes is thought to be undiagnosed. This misclassification is likely to bias estimates towards the null. Studies with laboratory based methods of diagnosis contributed more unbiased results in examining the association between diabetes and TB treatment outcome compared with those based on self-reported medical records for diagnosis only; therefore, such studies should be encouraged in the future.

The pooled analysis from 14 studies showed that TB patients with diabetes had double the odds of having MDR-TB compared to those with TB alone. However, less than half of the primary studies reported the distribution of MDR-TB among new and retreatment cases. Moreover, the timing of drug susceptibility test was often not clearly reported in the articles which made it more difficult to distinguish whether a primary MDR-TB or acquired MDR-TB occurred, and only one study adjusted for TB history when examining the association of interest. This single study however confirmed that there was an increased odds of MDR-TB among TB patients with diabetes.26

**Study design**

In some reports, study designs were incorrectly self-identified as case-control or cohort studies. The study design used affects their appropriate analysis. A wrong analysis can lead to overestimation/underestimation of the association.

Case-control and cohort studies are both observational studies. The main difference between them is how the study population is identified. Cohort studies identify the study subjects by exposure, and follow up until the outcome occurs. For example, TB patients who were admitted to a specific hospital between March 2000 and September 2000 were recruited for a cohort study and stratified on the basis of their exposure (with or without diabetes). This cohort is then followed for a period of time, with typically all-cause mortality and other TB treatment outcomes recorded as the study outcomes. In practice, data for a cohort study can collated prospectively or retrospectively (usually with previously collected administrative or medical records), and it is the latter type of retrospective cohort study that is sometimes confused with case-control studies.

Case-control studies identify the study subjects by outcome (i.e., whether the subjects have the outcome or not, such as mortality or poor treatment outcome). Then the case and control group could be compared with respect of main exposure (diabetes) or other risk factors. Case-control studies are usually, but not always, retrospective.

**Standardisation of TB treatment outcomes**

It has been established previously that reporting of treatment outcomes can vary substantially between studies. Some of the studies included in our review used treatment outcomes definitions that differ from those recommended by WHO; for example, some treatment outcomes used were not included in WHO guidelines (e.g. transferred to MDR treatment, death from pulmonary TB, refusal of treatment), while some did not precisely follow WHO guidelines (e.g., failure defined as at sixth month instead of fifth month, lost to follow up defined as after 30 days instead of the standard two months).3, 27-29 These different definitions for treatment outcomes, in addition to different TB treatment length, follow-up duration and treatment regimen, increase heterogeneity between studies, and further reduced the capacity to compare.

TB relapse and recurrence were not always distinguished adequately in research studies, and this is partially because definition was not clearly explained in guidelines. In WHO 2013 report, TB relapse (used to be called as recurrence) is defined as patients had been previously treated successfully but having another episode of TB; the relapse may be due to the same strain (true relapse) or a different strain (reinfection).29 The terminology change (from recurrence to relapse) was proposed in 2011, as relapse is more useful when explaining the estimation of TB incidence (i.e. defined as the number of new and relapse cases of TB).30 However, the recent definition/terminology change in guidelines has not been recognised by researchers, which led to more confusion in defining longer-term TB outcomes in publications.

Another issue noted above regarding proxy treatment outcomes (smear conversion) is the potential for misclassification. Smear conversion at second or third month is not a good proxy for culture conversion (which is itself only a surrogate for poor treatment outcomes). Some reports have shown that the sensitivity of smear conversion at two months to predict culture conversion is only 65% or lower.31 Smear accuracy may be highly dependent on many factors (including the reader’s experience, and quality assurance schemes);32 smear sputum is thus not the best proxy for TB treatment outcomes. Most alarmingly, many studies did not clearly state whether their sputum results were for smear or culture.33, 34

**Publication quality**

A review from 2011, including 33 studies,35 found that TB treatment outcomes were poorer among individuals with diabetes and authors emphasised the low quality of available evidence. Many new studies have since been published including some with large samples from national TB programmes. However, it was disappointing that after we reviewed this enlarging body of evidence, among 88 publications we reviewed, only a few of them could be classified as good quality. Whilst in some cases authors are limited by the quality of data available, often collected for other purposes, we strongly suggest authors follow STROBE statement (<http://www.strobe-statement.org/?id=available-checklists>) while writing up publications. STROBE provides checklists guidance for observational studies and aims at improving the quality of medical research and communication. We also recommend that the editors and reviewers could also follow the guidelines to help producing better quality publications in the future.

**Online materials**

There are a lot learning materials online which are free and easy to understand. Readers can fit in their own time schedule with online learning environment. We have a few suggestions listed below, but the learning materials are not only limited to these:

* BMJ (<http://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated>)
* Principles of Epidemiology in Public Health Practice, Third Edition, An Introduction to Applied Epidemiology and Biostatistics (<https://www.cdc.gov/ophss/csels/dsepd/ss1978/> )
* Health knowledge (<https://www.healthknowledge.org.uk/>)
	+ Survival analysis (<https://www.healthknowledge.org.uk/e-learning/statistical-methods/specialists/survival-analysis>
	+ Confounding factors (<https://www.healthknowledge.org.uk/public-health-textbook/research-methods/1a-epidemiology/confounding-interactions-methods>)

Some online courses (not free) also offer survival analysis learning:

* Survival analysis by UMC Utrecht and Utrecht University (<http://elevatehealth.eu/online-medical-courses/survival-analysis>)
* Survival analysis by Netherlands Institute for Health Sciences, Erasmus University Rotterdam (<http://www.shortcoursesportal.com/studies/23347/survival-analysis.html#content:fees_and_funding>)
* Survival analysis by The Institute for Statistics Education (<http://www.statistics.com/survival-analysis/#syllabus>)
* Statistical reasoning for public health 2: regression methods by Johns Hopkins University (<https://www.coursera.org/learn/statistical-reasoning-2>)

**Conclusion**

This article discussed a few important methodological issues found in studies investigating the relationship between diabetes and TB treatment outcome. Whilst our examples are of diabetes as a risk factor for poor TB treatment outcomes, the same issues apply when completing or reviewing research on other TB risk factors such as smoking, indoor air pollution, alcohol, or substance abuse. Better study design and analyses are critical for countries to really “know their epidemic”, and would benefit TB control globally.

**Acknowledgement**

This publication was made possible by NPRP grant number 7-627-3-167 from the Qatar National Research Fund (a member of Qatar Foundation). JC is also funded by the Higher Education Funding Council for England. CU was supported by Program for Advanced Research Capacities for AIDS in Peru (PARACAS) at Universidad Peruana Cayetano Heredia (D43TW00976301) from Fogarty International Center at the U.S. National Institute of Health (NIH). The statements made herein are solely the responsibility of the authors and the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscripts.

**Conflict of interest**

There is no conflict of interest.

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**Table 1 Example—2x2 table**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Relapse | No relapse | Total |
| DM | 10 | 38 | 48 |
| Non-DM | 13 | 89 | 102 |
| Total  | 23 | 127 | 150 |
| Odds ratio=$(\frac{10}{38})/(\frac{13}{89})$=1.80$$)$$ |

**Table 2 Example—descriptive table for censoring**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Transferred out  | Lost to follow-up | Total  |
| DM | 17 | 3 | 20 |
| Non-DM | 13 | 8 | 21 |
| Total | 30 | 11 | 41 |
| 41 patients “lost” the chance of having TB relapse due to transferring out or loss of follow-up |

**Table 3 Survival analysis online source**

|  |  |  |
| --- | --- | --- |
| **Software** | **Link**  | **Note** |
| Epi info | https://www.cdc.gov/epiinfo/index.html | Free |
| XLSTAT | https://www.xlstat.com/en/ | Free 30-day trial |
| SYSTAT | https://systatsoftware.com/ | 30-day evaluation version is available for download |
| Power and precision | http://www.power-analysis.com/ | 30-day free trial download |
| MEDCALC | https://www.medcalc.org/manual/cox\_proportional\_hazards.php | Free |
| StatsDirect | http://www.statsdirect.co.uk/Buy.aspx | Three-year renewable license keys for:* Academic (including NHS or charity-funded): from £99
* Commercial and other non-academic: from £179
* Students and [low income countries](http://web.worldbank.org/WBSITE/EXTERNAL/WBI/EXTWBISFP/0%2C%2CcontentMDK%3A20296359~menuPK%3A551559~pagePK%3A64168445~piPK%3A64168309~theSitePK%3A551553%2C00.html): from £49
 |

Exposure

(e.g. diabetes)

Confounders

(e.g. HIV treatment)

Outcome

(e.g. TB death)

**Figure 1 Confounders**

Diabetes

Poor TB treatment outcomes

HIV

Age

Sex

Culture conversion at 2/3 months

BMI

**Figure 2 Causal diagram of association between diabetes and TB treatment outcomes**

End of study

Died

Relapse

Relapse

Relapse

Died

Relapse

**Figure 3 Survival analysis example**