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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 (adjusted 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 aPRs) 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 S1, 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 IGRAs 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 IGRAs 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 TB patient, and immunosuppression (Table 1). IGRAs 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 IGRAs 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	0.012
	Yes	238 (31.5)	518 (68.5)	1.15 (1.03-1.29)	
Sex (n = 9107)	Male	1406 (30.9)	3149 (69.1)	Referent	<0.001
	Female	1116 (24.5)	3436 (75.5)	0.79 (0.74-0.85)	
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 (1.14-1.37)	
	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)	
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 (0.50-0.63)	
Ethnicity (n = 8934)	Indian	1043 (27.8)	2716 (72.3)	Referent	<0.001
	White	233 (21.0)	879 (79.1)	0.76 (0.67-0.86)	
	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)	
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 (0.81-0.92)	
Previous BCG vaccination (n = 7759)	No	394 (27.8)	1024 (72.2)	Referent	0.65
	Yes	1724 (27.2)	4617 (72.8)	0.98 (0.89-1.07)	
Previous TB diagnosis (n = 9012)	No	2321 (26.7)	6368 (73.3)	Referent	<0.001
	Yes	180 (55.7)	143 (44.3)	2.09 (1.88-2.31)	
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 (1.03-1.25)	
HIV positive (n = 8539)	No	2366 (27.9)	6121 (72.1)	Referent	0.88
	Yes	14 (26.9)	38 (73.1)	0.97 (0.62-1.51)	
Other immunosuppression ^a (n = 9150)	No	2483 (27.9)	6425 (72.1)	Referent	0.007
	Yes	49 (20.3)	193 (79.8)	0.73 (0.56-0.93)	

Smoking (n = 9125)	No	2038 (27.6)	5352 (72.4)	Referent	0.61
	Yes	489 (28.2)	1246 (71.8)	1.02 (0.94-1.11)	
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 (0.88-1.23)	
	≥25	1122 (28.5)	2813 (71.5)	1.09 (0.92-1.28)	
Any social risk factor ^b (n = 9157)	No	2407 (27.6)	6328 (72.4)	Referent	0.26
	Yes	127 (30.1)	295 (69.9)	1.09 (0.94-1.27)	

^a Other immunosuppressive factors considered were: history of using anti-TNF- α or other immunosuppressive drugs, solid organ transplant, haematological malignancy, jejunioleal bypass, 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; Table S2 compares these 8336 participants with the 821 with incomplete data). Adjusting for sex, age group, ethnicity, immunosuppression and BMI, the aPR for the association between DM and LTBI was 1.15 (95% CI 1.02-1.30, $p=0.025$, 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 ($p=0.055$, Table S4). Sensitivity analyses produced similar results, although the aPR increased to 1.29 (95% CI 1.09-1.52, $p=0.002$) when analysis was restricted to contacts (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 [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 (e.g. by socioeconomic status) could inflate our estimated aPRs. 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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CONTRIBUTORSHIP STATEMENT

IA conceived and oversaw design and conduct of this analysis. JS co-ordinated the study and contributed to study design. CG, 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.

DECLARATION OF 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 plc, Abingdon, UK) from which Oxford University and AL have royalty entitlements.

JS, FD, AI, OMK, SM, VN, MR-R, CJG, ML, GHB, JJD, AS, SS, C-YT, HW and IA declare no conflicts of interest.

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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).

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas (7th edition). 2015.
2. World Health Organization. Global Tuberculosis Report 2016. 2016.
3. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS medicine*. 2008;**5**:e152 doi: 10.1371/journal.pmed.0050152 [published Online First: 2008/07/18].
4. Lee MR, Huang YP, Kuo YT, et al. Diabetes mellitus and latent tuberculosis infection: a systemic review and meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2016; doi: 10.1093/cid/ciw836 [published Online First: 2016/12/18].
5. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *American journal of epidemiology*. 2003;**157**:940-3 Online First: 2003/05/15].
6. Textor J, Hardt J, Knoppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology (Cambridge, Mass)*. 2011;**22**:745 doi: 10.1097/EDE.0b013e318225c2be [published Online First: 2011/08/04].
7. Kamper-Jorgensen Z, Carstensen B, Norredam M, Bygbjerg IC, Andersen PH, Jorgensen ME. Diabetes-related tuberculosis in Denmark: effect of ethnicity, diabetes duration and year of diagnosis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 2015;**19**:1169-75 doi: 10.5588/ijtld.14.0932 [published Online First: 2015/10/16].

8. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *International journal of epidemiology*. 1999;**28**:964-74 Online First: 1999/12/22].
9. Zou G. A modified poisson regression approach to prospective studies with binary data. *American journal of epidemiology*. 2004;**159**:702-6 Online First: 2004/03/23].
10. Faurholt-Jepsen D, Aabye MG, Jensen AV, et al. Diabetes is associated with lower tuberculosis antigen-specific interferon gamma release in Tanzanian tuberculosis patients and non-tuberculosis controls. *Scandinavian Journal of Infectious Diseases*. 2014;**46**:384-91 doi: doi:10.3109/00365548.2014.885657 [published Online.