**Tuberculosis and diabetes: bidirectional association in a UK primary care dataset**

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**Abstract**

**Background**

Many studies have found an increased risk of pulmonary tuberculosis (PTB) among those with diabetes mellitus (DM). However, evidence on whether the association is bidirectional remains sparse. This study investigates DM rates among those with and without prior tuberculosis (TB) disease as well as the reverse.

**Methods**

Data on a UK general practice population, between 2003 and 2009, were obtained from The Health Improvement Network database. A series of retrospective cohort studies were completed. Individuals were successively classified as ’exposed’ or ’unexposed’ to TB, PTB, extrapulmonary TB (EPTB) or DM. Multivariate negative binomial regression was used to calculate incidence rate ratios (IRR) among each exposure group for outcomes of interest (TB, PTB, EPTB, or DM in turn) adjusting for plausible confounding variables (age, sex, region, Townsend quintile and smoking status). Potential confounding due to ethnicity was adjusted for using McNamee’s external method.

**Results**

DM risk was substantially raised among individuals with a history of TB disease (IRR 5.65 (95%CI 5.19 to 6.16)), PTB (IRR 5.74 (95% CI 5.08 to 6.50)) and EPTB (IRR 4.66 (95% CI 3.94 to 5.51)) compared with those without; results were attenuated after external adjustment for ethnicity (IRR 2.33 (95% CI 2.14 to 2.53)). TB risk was raised modestly among individuals with DM (IRR 1.50 (95% CI 1.27 to 1.76)) and was attenuated slightly after adjustment for ethnicity (IRR 1.26 (95% CI 1.07 to 1.48)).

**Conclusion**

DM risk was raised among those with previous TB disease; this finding has implications for follow-up and screening of patients with TB, who may be at high risk of developing DM or related complications.

**Introduction**

Despite consolidated control efforts, the tuberculosis (TB) burden remains high in many places in the world. In 2016 an estimated 10.4 million people were diagnosed with TB and 1.7 million died from the disease.1 Global diabetes mellitus (DM) prevalence has been steadily increasing in recent decades. Estimates produced by the International Diabetes Federation suggest that by 2045 a 55% increase in DM burden will occur worldwide, with the greatest increases projected to occur in regions where TB remains endemic([2](#_ENREF_2)).

An association between TB and DM has long been known although its importance has been under recognised([3-5](#_ENREF_3)). Two systematic reviews published nearly 10 years ago revitalised awareness of this link showing that DM increases TB risk by three-fold([3](#_ENREF_3), [6](#_ENREF_6)). This association has since been further confirmed by more contemporaneous studies conducted in both TB endemic regions and developed countries([7-11](#_ENREF_7)) but not always by those completed in low TB burden countries([12](#_ENREF_12)). To date, most studies of the association have been cross-sectional or cohort in design with DM as the ‘exposure’ and TB as the ‘outcome’.

A bidirectional association between TB and DM is biologically plausible([13](#_ENREF_13), [14](#_ENREF_14)), but there is limited evidence to support or refute whether people with a history of TB are at increased risk of developing DM([8](#_ENREF_8)). It remains important to identify epidemiologically whether the increased risks of TB seen among patients with DM are truly bidirectional, and clinically whether patients with TB might benefit from future screening for DM. Patients with TB often develop hyperglycaemia during TB treatment, although this may be transient([10](#_ENREF_10)). Whether or not future risk of DM is raised for those with ‘transient hyperglycaemia’ is unknown, although logical([15](#_ENREF_15)).

It is generally thought that DM increases the risk of pulmonary tuberculosis (PTB) rather than extrapulmonary TB (EPTB)([3](#_ENREF_3), [16](#_ENREF_16)). However, there is limited available evidence at present on the associations between different TB manifestations (PTB, EPTB) and DM subtypes (type 1 DM (T1DM), type 2 DM (T2DM)([8](#_ENREF_8)). Most studies are underpowered to explore these potential associations as EPTB accounts for less than 20% of global TB and only around 10% of DM is T1DM, thus it is difficult to confirm cases with diagnosis of both in many low-income and middle-income countries (LMIC), where TB burden is high. The Health Improvement Network (THIN)—a very large, widely validated and used administrative data set of UK primary care health data ([17](#_ENREF_17))—was used in this study to facilitate the investigation in this research area.

**Methods**

Data source, definition of exposures and outcomes

Data were obtained from THIN database, which contains the electronic medical records of 6.9 million patients collated over 385 general practices (GP) in the UK, covering approximately 5.7% of the total population in a representative manner([17](#_ENREF_17)). The study population comprised all individuals in THIN database with active records between 2003 and 2009 that met THIN minimum data acceptability standards at both practice and patient levels with no gaps in practice records. All patients were actively registered either currently or historically. Each exposure cohort (DM, TB, PTB, and EPTB) was constructed in the same way, dynamically with individuals selected in from the date of their first record on file for said exposure between 1 January 2003 and 31 December 2009. Each individual’s files were then searched for a subsequent record of an outcome of interest. Individuals left each cohort either on the study end date (31 December 2009), on their date of death, or GP deregistration. Unexposed cohorts were constructed from aggregated denominator data provided by CSD-Medical Research UK, the gatekeepers to THIN at the time this study was completed. Records from the THIN database undergo inhouse data quality checks and only data flagged as passing these checks were used. Further data quality checks were completed to ensure no implausible values existed for any variable of interest and that date of birth, registration and death occurred sequentially.

Using a combination of hierarchical Read codes, individuals were categorised as having: TB, PTB, EPTB, or DM. We present findings for ‘all diabetes’, the vast majority of which (roughly 90%) will be T2DM. TB diagnosis codes refer to TB disease, and do not include latent TB infection. When there was uncertainty on how a Read code should be categorised, a third opinion was sought by a chest physician as appropriate (see online supplementary appendices 1–4). The majority of, but not all, individuals within the TB cohort are subcategorised into the PTB or EPTB cohort (figure 1). Data on key confounders including age, sex, socioeconomic status ((SES) based on Townsend quintile, a score of material deprivation linked to each individual’s postcode, and smoking status were obtained from the appropriate THIN data fields.

*Statistical methods*

Univariate analyses were conducted to identify which variables were associated with both TB and DM. Results were calculated as incidence rate ratio (IRR) with 95% CI and an alpha value of p<0.05 was used as standard. Following this, multivariate analyses using a negative binomial model were completed to explore whether DM was associated with TB, PTB or EPTB, and the converse accounting for plausible confounding. Ethnicity could be an important confounder of the explored relationships, in particular where TB is the exposure and DM the outcome. Unfortunately, ethnicity has been poorly recorded in UK primary care data sets. Therefore, we have externally adjusted for ethnicity as a confounder of the bidirectional association between TB and DM using a method outlined by McNamee18; the detailed method can be found in online supplementary appendix 5. Individuals with missing data for the main variables of interest were excluded from data sets since the total number with missing data was small (<1%).

**Results**

Within the THIN data set there were 224 508 individuals in the DM cohort, 5470 in the TB cohort, 1589 in the PTB cohort and 1006 in the EPTB cohort. The mean age of entry into the DM cohort was 60 years, TB cohort 48 years, PTB cohort 53 years and EPTB cohort 47 years respectively. The average follow-up for each cohort was 4.1, 3.7, 3.7 and 4 years, respectively. Sex, age, SES and smoking distributions for the DM and TB cohorts are given in table 1. The rate of DM was significantly increased among those who had previously had TB disease (all subtypes) (IRR 5.65 (95% CI 5.19 to 6.16)). This was also the case for both PTB (IRR 5.74 (95% CI 5.08 to 6.50)) and EPTB (IRR 4.66 (95% CI 3.94 to 5.51)), compared with those who had not had TB (see table 2). We estimated that IRRs may be inflated by about 2-fold to 2.5-fold due to residual confounding by ethnicity (online supplementary appendix 5), suggesting that after this external adjustment for ethnicity the true IRR could be attenuated from 5.65 to around 2.33 (95% CI 2.14 to 2.53) up to 2.90 (95% CI 2.66 to 3.16). The IRR of TB was significantly increased among individuals with DM (IRR 1.50 (95% CI 1.27 to 1.76)) compared with those without (see table 2). The rate of PTB among individuals with DM (IRR 1.24 (95% CI 0.93 to 1.64)) and the rate of EPTB among those with DM (IRR 1.43 (95% CI 0.99 to 2.07)) when compared with those without DM were not significantly raised. External adjustment for ethnicity attenuated the estimates of DM among those with TB by 1.2-fold to 1.4-fold (see online supplementary appendix 5).

**Discussion**

The key finding of this study is the increased risk of DM following TB: over a fivefold increased risk of DM in a multivariate analysis, possibly reducing to around a twofold to threefold increased risk after external control of confounding. As far as we are aware, no other cohort study has been able to adequately quantify the risk of DM among people who have had TB, although many experts have speculated that this risk might be bi-directional([13](#_ENREF_13), [19](#_ENREF_19)). Whilst studies in high TB incidence countries are ideally needed to confirm this risk and its population importance, they may be difficult to conduct in practice, due to the large sample size (and length of follow-up) required. Thus, other studies using big data sets, more routinely available in the developed world, should be analysed to confirm this association.

 Although data are limited it could be biologically plausible that the risk of developing DM is higher after TB disease. Some recent animal models of Mycobacterium tuberculosis (Mtb) have seen unexpected development of DM (e.g. among guinea pigs), particularly those treated with anti-glycaemic therapy as host-directed therapy for TB([20](#_ENREF_20)). Studies have shown induced hyperglycaemia and/or impaired glucose tolerance occur during the early phases of active TB disease([21](#_ENREF_21), [22](#_ENREF_22)), and these metabolic states themselves are linked with progression to overt DM amongst 20-50% of individuals after three to five years([23](#_ENREF_23)). In several recent cohort studies, TB patients with newly diagnosed DM had markedly lower HbA1c values (although still abnormal) compared to those with known DM, suggesting that TB might, at least transiently, stimulate progression from intermediate hyperglycaemia to frank DM, or identify those individuals who may be more prone to metabolic alterations or DM in the future([24](#_ENREF_24), [25](#_ENREF_25)). Thus, TB disease may identify individuals at higher risk of progression to DM, in much the same as gestational DM identifies groups at high risk of progression to overt DM. Another possible mechanism by which TB may increase DM risk is through changes in body composition during and following the illness. Patients with TB frequently lose a substantial amount of weight before and in early stages of treatment; limited evidence from cohort studies suggests that weight regain during treatment could increase the proportion of body fat in recovered patients([26](#_ENREF_26), [27](#_ENREF_27)); hence increasing their future risk of DM.

This study found modest associations between DM (as exposure) and TB (as outcome) after controlling for key confounders([15](#_ENREF_15)). However, the novelty of this analysis is the large sample size and hence power to show an increased risk of EPTB as well as PTB (of similar magnitude; 1.4-fold to 1.5-fold increases). Some studies from LMIC have suggested that only PTB risk is increased among patients with DM, which may be explained by a cell-mediated immune response in patients with DM inhibiting dissemination outside the lung([28](#_ENREF_28)). In the UK, most TB cases are likely to be due to reactivation compared with LMIC, so it is possible that in the UK individuals may have seeds of latent Mtb at extrapulmonary sites that occurred prior to the onset of DM, and suggests that immune containment of Mtb is generally deficient among people with DM. The magnitude of the increased risk of TB in people with DM (about 1.3-fold increased risk over both subtypes) is lower than that first reported in systematic reviews([29](#_ENREF_29), [30](#_ENREF_30)), but in line with more recent and larger studies, particularly those in developed countries, including one recently published from the Clinical Practice Research Database (CPRD) in the UK([11](#_ENREF_11), [31](#_ENREF_31)). The slightly weaker association in these recent studies may reflect a strong primary care health system with relatively good glycaemic control and management of comorbidities among patients with DM([11](#_ENREF_11)). This hypothesis is supported by the stronger association (about a 2.5-fold association) found in the early NHANES II study (1978-80), even after control for key confounders([7](#_ENREF_7)), and several recent studies suggesting stronger associations between DM and TB risk where glycaemic control is poor([32](#_ENREF_32)).

Our finding of an increased DM risk after TB needs to be interpreted cautiously. Some studies have noted that the hyperglycaemia observed among populations of individuals with TB is transient, reversing after the early, acute phase of TB infection([22](#_ENREF_22), [33](#_ENREF_33)), although others have suggested it is permanent([34](#_ENREF_34)). It could be that some of these observations of hyperglycaemia are due to short-term side effects of treatment with rifampicin and isoniazid([35](#_ENREF_35)), or to stress hyperglycaemia, rather than being signs of true metabolic dysfunction and DM. Our findings by TB subtype also need to be carefully assessed as many patients did not have TB type classified, although most likely these are PTB cases.

Diagnosis with T2DM is often delayed, even in developed countries with strong primary healthcare systems such as the UK([36](#_ENREF_36)). With the majority of DM cases in the UK being T2DM we therefore cannot be certain if the TB disease occurred prior to DM onset, even among those individuals without a previous diagnosis of DM. Longer follow-up time periods are ideally required to fully tease out whether TB disease is itself increasing the risk of DM or whether it is a more a presenting feature of DM. However, T1DM is more commonly rapid in onset and should be quickly diagnosed in the UK([37](#_ENREF_37)), so possible reverse causality is less likely when T1DM is diagnosed after having TB disease. Given the lack of any screening programmes for TB and DM, the effect of misclassification may be non-differential, biasing estimates towards the null. However, even if uncertainties concerning the mechanism and direction of the association remain, our finding of an increased risk of DM among former patients with TB could have important clinical and public health implications. Lifetime risk of developing DM is already very high in many TB endemic countries([2](#_ENREF_2)); assuming the increased risk among patients with TB is real, it could turn out to be highly cost-effective to screen former patients with TB at regular intervals for DM, thus reducing the risks of expensive complications and improving long-term health outcomes from DM. Patients with TB with DM also appear to be more infectious (having both a higher bacterial load and remaining smear-positive for longer) than patients without DM, and also experience more recurrent TB([3](#_ENREF_3), [38](#_ENREF_38)). These factors also suggest patients with TB at risk of, or already with, overt DM may be driving continued TB transmission disproportionate to their population size and may require different treatment guidelines([39](#_ENREF_39)).

The key strengths of our analyses are the true cohort design and size of the database. The very large size, several orders of magnitude larger than most of studies on this topic, has allowed us to assess the associations with disease subgroups (PTB and EPTB) and also the risk of TB disease leading to future DM, topics barely covered (subtypes) or assessed at all (TB leading to DM) in previous analyses. Our study was based on aggregated routine healthcare records collated in primary care. DM is routinely managed in primary care, and the UK GP Quality and Outcomes Framework (implemented after 2004) incentivised GPs to diagnose and treat patients with DM([40](#_ENREF_40)), thus DM status was highly likely being recorded accurately([41](#_ENREF_41)). However, an examination of the data suggested that sub-types of diabetes may be less well recorded, perhaps related to the fact that accurately sub-typing diabetes requires tests rarely performed in routine general practice (for example c peptide and auto-antibodies testing). With the possibility for a small but unknown degree of misclassification between DM subtypes, it was decided only to present the findings for ‘all diabetes’, the vast majority of which (roughly 90%) will be type 2.

Further work is required to determine if previous TB confers different risks for different diabetes subtypes. Our data set may slightly underestimate the true incidence of TB as care will mainly be instigated and completed by secondary providers. However, we believe that in most cases TB-relevant information will be fed back to primary care, as TB is a serious, notifiable infection. Supporting this assumption is that the rates of TB identified in THIN were comparable with the UK rates (TB incidence of 14.6 per 100 000 in 2009), meaning it is unlikely that misclassification is occurring to a great extent. Further studies are required to confirm our finding, and particularly also to investigate the associations with different DM subtypes (T1DM or T2DM) and TB disease.

Although we adjusted for key confounders (SES, age, sex, smoking status)([7](#_ENREF_7), [11](#_ENREF_11)), our estimates could still be affected by residual confounding. We were unable to adjust directly for other confounders that could be of interest (such as ethnicity or body mass index (BMI)) with this data set. Our previous analyses using the NHANES data set from the USA did not find substantial attenuation of associations after adjusting for a more comprehensive range of potential confounders([7](#_ENREF_7)), and another recent analysis of data from primary care in the UK using the CPRD database also found no effect modification from ethnicity, age, or duration of DM([11](#_ENREF_11)). BMI is associated with the development of DM and TB; besides, patients with TB also lose weight, which is rapidly regained on treatment. Hence even single measurements of BMI may not be sufficient to adjust for potential confounding effects. More detailed analyses, potentially treating BMI as a time-varying exposure, are thus required, but are not currently available. We acknowledge that the potential for residual confounding by ethnicity is clearly important since DM risk is substantially increased in black Afro-Caribbean and South Asian populations, compared with white British people, and the majority of TB cases reported in the UK also occur in these minority groups. For this reason we performed an external adjustment for ethnicity, which suggested that the true RR for DM among those with prior TB could be reduced from 5.65 to around 2.33–2.90, but still remained statistically significant and clinically important.

Our analyses are the first globally to cautiously add epidemiological support to a hypothesis that the association between TB and DM could be bidirectional. This may have implications for future healthcare for people with a history of TB disease, who are not routinely assessed for DM or informed that they may be at higher risk for DM in the future. The WHO guidelines recommend screening all patients with TB for DM globally, but these are not yet routinely implemented; moreover, it is unknown what long-term health support may be needed for former patients with TB who developed hyperglycaemia. While this may be of most importance for population health in high TB-DM burden countries, it is also important among ethnic minority groups in low burden countries such as the UK, who may be at higher risk for both TB and DM([42](#_ENREF_42)).

**What is already known on this subject**

It is known that having diabetes increases the chance of developing active tuberculosis (TB). However, although plausible, it was not known if having TB increases future risk of developing diabetes mellitus (DM).

**What this study adds**

This study shows that having had TB, individuals are at an increased risk of developing DM. It is thus important to consider follow-up, in particular screening, for such long-term complications.

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**Contributors** NU and JAC originally conceived the ideas for the manuscript. FP performed the analyses, and JAC and PH helped with analyses of confounding by ethnicity. FP wrote the first draft of the manuscript with input from JAC and PH. MP, RM, PH and NU edited and critically appraised the manuscript.

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**Competing interests** None declared.

**Patient consent** Not required.

**Ethics approval** Data collection for THIN was approved by the South-East Multicentre Research Ethics Committee (MREC) in 2003. This individual study did not require separate ethical approval as only anonymised aggregated THIN data are used; however, it was reviewed by THIN independent scientific review committee.

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**Figure 1. Flow chart of cohorts within the study population.**

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AHD, additional health data file; DM, diabetes mellitus; EPTB, extrapulmonary TB; MED, medical data file; PTB, pulmonary tuberculosis; TB, tuberculosis; THIN, The Health Improvement Network.

**Table 1. Sex, age, SES and smoking distribution within all cohorts.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **DM Cohort** | **TB Cohort** |  |  |  |  |  |
|  |  |  |  | **TB** |  | **PTB** |  | **EPTB** |  |
| **Variables** |  | **Number** | **(%)**  | **Number** | **%** | **Number** | **%** | **Number** | **%** |
|  | Total  | 224,508 | 100 | 5,470 | 100 | 1,589 | 100 | 1,006 | 100 |
| **Sex** | Male | 123,264 | 54.9 | 2,698 | 49.3 | 856 | 53.9 | 440 | 43.7 |
| Female | 101,244 | 45.1 | 2,772 | 50.7 | 733 | 46.1 | 566 | 56.3 |
| **Age Group** | 0-15 | 3,045 | 1.3 | 394 | 7.2 | 68 | 4.2 | 67 | 6.7 |
| 16-30 | 8,696 | 3.9 | 1,035 | 19 | 236 | 14.9 | 174 | 17.4 |
| 31-45 | 29,576 | 13.1 | 375 | 19.3 | 78 | 16.4 | 239 | 23.8 |
| 46-60 | 63,977 | 28.5 | 1,109 | 20.3 | 328 | 20.7 | 211 | 21.1 |
| 61-75 | 80,235 | 35.7 | 1,268 | 23.2 | 473 | 29.8 | 226 | 22.6 |
| 76+ | 38,979 | 17.4 | 584 | 10.7 | 219 | 13.8 | 85 | 8.5 |
| **Townsend quintile** | 1 | 45,608 | 20.3 | 774 | 14.1 | 210 | 13.2 | 152 | 15.1 |
| 2 | 44,518 | 19.8 | 800 | 14.6 | 234 | 14.7 | 136 | 13.5 |
| 3 | 45,121 | 20.1 | 1,017 | 18.6 | 280 | 17.6 | 216 | 21.5 |
| 4 | 43,283 | 19.3 | 1,193 | 21.8 | 376 | 23.7 | 221 | 22.0 |
| 5 | 32,502 | 14.5 | 1,252 | 22.9 | 364 | 22.9 | 212 | 21.1 |
| **Smoker** | Yes | 62,288 | 27.7 | 1,449 | 26.5 | 420 | 26.4 | 254 | 25.2 |
| Past | 119,619 | 53.3 | 2,236 | 40.9 | 781 | 49.2 | 410 | 40.8 |
| No | 42,601 | 19.0 | 1,785 | 32.6 | 388 | 24.4 | 342 | 34.0 |

Table 2. IRRs, 95%CI and P-values for the occurrence of DM amongst people with TB.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Exposure**  | **Outcome**  | **Unadjusted IRR (95%CI)** | **P-value** | **Adjusted IRR (95%CI)1** | **P-value** |
| TB | DM | 6.38 (5.69-7.16) | <0.001 | 5.65 (5.19-6.16) | <0.001 |
| PTB | DM | 8.03 (6.90-9.34) | <0.001 | 5.74 (5.08-6.49) | <0.001 |
| EPTB | DM | 5.42 (4.46-6.58) | <0.001 | 4.66 (3.94-5.51) | <0.001 |
| DM | TB | 1.62 (1.37-1.92) | < 0.001 | 1.50 (1.27-1.76) | <0.001 |
| DM | PTB | 1.74 (1.30-2.32)  | <0.001 | 1.24 (0.93-1.64)  | 0.137 |
| DM | EPTB | 1.56 (1.09-2.24)  | 0.016 | 1.43 (0.99-2.07) | 0.055 |

1Adjusted for age, sex, region, Townsend score and smoking status