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). Binomial regression with a log link was used to estimate crude and adjusted prevalence ratios (PRs) and 95% 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 (adjusted PR=1.15, 95% CI 1.02 to 1.30, p=0.025).

Trial registration number PREDICT is registered on clinicaltrials.gov (NCT01162265)

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 to 38.55) and 12 cross-sectional studies which generated a pooled adjusted OR of 1.18 (95% CI 1.06 to 1.30).[4]

The Prognostic Evaluation of Diagnostic IGRAs Consortium (PREDICT) study was a prospective, multisite 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 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, Hilden, Germany) 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 online Supplementary data.

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] (online supplementary 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 Supplementary data.

Nine thousand one hundred and fifty seven participants were included in the analysis (table 1, online Supplementary table S1, figure S2). Seven hundred and fifty six 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% among those with and without DM, respectively (table 1: unadjusted PR=1.15, 95% CI 1.03 to 1.29, p=0.012). Characteristics associated with a positive IGRA on univariate analysis included increasing age, male sex, being born outside the UK, being a contact, having had a previous TB diagnosis or previous contact with a patient with TB and immunosuppression (table 1). IGRA positivity varied by ethnicity, being highest in the Black African ethnic group and lowest among Black Caribbean participants. There was no evidence that having a positive IGRA was associated with

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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 values
Total	2534 (27.7)	6623 (72.3)		
Diabetes (n=9157)				
No	2296 (27.3)	6105 (72.7)	Referent	0.012
Yes	238 (31.5)	518 (68.5)	1.15 (1.03 to 1.29)	
Sex (n=9107)				
Male	1406 (30.9)	3149 (69.1)	Referent	<0.001
Female	1116 (24.5)	3436 (75.5)	0.79 (0.74 to 0.85)	
Age group (years) (n=9152)				
16–25	510 (22.6)	1747 (77.4)	Referent	<0.001
26–35	887 (28.2)	2258 (71.8)	1.25 (1.14 to 1.37)	
36–45	470 (33.1)	949 (66.9)	1.47 (1.32 to 1.63)	
>45	666 (28.6)	1665 (71.4)	1.26 (1.14 to 1.40)	
Country of birth (n=9131)				
Non-UK	2279 (29.7)	5385 (70.3)	Referent	<0.001
UK	245 (16.7)	1222 (83.3)	0.56 (0.50 to 0.63)	
Ethnicity (n=8934)				
Indian	1043 (27.8)	2716 (72.3)	Referent	<0.001
White	233 (21.0)	879 (79.1)	0.76 (0.67 to 0.86)	
Black African	403 (37.0)	687 (63.0)	1.33 (1.21 to 1.46)	
Mixed	270 (30.9)	603 (69.1)	1.11 (1.00 to 1.25)	
Pakistani	264 (30.1)	614 (69.9)	1.08 (0.97 to 1.21)	
Bangladeshi	134 (19.3)	561 (80.7)	0.69 (0.59 to 0.82)	
Black Caribbean	37 (16.8)	183 (83.2)	0.61 (0.45 to 0.82)	
Black Other/Chinese/Other	78 (25.4)	229 (74.6)	0.92 (0.75 to 1.12)	
Type of participant (n=9157)				
Contact	1384 (29.6)	3286 (70.4)	Referent	<0.001
New entrant	1150 (25.6)	3337 (74.4)	0.86 (0.81 to 0.92)	
Previous BCG vaccination (n=7759)				
No	394 (27.8)	1024 (72.2)	Referent	0.65
Yes	1724 (27.2)	4617 (72.8)	0.98 (0.89 to 1.07)	
Previous TB diagnosis (n=9012)				
No	2321 (26.7)	6368 (73.3)	Referent	<0.001
Yes	180 (55.7)	143 (44.3)	2.09 (1.88 to 2.31)	
Previous contact with TB case (n=8833)				
No	2080 (27.1)	5599 (72.9)	Referent	0.01
Yes	355 (30.8)	799 (69.2)	1.14 (1.03 to 1.25)	
HIV positive (n=8539)				
No	2366 (27.9)	6121 (72.1)	Referent	0.88
Yes	14 (26.9)	38 (73.1)	0·97 (0.62 to 1.51)	
Other immunosuppression* (n=9150)				
No	2483 (27.9)	6425 (72.1)	Referent	0.007
Yes	49 (20.3)	193 (79.8)	0.73 (0.56 to 0.93)	
Smoking (n=9125)				
No	2038 (27.6)	5352 (72.4)	Referent	0.61
Yes	489 (28.2)	1246 (71.8)	1.02 (0.94 to 1.11)	
BMI (kg/m^2) (n=8589)				
<18.5	113 (26.3)	317 (73.7)	Referent	0.38
18.5–25	1155 (27.3)	3069 (72.7)	1.04 (0.88 to 1.23)	
≥25	1122 (28.5)	2813 (71.5)	1.09 (0.92 to 1.28)	

Continued

Table 1 Continued

	IGRA positive (n (%))	IGRA negative (n (%))	Prevalence ratio (95% CI)	P values
Any social risk factor† (n=9157)				
No	2407 (27.6)	6328 (72.4)	Referent	0.26
Yes	127 (30.1)	295 (69.9)	1.09 (0.94 to 1.27)	

*Other immunosuppressive factors considered were history of using antitumour necrosis factor alpha or other immunosuppressive drugs, solid organ transplant, haematological malignancy, jejunoileal bypass, chronic renal failure or haemodialysis and gastrectomy.
†Social risk factors considered were current or past homelessness, imprisonment or problem drug use.
BMI, body mass index; IGRA, interferon gamma release assay; LTBI, latent tuberculosis infection; TB, tuberculosis.

previous BCG vaccination, HIV status, body mass index (BMI), smoking or social risk factors (table 1).

Complete covariate data were available for 8336 participants (91.0% of the included participants; online Supplementary table S2 compares these 8336 participants with the 821 with incomplete data). Adjusting for sex, age group, ethnicity, immunosuppression and BMI, the adjusted PR for the association between DM and LTBI was 1.15 (95% CI 1.02 to 1.30, p=0.025, online Supplementary table S3). 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, online Supplementary table S4). Sensitivity analyses produced similar results, although the adjusted PR increased to 1.29 (95% CI 1.09 to 1.52, p=0.002) when analysis was restricted to contacts (online Supplementary table S5).

Our results are likely to be generalisable to migrants and contacts in the UK (although there were some differences between participants included and excluded from the analysis (online Supplementary tables S1 and S2)), 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 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 (eg, by socioeconomic status) could inflate our estimated adjusted 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, among 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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Contributors IA conceived and oversaw the design and conduct of this analysis. JS coordinated the study and contributed to study design. CJG, ML, GHB and OMK contributed to study design and recruitment. AL, FD and JJD contributed to study design. CJ conducted statistical analysis with support from AS and JJD and drafted the manuscript. AI and SM recruited participants. VN, MR-R, SS, C-YT and HW performed laboratory work supervised by AL and FD. All authors critically reviewed and contributed to the manuscript. IA is the chief investigator of the PREDICT study; FD and AL are co-PIs.

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Competing interests CJ has undertaken paid consultancy work for Otsuka Pharmaceutical unrelated to the content of this paper. AL has several issued patents underpinning immunodiagnostics for tuberculosis. The ESAT-6/CFP-10 interferon-gamma ELISpot was commercialised by an Oxford University spin-out company (Oxford Immunotec, Abingdon, UK) from which Oxford University and AL have royalty entitlements.

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