Estimates of the impact of diabetes on the incidence of pulmonary tuberculosis in different ethnic groups in England

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See Editorial, p 571

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ABSTRACT

Background There is good evidence that diabetes is a risk factor for pulmonary tuberculosis. In England, the rates of both diabetes and tuberculosis vary markedly by ethnic group.

Objective To estimate the proportion of incident cases of pulmonary tuberculosis attributable to diabetes (population attributable fraction, PAF) for Asian, black and white men and women aged ≥15 years in England.

Methods An epidemiological model was constructed using data on the incidence of tuberculosis, the prevalence of diabetes, the population structure for 2005 and the age-specific relative risk of tuberculosis associated with diabetes from a large cohort study.

Results The estimated PAF of diabetes for pulmonary tuberculosis is highest for Asian men (19.6%, 95% CI 10.9% to 33.1%) and women (14.2%, 95% CI 7.1% to 26.5%). The PAF for all ages is similar in white and black men (6.9%, 95% CI 3.1% to 12.4% and 7.4%, 95% CI 4.6% to 12.9%, respectively) and women (8.2%, 95% CI 3.0% to 15.6% and 8.9%, 95% CI 5.3% to 15.6%, respectively). The similarity of these overall figures, despite a higher prevalence of diabetes in the black population, reflects a much younger mean age of pulmonary tuberculosis in the black population. Overall, of 3461 new cases of pulmonary tuberculosis in England in 2005, 384 (202—780) were estimated to be attributable to diabetes.

Conclusion Given the nature of the data available, considerable uncertainty surrounds these estimates. Nonetheless, they highlight the potential importance of diabetes as a risk factor for pulmonary tuberculosis, particularly in groups at high risk of both diseases. Further research to examine the implications of these findings for tuberculosis control is urgently needed.

INTRODUCTION

It is acknowledged that both tuberculosis (TB) and diabetes mellitus (DM) are major global health problems. However, there is little recognition that the rapid escalation of DM in some places may conceivably have as great an impact on TB control as the spread of HIV.[1] TB is a major cause of illness and death worldwide; in 2006 there were an estimated 9.2 million new cases of TB with 1.6 million deaths attributable to tuberculosis.[2] For DM there were an estimated 246 million people with the condition worldwide in 2007.[3]

In the 1950s joint treatment clinics for TB and DM were held in the UK,[4 5] and the idea that there is an association between TB and DM is not new. Descriptions of this association have been traced back to Roman times[6] and, in the 5th century, 'phthisis' (TB) was portrayed as a 'complication' of diabetes[7]—echoing the description by Root in 1934 that DM precedes TB.[8]

The association between TB and DM is now becoming an area of increasing interest and significance because of their global impact,[9 10] although this link is rarely highlighted in current research or control priorities. For example, the action plan 'Stopping Tuberculosis in England'[11] published by the Department of Health makes no mention of the increased risks associated with diabetes.

A previous literature review, co-authored by one of the authors of this paper, of analytical studies assessing the possible association between pulmonary TB and DM found nine studies, all of which showed a positive association.[1] It was concluded that the risk of TB is 2—3 times higher in people with DM than in those without DM, but it can be up to 8 times higher.[1] More recently a systematic review of 13 observational studies also found a consistent positive relationship and, in a meta-analysis of three cohort studies (one an occupational-based cohort, the other two in patients with renal disease), the overall relative risk (RR) was 3.11 (95% CI 2.27 to 4.26).[12] In three studies that provided age-specific relative risks, these were highest in the younger age groups. The mechanisms by which DM increases the risk of TB are not fully understood. Hypothesised mechanisms include changes in immune function associated with DM, including reduced macrophage activation and less efficient immune signalling and deficiencies in micronutrients such as vitamin D which may increase the risk of both diseases.[1]

The prevalence of DM tends to vary markedly by ethnic group with, for example, black and South Asian populations in the UK having an age-specific prevalence of DM several times higher than the white population.[13] TB also varies greatly by ethnic group. In 2008, for example, there were four cases per 100 000 in the UK-born population compared with 86 per 100 000 in the non-UK-born population. Among the latter, those belonging to the Indian, Pakistani and Bangladeshi ethnic groups accounted for the largest number of cases (n=2838), while the highest rates occurred in the black African ethnic group (314 per 100 000). Among populations born in the UK, the lowest rates occur in the white population (3 per 100 000), with much higher rates in those of Indian/Pakistani/Bangladeshi origin (41/46/17 respectively per 100 000) and black African origin (53 per 100 000).[14]

It is within this context that we wished to define better the impact that increasing levels of DM may have on the incidence of TB and, subsequently, the control of TB in the community. The aim of the work presented here was to model the potential impact of DM on pulmonary TB for different ethnic groups in England. Pulmonary TB was chosen as the evidence is strongest for this type of TB, with some evidence that the association between DM and extrapulmonary TB is less strong.[1] Pulmonary TB is responsible for the majority of the TB incidence in England, accounting for 55% of all reported TB cases in 2008.[14]

METHODS

Sources of data

Data were obtained from the Health Protection Agency (HPA) for pulmonary TB. Incidence was stratified by gender, age and ethnic group. Analyses were based on the adult population aged ≥15 years split into five age categories (table 1). In addition, data from the Yorkshire and Humber Public Health Observatory (YHPHO) on the prevalence of DM by gender, age and ethnic group were obtained (table 2).[15] Note that the DM prevalence estimates are based on total (diagnosed and undiagnosed) DM. Denominator populations were the same as those used by the YHPHO and were based on the Office of National Statistics 2005 mid-year population estimates.

Age-specific relative risks for the association between DM and incident TB (for total pulmonary TB) were taken from a study of 814 713 South Korean civil servants.[16] This is the best quality study available that provides age-specific RRs. The only other two other studies that report age-specific RRs, one from Mexico and one from Saskatchewan, Canada, are of a lower quality design, neither cohort or case control, but combining DM prevalence data with prospective TB accrual.[12]

The upper and lower 95% confidence limits on the age-specific RR estimates from the Korean study (table 3) were used to calculate upper and lower levels (effectively 95% CIs)[17] of the population attributable fraction (PAF).

Ethnic group categories

The data from the YHPHO are available for only four ethnic group categories: white, black, Asian (which includes South Asian but not Chinese) and other (which includes Chinese). The data from the HPA are available in the following categories: white, black African, black Caribbean, Indian, Pakistani, Bangladeshi, Chinese, other and unknown. The data from the HPA were therefore combined into the same four categories as the YHPHO and in the analyses the 'other/unknown' category was not included.

Estimation of population attributable fraction

The data were used to construct an epidemiological model, as previously described,[18] to calculate for each ethnic group, men and women, the estimated PAF for pulmonary TB associated with DM. The following formula was used:

Table 1 Cases of pulmonary tuberculosis by age, sex, and ethnic group in England, 2005

	Men			Women		
Age	White	Black	Asian	White	Black	Asian
15–24	45	126	153	31	127	130
25–34	79	205	219	65	198	155
35–44	134	166	83	60	104	52
45–64	244	65	127	90	42	87
65+	267	17	115	150	21	104

Source: Health Protection Agency.

Table 2 Estimated prevalence (%) of diabetes by age, sex and ethnic group in England, 2005

	Men			Women		
Age	White	Black	Asian	White	Black	Asian
15–24	0.3	0.3	0.9	0.5	0.4	0.8
25–34	0.6	0.6	3.5	0.6	0.4	2.2
35–44	2.2	3.7	9.3	1.9	5.9	5.3
45–64	5.8	10.1	21.0	6.1	23.0	16.8
65+	10.8	22.8	37.2	16.3	32.8	26.6

Source: Yorkshire and Humber Public Health Observatory.

$$\mathrm{AF}(P) = \frac{P_e(RR-1)}{1+P_e(RR-1)}$$

where P_e is the prevalence of diabetes and RR is the RR for TB in people with DM compared with people without.

As both the prevalence of DM and the RR associated with TB varies by age, the PAF was calculated separately for each for each age group. The PAF can be defined as the proportion by which the incidence rate of the outcome of interest (incident TB) in the entire population would theoretically be reduced if the exposure of interest (DM) was eliminated. Assumptions in this interpretation include that the exposure is causal and that other causative factors are equally distributed between those with and without the exposure.[19] It clearly therefore provides an idealised estimate of the potential impact of the exposure (DM) on the outcome (pulmonary TB) and needs to be interpreted in this light.

This study did not require ethical approval, being based on routinely collected and fully anonymised data. No external funding was required for the study.

RESULTS

The highest estimated PAF for TB attributable to DM in people aged ≥15 years was in Asian men (19.6%, 95% CI 10.9% to 33.1%) and women (14.2%, 95% CI 7.1% to 26.5%) (table 4). The figures for black and white subjects were similar, being 7.4% (95% CI 4.6% to 12.9%) and 6.9% (95% CI 3.1% to 12.4%), respectively, in men and 8.9% (95% CI 5.3% to 15.6%) and 8.2% (95% CI 3.0% to 15.5%) in women. However, the age structure of incident TB cases is markedly younger in black people than in white people (table 1), and the similarity in PAF for all ages between white and black people hides marked differences in age-specific PAF estimates (table 4). For example, in the age group 45–64 years, the estimated PAF in black and white men is 11.6% and 7.0%, respectively, and in women it is 23.0% and 7.4%, respectively. These age-specific differences in PAF reflect age-specific differences in the prevalence of DM, being higher in black people than in white people.

Out of 3461 new cases of pulmonary TB in the three ethnic groups (table 4) in England in 2005, it is estimated that 384

Table 3 Relative risks (RR) for diabetes and tuberculosis

Age	RR	95% CI
15–24	7.8	1.2 to 51.3
25–34	10.0	6.8 to 14.5
35–44	4.7	3.6 to 6.2
45–64	2.3	1.8 to 2.9
65+	1.8	1.1 to 2.9

Source: Kim *et al*.[16]

(11.1%, 95% CI 5.8% to 19.6%) were attributable to DM. Of these, 212 (55%) were in people in the Asian group and the rest were evenly divided between white and black people (22% and 23%, respectively).

DISCUSSION

The objective of this study was to estimate the proportion of incident cases of pulmonary TB in adults in England that may be attributable to DM. Part of the motivation for doing this is that, despite the evidence recently summarised in two reviews,[1 12] DM is a strong risk factor for TB but currently receives very limited attention in guidance on TB control. The results of this study suggest that around 11% of cases may be attributable to DM, over half of which will be in people of Asian origin (who are at high risk of DM and a comparatively high risk of TB). In black and white subjects roughly 8% of cases were attributable to DM.

Before considering the potential implications of these findings, it is essential to acknowledge the limitations and uncertainties inherent in this study. The most robust data that were used are those from the HPA on the number of cases of pulmonary TB in England in 2005 by age, sex and ethnic group. The prevalence estimates for DM by ethnic group are taken from the data source used nationally for public health planning and include those with diagnosed and undiagnosed DM (around 40% of the total). Despite being the best available source of data on total prevalence of DM in England, these estimates are based on extrapolations from old and relatively small population-based studies[15] and hence must contain a large degree of (unacknowledged) uncertainty. The denominator populations are based on the Office of National Statistics mid-year estimates.

Finally, age-specific RRs for TB in people with DM from a large cohort study in Korea were applied. There are only three studies available at the time of writing that present age-specific RRs.[12] As age is related to the risk of both TB and DM and the age structures of the populations in this paper are quite different, particularly the older white population compared with the younger Asian and black populations, it is essential to use age-specific RRs. As described in the Methods section, the Korean study is by far the best quality study of the three to provide age-specific RRs. The study by Ponce-de-Leon *et al*[20] from Mexico found a very similar relationship between age and the RR of TB in people with DM (eg, RR of 10.8 in those aged 20–44 years and 2.6 in those age ≥65 years). It is impossible to know, given the currently available published data, to what extent the same age-specific RRs from the Korean study will apply in the three ethnic groups considered in this paper. For example, there is evidence from a cohort study in Hong Kong in patients aged ≥65 years that the risk of pulmonary TB associated with DM is directly related to blood glucose control.[21] It may seem reasonable to assume, in the absence of comparable data, that this finding will also apply to younger age groups and that control of DM in England in 2005 may be better than it was in Korea in 1988–90. This could suggest that the RRs from the Korean study are too high. However, a comparison with the only available study from the UK suggests that, overall, the strength of the association is similar. The UK study was a case–control study from the General Practice Research Database based on data collected between 1990 and 2001.[22] It found an overall OR for TB in people with DM, adjusted for age, glucocorticoid use and several other potential confounders, of 3.8 (95% CI 2.3 to 6.1), not dissimilar to the overall age-adjusted RR of 3.57 (95% CI 3.07 to 5.16) from the Korean study. Nonetheless, for all the reasons discussed here, the results should be interpreted as providing an illustration, based on the best available data, of the potential contribution DM makes to the incidence of TB in England and how this contribution may differ between different ethnic groups.

Assuming that the estimates presented of the impact of DM on the incidence of TB are about right, what are their implications? They fall into three broad categories. One category

Table 4 Estimated number of cases of pulmonary tuberculosis attributable to diabetes and population attributable fraction (PAF) for white, black and Asian ethnic groups in England, 2005

	Men				Women			
		Diabetes attributable cases				Diabetes attributable cases		
Age	N	Estimate	Range*	PAF %	N	Estimate	Range*	PAF %
White								
15–24	45	1.0	0.0–6.2	2.1	31	1.1	0.0–6.5	3.5
25–34	79	4.0	2.7–5.9	5.1	65	3.3	2.2–4.9	5.1
35–44	134	10.0	7.2–13.7	7.5	60	4.0	2.9–5.5	6.7
45–64	244	17.2	10.9–24.3	7.0	90	6.6	4.2–9.4	7.4
65+	267	21.2	2.8–45.4	7.9	150	17.3	2.4–35.4	11.5
Total	769	53.4	23.6–95.6	6.9 (3.1 to 12.4)*	396	32.3	11.7–61.7	8.2 (3.0 to 15.6)*
Black								
15–24	126	2.7	0.1–17.5	2.1	127	3.2	0.1–20.4	2.5
25–34	205	10.3	6.8–15.1	5.0	198	7.7	5.0–11.3	3.9
35–44	166	19.9	14.5–26.7	12.0	104	18.6	13.8–24.4	17.9
45–64	65	7.5	4.9–10.5	11.6	42	9.7	6.5–12.8	23.0
65+	17	2.6	0.4–5.1	15.4	21	4.4	0.7–8.1	20.8
Total	579	43.1	26.6–74.9	7.4 (4.6 to 12.9)*	492	43.6	26.2–77.0	8.9 (5.3 to 15.6)*
Asian								
15–24	153	9.1	0.3–48.8	5.9	130	6.5	0.2–36.6	5.0
25–34	219	52.9	37.3–70.8	24.2	155	26.0	17.8–36.0	16.8
35–44	83	21.3	16.2–27.1	25.7	52	8.6	6.3–11.3	16.4
45–64	127	27.2	18.3–36.2	21.4	87	15.6	10.3–21.0	17.9
65+	115	26.4	4.1–47.6	22.9	104	18.3	2.7–35.0	17.6
Total	697	136.9	76.2–230.5	19.6 (10.9 to 33.1)*	528	75.0	37.3–139.9	14.2 (7.1 to 26.5)*

*Based on the age-specific 95% CIs shown in table 3.

concerns the management and treatment of people with newly diagnosed TB. Given that DM is a strong risk factor for TB, one would expect a high proportion of incident cases of TB to have DM. For example, based on the attributable risk calculations, about one-third of Asians with newly diagnosed TB will have DM. There is evidence that DM is associated with worse TB outcomes,[1] and 50 years ago in some parts of Britain there were joint TB and DM clinics.[5] Whether it would be worth systematically screening new cases of TB for DM in order to offer them both DM care and perhaps closer management of their TB treatment is something that requires further investigation.

In addition, there may be implications for TB case finding. The American Thoracic Society, for example, recommends screening people with DM for latent TB, and that there should be a low threshold for investigation for TB in people with DM and unexplained symptoms.[23] Whether guidelines in the UK and elsewhere should recommend screening for TB in people with DM and whether this should vary by ethnic group (eg, particularly focus on groups with a high risk of both diseases) requires further investigation. Ideally, further work should include studies to measure the strength of the association between TB and DM in UK populations and estimate the potential yields and cost effectiveness of case finding in people with DM.

Finally, the findings highlight the potential importance of DM as a risk factor for TB and that, other things being equal, an increasing prevalence of DM in a population would be expected to lead to an increased incidence of TB. Projections of TB epidemiology should perhaps therefore be guided by trends in DM prevalence, as well as trends in other important risk factors such as HIV.

In conclusion, this paper has highlighted the potential importance of DM as a risk factor for TB, particularly in populations with high levels of both diseases. New work is urgently needed to define better the strength the association between these diseases in different populations, and the implications of their association for case finding, treatment and projecting future rates of TB.

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