Diabetes mellitus and latent tuberculosis infection: baseline analysis of a large UK cohort

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ABSTRACT

We conducted a cross-sectional analysis of baseline data from a UK cohort study which enrolled participants at risk of latent tuberculosis infection (LTBI, defined as a positive result for either of the two interferon gamma release assays (IGRAs)). Binomial regression with a log link was used to estimate crude and adjusted prevalence ratios (PRs) and 95% confidence intervals (CIs) for the relationship between diabetes mellitus (DM) and LTBI. Adjusted for age, sex, ethnicity, body mass index and the presence of other immunocompromising conditions, DM was associated with a 15% higher prevalence of LTBI (PR=1.15, 95% CI 1.02-1.30, p=0.025).

Key words: Tuberculosis; Clinical epidemiology

To the editor:

Diabetes mellitus (DM) and tuberculosis (TB) are major global public health priorities (1, 2).

Many studies have assessed the relationship between DM and active TB disease (3). Data

on the effect of DM on the risk of latent TB infection (LTBI) are more limited. A recent

systematic review identified one cohort study, with an adjusted risk ratio of 4.40 (95% CI

0.50-38.55), and 12 cross-sectional studies which generated a pooled adjusted odds ratio of

1.18 (95% CI 1.06-1.30) (4).

The PREDICT (Prognostic Evaluation of Diagnostic IGRAs Consortium) study was a

prospective, multi-site UK cohort study aiming to evaluate the predictive values of interferon

gamma release assays (IGRAs) for the development of active TB among recent entrants to

the UK from high-burden countries and contacts of active TB cases ("contacts"). PREDICT

was approved by the Brent Research Ethics Committee (reference 10/H0717/14) and is

registered on clinicaltrials.gov (NCT01162265). In this study, we use baseline data from

PREDICT to investigate the association between DM and LTBI.

Recruitment took place between January 2011 and July 2015. After giving informed consent,

participants completed a questionnaire and provided blood samples for IGRAs. Participants

with evidence of active TB were excluded. The main exposure of interest in this secondary

analysis was a self-reported history of DM. Data were also collected on the method of DM

control used. The outcome of interest was LTBI, defined as a positive result for either or both

of the two commercially available IGRAs, Quantiferon-TB Gold In-Tube (QFT-GIT – Qiagen)

and TSpot.*TB* (Oxford Immunotec, Abingdon, UK). Participants with no valid IGRA results

were excluded from this analysis. Other covariates on which data were collected are

described in the Supplement.

Binomial regression with a log link was used to estimate crude and adjusted prevalence

ratios (PRs) and 95% CIs for the relationship between DM and LTBI (5). Age and sex were

treated as *a priori* confounders. A causal diagram of the relationships between potential confounders and outcomes using directed acyclic graphs, interpreted using dagitty.net (6) (Figure S1), was used to identify the minimum set of other covariates required for adjustment. P values were derived from likelihood ratio tests. We assessed potential interactions between DM and age (3) and DM and ethnicity (7), as observed for active TB (3, 7). All analyses used a complete-case approach. We conducted sensitivity analyses: 1) adjusting for age as a continuous variable using fractional polynomials (8); 2) using Poisson regression with robust standard errors (9); 3) restricting analysis to contacts; 4) including only participants who had concordant results for the two IGRAs; 5) repeating the primary analysis additionally adjusting for country of birth. Further methodological details and the questionnaire are provided in the Supplement.

9157 participants were included in the analysis (Table 1, Table S2, Figure S2). 756 participants (8.3%) reported having diabetes, of whom 535 provided information about how they controlled the condition: 409 taking medication, 55 on insulin, 20 using both insulin and other medication(s) and 51 through monitoring and/or diet only.

Prevalence of a positive IGRA was 31.5% and 27.3% amongst those with and without DM, respectively (Table 1: unadjusted PR=1.15, 95% CI 1.03-1.29, p=0.012). Characteristics associated with a positive IGRA included increasing age, male sex, being born outside the UK, being a contact, having had a previous TB diagnosis or previous contact with a TB patient, and immunosuppression (Table 1). IGRA positivity varied by ethnicity, being highest in the Black African ethnic group and lowest amongst Black Caribbean participants. There was no evidence that having a positive IGRA was associated with previous BCG vaccination, HIV status, BMI, smoking, or social risk factors (Table 1).

Table 1: Characteristics of participants with and without LTBI, and unadjusted prevalence ratios for the association with LTBI

		IGRA positive [n (%)]	IGRA negative [n (%)]	Prevalence ratio (95% CI)	p
Total		2534 (27.7)	6623 (72.3)		
Diabetes (n = 9157)	No	2296 (27.3)	6105 (72.7)	Referent	
	Yes	238 (31.5)	518 (68.5)	1.15 (1.03-1.29)	0.012
Sex (n = 9107)	Male	1406 (30.9)	3149 (69.1)	Referent	
	Female	1116 (24.5)	3436 (75.5)	0.79 (0.74-0.85)	<0.001
Age group (years) (n = 9152)	16-25	510 (22.6)	1747 (77.4)	Referent	
	26-35	887 (28.2)	2258 (71.8)	1.25 (1.14-1.37)	
	36-45	470 (33.1)	949 (66.9)	1.47 (1.32-1.63)	
	>45	666 (28.6)	1665 (71.4)	1.26 (1.14-1.40)	<0.001
Country of birth (n = 9131)	Non-UK	2279 (29.7)	5385 (70.3)	Referent	
	UK	245 (16.7)	1222 (83.3)	0.56 (0.50-0.63)	<0.001
Ethnicity (n = 8934)	Indian	1043 (27.8)	2716 (72.3)	Referent	
	White	233 (21.0)	879 (79.1)	0.76 (0.67-0.86)	
	Black African	403 (37.0)	687 (63.0)	1.33 (1.21-1.46)	
	Mixed	270 (30.9)	603 (69.1)	1.11 (1.00-1.25)	
	Pakistani	264 (30.1)	614 (69.9)	1.08 (0.97-1.21)	
	Bangladeshi	134 (19.3)	561 (80.7)	0.69 (0.59-0.82)	
	Black Caribbean	37 (16.8)	183 (83.2)	0.61 (0.45-0.82)	
	Black Other / Chinese / Other	78 (25.4)	229 (74.6)	0.92 (0.75-1.12)	<0.001
Type of participant (n = 9157)	Contact	1384 (29.6)	3286 (70.4)	Referent	
	New entrant	1150 (25.6)	3337 (74.4)	0.86 (0.81-0.92)	<0.001
Previous BCG vaccination (n = 7759)	No	394 (27.8)	1024 (72.2)	Referent	
	Yes	1724 (27.2)	4617 (72.8)	0.98 (0.89-1.07)	0.65
Previous TB diagnosis (n = 9012)	No	2321 (26.7)	6368 (73.3)	Referent	
	Yes	180 (55.7)	143 (44.3)	2.09 (1.88-2.31)	<0.001
Previous contact with TB case (n = 8833)	No	2080 (27.1)	5599 (72.9)	Referent	
	Yes	355 (30.8)	799 (69.2)	1.14 (1.03-1.25)	0.01
HIV positive (n = 8539)	No	2366 (27·9)	6121 (72·1)	Referent	
	Yes	14 (26·9)	38 (73·1)	0·97 (0·62-1·51)	0.88
Other immunosuppression[a] (n = 9150)	No	2483 (27.9)	6425 (72.1)	Referent	
	Yes	49 (20.3)	193 (79.8)	0.73 (0.56-0.93)	0.007

Smoking (n = 9125)	No	2038 (27.6)	5352 (72.4)	Referent	
	Yes	489 (28.2)	1246 (71.8)	1.02 (0.94-1.11)	0.61
BMI (kg/m^2) (n = 8589)	<18.5	113 (26.3)	317 (73.7)	Referent	
	18.5 – 25	1155 (27.3)	3069 (72.7)	1.04 (0.88-1.23)	
	≥25	1122 (28.5)	2813 (71.5)	1.09 (0.92-1.28)	0.38
Any social risk factor[b] (n = 9157)	No	2407 (27.6)	6328 (72.4)	Referent	
	Yes	127 (30.1)	295 (69.9)	1.09 (0.94-1.27)	0.26

[a] Other immunosuppressive factors considered were: history of using anti-TNF-α or other immunosuppressive drugs, solid organ transplant, haematological malignancy, jejunoilealbypass, chronic renal failure or haemodialysis, gastrectomy.

[b] Social risk factors considered were: current or past homelessness, imprisonment or problem drug use.

Complete covariate data were available for 8336 participants (91.0% of the included participants). Adjusting for sex, age group, ethnicity, immunosuppression and BMI, the PR for the association between DM and LTBI was 1.15 (95% CI 1.02-1.30, p=0.025, Table S2). There was no evidence of interaction between DM and age group (p=0.22) and weak evidence of interaction between DM and ethnicity (p=0.055, Table S3). Sensitivity analyses produced similar results, although the PR increased to 1.29 (95% CI 1.09-1.52, p=0.002) when analysis was restricted to contacts (Table S4).

Our results are likely to be generalisible to migrants and contacts in the UK (although there were some differences between participants included and excluded from the analysis [Table S1]), but perhaps not to other settings with different distributions of risk factors including country of birth and ethnicity. We used both of the commercially available IGRAs, and conducted a sensitivity analysis restricted to participants with concordant results, providing additional certainty regarding the diagnosis of LTBI. Limitations of the study include the self-reported nature of DM status, although this was frequently supported by reported use of insulin or oral hypoglycaemic agents. Any participants with undiagnosed DM would be

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misclassified; this would be non-differential with respect to IGRA status and could bias our estimates towards the null. It is also possible that DM (and other forms of immunosuppression) influences the response to IGRA (10).

This is a cross-sectional analysis so we cannot be certain whether DM onset preceded LTBI. However, the association persisted when analysis was restricted to contacts, who were considered likely to have acquired infection recently. Residual confounding (e.g. by socioeconomic status) could inflate our estimated PRs. Reported HIV prevalence was low and may be an underestimate as it was based on self-report.

Consistent with a previous systematic review and meta-analysis (4), this study suggests that, after adjustment for age, sex, BMI, ethnicity and immunosuppression, DM is associated with a small increase in the prevalence of positive IGRA results, amongst individuals at high risk of LTBI. Prospective studies are needed to further investigate the temporal relationship between DM and both infection and disease onset.

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PREVIOUS PRESENTATION OF DATA

Interim results of this study were presented at the British Thoracic Society Winter Meeting, London, December 2013 (abstract number S57).

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