Diabetes-related tuberculosis in Denmark: effect of ethnicity, diabetes duration and year of diagnosis

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BACKGROUND: The association between diabetes mellitus (DM) and tuberculosis (TB) has been established on the basis of cross-sectional studies; however, only a few longitudinal studies have been conducted, with inconsistent results.
OBJECTIVE: To study the effect of ethnicity and the presence and duration of DM on the risk of incident TB based on 15 years of follow-up of the entire Danish population.
DESIGN AND METHODS: Using Poisson regression analysis, we estimated TB incidence in individuals with DM vs. those without DM by linking nationwide DM and TB registers to the National Civil Register at case level.
RESULTS: The TB rate ratio was 1.9 in individuals with

DM compared to non-DM individuals, regardless of country of birth, with the exception of African-born individuals (rate ratio 0.5). The risk decreased drastically within the first 2 years after the diagnosis of DM; no association was found with longer durations of DM. The risk also decreased the later the year of DM diagnosis.
CONCLUSIONS: The study confirmed DM as a risk factor for TB, except in the case of African-born individuals. Other non-DM risk factors for TB could act as effect-modifiers on the DM-TB association. Implementing earlier DM diagnosis and improving metabolic control may reduce the risk of DM-related TB.
KEY WORDS: comorbidity; immigrants; glycaemic control

NUMEROUS STUDIES have found an increased prevalence of tuberculosis (TB) among individuals with diabetes (DM) compared to those without.[1–3] While the majority of studies are cross-sectional, some controversy over the directionality of the association remains due to observations that TB induces hyperglycaemia. We found only eight longitudinal studies on DM-associated risk of TB,[4–11] of which two were conducted among renal transplant patients.[4,5] Among the six population-based studies, three studies from Hong Kong, Taiwan and the United Kingdom found a significantly increased risk of TB among DM patients compared with individuals without DM, with relative risks (RRs) of 1.31–1.83;[6–8] one study from Korea with a very short follow-up period found an RR of 3.57.[9] The lack of an association in some studies may be due to limited statistical power.[10,11] The double disease burden is

also relevant for high-income countries receiving migrants from high TB burden regions.

We aimed to study the incidence of TB associated with DM in a nationwide study with 15 years of follow-up among migrants and the Danish-born population. A secondary aim was to study the effect of the duration of DM on incident TB. Third, as DM care has improved substantially in Denmark, calendar time trends in the association between DM and TB were assessed.

TUBERCULOSIS AND DIABETES TRENDS IN DENMARK

The annual rate of TB is low in the majority of the Danish population (3 per 100 000 population per year) and high in the immigrant population (44/100 000),[12] with 60–70% of TB cases diagnosed in immigrants.[12] Migrants rarely become infected in

Denmark, and even when they are infected, this usually occurs within their own ethnic groups.[13] The main sources of TB in Denmark are TB reactivation in immigrants from high TB burden countries,[14] ongoing microepidemics caused by a single strain in young or middle-aged homeless Danish-born males with reported substance abuse[15,16] and reactivation of distant *Mycobacterium tuberculosis* infection in elderly Danes aged >60 years.[14]

The overall trend is towards an increase in infectiousness at the time of diagnosis and an increase in the proportion of cases arising from a single strain, spreading from Danes to other nationalities.[15] These trends reflect increased patient and doctor delays and insufficient awareness about high-risk groups and initiatives targeting these groups.

DM prevalence has doubled during the last decade,[17] primarily due to an increase in the number of type 2 DM cases among the elderly aged ⩾65 years. In the period 1997–2006, the number of individuals diagnosed annually with DM increased from 15 500 to around 23 000, corresponding to a 5% annual increase in DM incidence.[18]

MATERIAL AND METHODS

Study population
The study sample comprises the entire Danish population during the period from 1 January 1995 to 31 December 2009, i.e., all individuals with a personal identification number (PIN) in the Danish Civil Registration System (CRS). Study subjects were linked to the Danish Tuberculosis Notification Register (TBNR) and the National Diabetes Register (NDR) via the PIN. From the CRS, all individuals with a PIN, and from the TBNR and NDR all individuals with a date of disease diagnosis within the study period, were included in the study. The patient's date of birth is built into the PIN.

Every individual had a date of entry into the study (1 January 1995, date of birth or date of immigration, whichever was most recent), possibly dates of TB, DM and death, and a date of exit from the study (death, TB, emigration or 31 December 2009, whichever was earliest). Individuals with a TB diagnosis before 1 January 1995 were excluded.

The Danish Civil Registration System
The CRS is a nationwide register of vital parameters managed by the Danish Civil Registration Office.[19] This register includes information on immigration, emigration, death and country of birth of all residents of Denmark.

The Danish Tuberculosis Notification Register
In Denmark, TB is mandatorily notified to the TBNR register once per episode. Cases were categorised as being new/reinfection or recurrent according to

World Health Organization (WHO) definitions, and only new/reinfection cases were included. TB is diagnosed on the basis of microbiology and/or laboratory results, or solely on clinical evaluation. In Denmark, around 70–75% of all notified cases are verified using culture, followed by species identification.[20] Date of diagnosis was the date of entry into the register, reflecting the earliest date available in the following hierarchy: 1) date of symptoms, self-reported, 2) date of admission, reported by physician or 3) date of receiving notification of the individual's TB.

The Danish National Diabetes Register
The NDR was established in 2006 by linking information from several registers.[21–23] Briefly, individuals are included in the NDR as soon as they meet one of a number of criteria defining them as DM patients, such as use of health services (blood glucose testing, foot treatment) or purchase of anti-diabetes drugs. The date of diagnosis was used for the study; however, we were unable to distinguish between type 1 and 2 DM.

Covariates
Individuals were categorised as Danes if they were born in Denmark and immigrants if they were born abroad; ethnicity was defined according to region of birth and classified according to the following groups: 1) Denmark, 2) Asia, 3) Africa or 4) Other. 'Other' included individuals born mainly in Europe (including Greenland), primarily former Soviet countries, and North and South America. Follow-up was classified by TB and DM status (Figure 1).

Tabulation of follow-up data
Follow-up (person-time and TB events) among individuals with DM or non-Danish born individuals was tabulated by DM status, sex, date and region of birth, age and date at follow-up (1-year groups). This constituted the first part of the data set. The risk time for the entire Danish population was obtained from the Statistics Denmark data bank, classified by sex, date of birth, age and calendar time in 1-year intervals. The tabulated person-time from the registers among non-Danish born individuals, or after TB or DM, was subtracted from this to estimate the person-time among Danish-born non-DM, non-TB individuals. The number of TB cases without DM diagnosis among Danish-born individuals was tabulated using the same method, and merged with the data from the Danish population without TB or DM. This constituted the second part of the data set.

For the analysis including duration of DM, data were also classified by duration of DM in intervals of 0.2 year. Prevalent DM cases as of 1 January 1995 were excluded from the analysis. A graphic overview
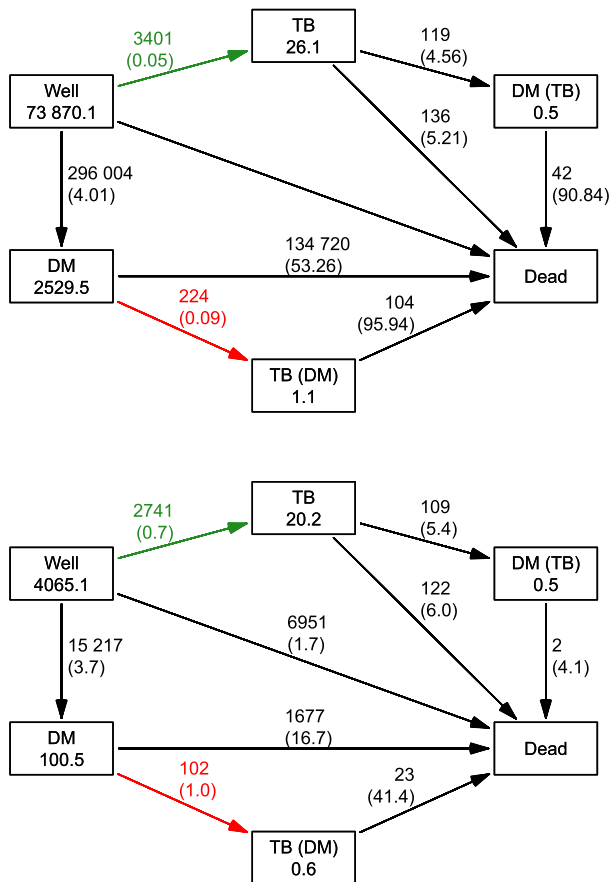
Figure 1 Transitions between disease states in the entire Danish population in the follow-up period 1 January 1995–31 December 2009, including persons with DM diagnosed before 1 January 1995. The top panel refers to the Danish born, and the bottom panel to the foreign-born. Numbers in boxes = person-years (in 1000s); numbers above arrows = the number of transitions and rates per 100 000 person-years. The analyses in this paper only concern the black arrows (red and green in the online version), i.e., the transitions to TB. TB = tuberculosis; DM = diabetes mellitus. This image can be viewed online in colour at http://www.ingentaconnect.com/content/iuatld/ijtld/2015/00000019/000000010/art00008

of the entire follow-up period of the total data set is shown in Figure 1.

Statistical analysis

Follow-up data were analysed using Poisson models, with TB events as outcome and log-person-years as offset, using natural splines to model the effect of continuous variables such as age, date of follow-up and DM duration. Knots for the natural splines were chosen such that the number of TB events was the same between consecutive knots. All analyses and graphs were created using *R*, version 3.0.1 (R Development Core Team. R: A Language and Environment for Statistical Computing, 2011).

A model for the effect of DM status, sex, ethnicity, age at follow-up and date at follow-up was fitted, and interactions between sex, ethnicity, age and date of follow-up and DM status were tested. We also included duration of DM, and tested this for interactions with ethnicity and date of follow-up. A complete account of all data processing and statistical analyses is available on http://bendixcarstensen.com/DMreg/DMTB/dmtb.pdf.

The study was approved by the Danish Data Protection Agency, Copenhagen, Denmark. No further ethics approval was required according to Danish law for register-based studies.

RESULTS

A total of 6142 non-DM TB cases and 326 TB cases with DM were followed up for respectively 77.9 and 2.6 million py (respectively 7.9/100 000 and 12.4/100 000 py) (Table 1).

Follow-up is shown separately for Danish- and non-Danish-born individuals in Figure 1. Poisson modelling revealed that TB rates and the TB rate ratio/RR of DM and non-DM individuals varied between ethnic groups (Figure 2). In the Danish-born, the RR for TB between DM and non-DM individuals was 1.8: 1.8 among Asians and 2.3 in 'Others', but only 0.5 among the African-born (Figure 2A). The

Table 1 Individuals developing tuberculosis during the study period 1 January 1995–31 December 2009

Region	Non-diabetes n (%)	Diabetes n (%)	Diabetes* n (%)
Denmark	3401 (55.4)	224 (68.7)	148 (66.4)
Africa	1242 (20.2)	18 (5.5)	17 (7.6)
Asia	782 (12.7)	51 (15.6)	31 (13.9)
Asia, excluding Oceania	781 (12.7)	51 (15.6)	31 (13.9)
Oceania	1 (0)	0	0
Other	716 (11.7)	33 (10.1)	27 (12.1)
East Europe and former Soviet Union	161 (2.6)	10 (3.1)	10 (4.5)
Other European countries	373 (6.1)	16 (4.9)	11 (4.9)
Americas, including Greenland	24 (0.4)	0	0
Remaining countries	158 (2.6)	7 (2.1)	6 (2.7)
Total	6142 (100)	326 (100)	223 (100)

* Individuals diagnosed with diabetes after 1 January 1995, with available information on duration of diabetes.
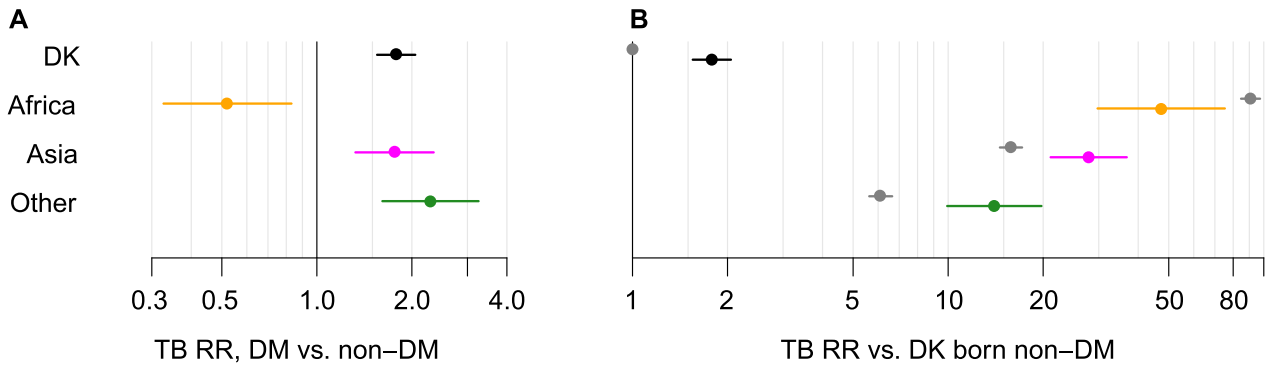
Figure 2   Rate ratio of TB: **A)** compared to individuals without DM in the same ethnic group, and **B)** compared to Danish born non-DM individuals. Grey points refer to non-DM individuals. TB = tuberculosis; DM = diabetes mellitus. This image can be viewed online in colour at http://www.ingentaconnect.com/content/iuatld/ijtld/2015/00000019/000000010/art00008
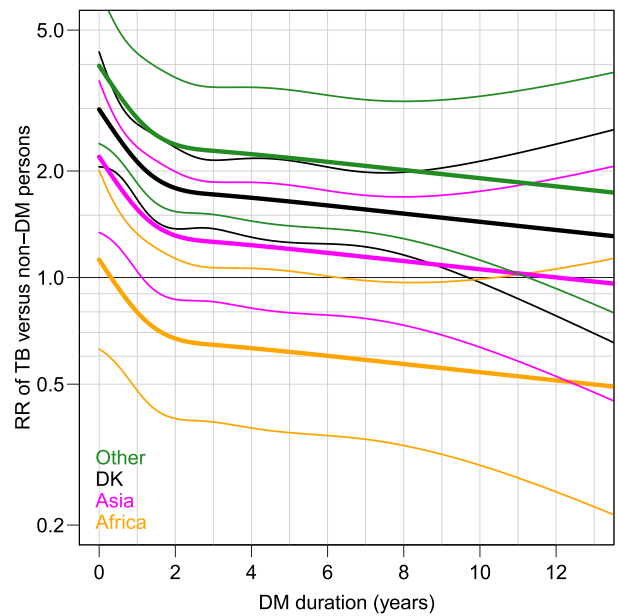
RR of TB relative to non-DM individuals in Denmark showed an increased risk from 'Other' over Asia to Africa in both DM and non-DM individuals; however, the rate among African-born non-DM individuals was very high (RR 90.8), and higher than the rate among African-born DM individuals, resulting in a RR relative to non-DM African-born individuals of 0.5 (Figure 2B).

When we included interactions between age and sex and age and ethnicity, we found that women had 20–30% lower rates of TB after age 40 years (Figure 3), and that immigrants had a peak in incidence at around 30 years, whereas Danish-born individuals had peak rates at around 50 years. The second peak in TB incidence among immigrants at age >60 years was not statistically significant due to the limited number of cases in this age group, leading to wide confidence intervals. This did not occur among Danes. Curves for DM and non-DM individuals were parallel. There was remarkably little difference in the age-shape of TB rates among the three different immigrant groups: the interaction was entirely between Danes and immigrants. We found no deviation from a constant decrease in TB rates over time ($P = 0.080$); however, rates of decline in TB among ethnic groups and by DM status differed considerably (Table 1), with TB rates among the African-born decreasing by more than 10% per year.
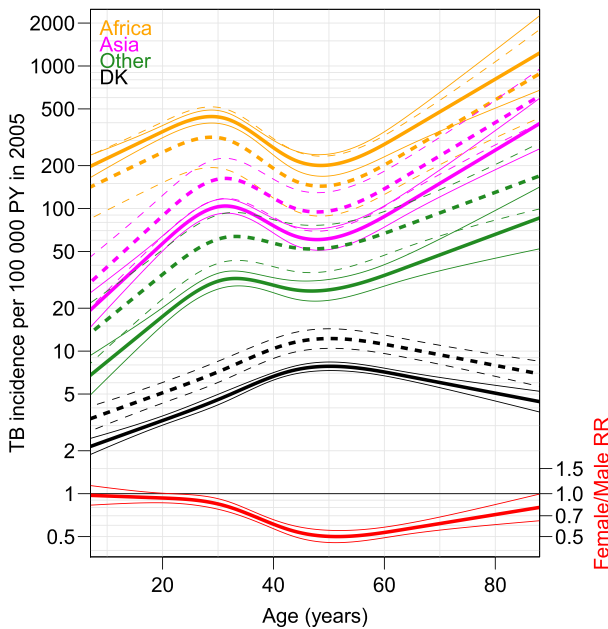

Figure 3   Age-specific TB incidence rates in males by place of birth. ____ = non-DM individuals; ——— = DM patients. The thick curve at the bottom (red in the online version) is the rate ratio between females and males (all groups); thin lines = 95% confidence intervals. TB = tuberculosis; DM = diabetes mellitus; py = person-years. This image can be viewed online in colour at http://www.ingentaconnect.com/content/iuatld/ijtld/2015/00000019/000000010/art00008

Figure 4   RR of TB by duration of DM and region of birth, relative to non-DM individuals. Thin lines = 95% confidence intervals. RR = rate ratio; TB = tuberculosis; DM = diabetes mellitus. This image can be viewed online in colour at http://www.ingentaconnect.com/content/iuatld/ijtld/2015/00000019/000000010/art00008
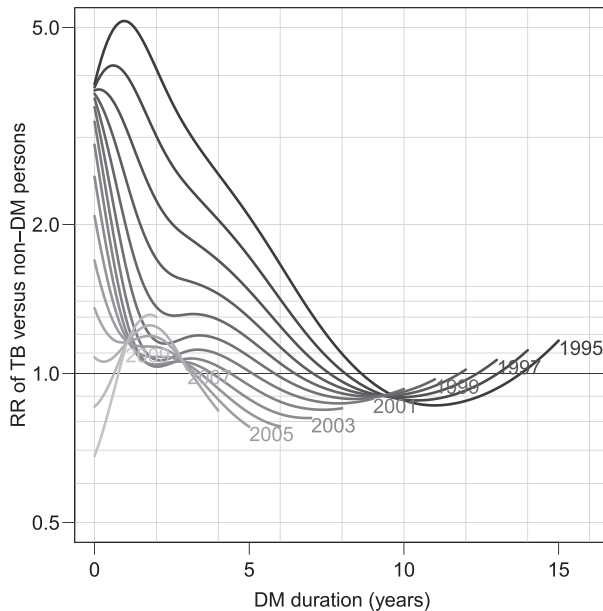
Figure 5 RR of TB in Danish-born individuals by duration of DM and date of DM diagnosis: estimates from a model with association between date of follow-up and duration of diabetes. RR = rate ratio; TB = tuberculosis; DM = diabetes mellitus.

TB rates decreased more rapidly in DM than in non-DM individuals.

The TB incidence rate decreased as duration of DM increased, mainly during the first 2 years following DM diagnosis (Figure 4). However, the curves were not significantly different among ethnic groups ($P = 0.911$); RRs between the groups were similar to those found in the analysis without duration of DM. There was a significant association between duration and calendar time, which suggests that the duration effect varied according to date of diagnosis. The effect of duration decreased substantially according to the date of DM diagnosis (Figure 5).

DISCUSSION

Based on a 15-year follow-up of the Danish population, we found an overall RR for TB of 1.9 (95%CI 1.7–2.1) in individuals with DM vs. non-DM. When adjusted for country of birth, Denmark, Asia and 'Other' had an increased risk of TB in DM individuals, with RRs of 1.8–2.3.

Among the African-born, the risk of TB was lower in DM than in non-DM individuals (RR 0.5). As for all regions, the risk of TB in DM patients decreased drastically in the first 2 years after DM diagnosis. For longer durations of DM, no association with TB was observed. For all regions, the risk of TB decreased equally with increase in calendar year, particularly after 2005.

TB incidence rates
In low TB incidence countries such as Denmark, peak

TB incidence at an older age is expected, as the majority of TB cases are due to reactivation of distant tuberculous infection. It was observed in this and other Danish studies that the TB incidence rate increased with age. In Denmark, apart from the peak among the elderly, an unexpected (for a low TB incidence country) incidence peak at age 50 among young/middle-aged Danish-born males was observed in this study (Figure 3). The peak was determined through nationwide genotyping studies to represent recent transmission in cases with substance abuse and among the homeless.[15,16]

Effect of ethnicity
In terms of the effect of country of birth on the DM-TB association, based on nationwide longitudinal register data with high internal validity, we examined the DM-TB association in different settings. Using the country of birth in high-income settings as a proxy for ethnicity and low-middle-income settings would be a simplification; also, relating ethnicity to risk estimates would imply potential confounders/effect modifiers such as other prevalent diseases, access to health care services and treatment, genetic predisposition to disease and socio-economic status. Differences in the age of peak TB incidence observed among Danes and immigrants can be explained by differences in infection pressure in the country of birth.

Although DM generally led to an increase in the risk of TB, it is surprising that this did not apply to African-born individuals. We believe that differences in risk between high- and middle-income regions such as Denmark, 'Other' and Asia, and low-income regions such as Africa may be due to differences in the main factors driving TB in the region of origin. 'Other' regions and Asia are on the whole more Westernised than the African region, with a lower prevalence of human immunodeficiency virus (HIV). Greater malnutrition in Africa may offset DM as a risk factor. However, with the global emergence of DM and other non-communicable diseases (NCDs), the African region is predicted to have the greatest increase in DM, and it is likely that, in future, DM will play a larger role as a risk factor for TB in Africa as well. These views are in line with the findings of the WHO and the International Union Against Tuberculosis and Lung Disease.[24]

In middle- and particularly high-income regions, such as Denmark, the driving force behind TB in elderly populations has been NCD comorbidity. A recent larger Danish DM-TB comorbidity case-control study covering one third of the Danish population based on hospital-diagnosed TB and DM found risk estimates that were in line with those in our study (Danes, odds ratio [OR] 1.48, 95%CI 1.19–1.82 vs. immigrants, OR 1.32, 95%CI 0.85–2.03).[11] As the previous study was not stratified by country of birth,

Table 2 Annual decrease in tuberculosis incidence rates (% per year) over the study period January 1995–31 December 2009

Region	Non-diabetes % (95%CI)	Diabetes % (95%CI)
Denmark	2.6 (1.8–3.3)	6.0 (13.5–8.4)
Africa	11.1 (9.9–12.3)	14.2 (11.7–16.7)
Asia	4.1 (2.6–5.7)	7.5 (4.8–10.2)
Other	9.1 (7.5–10.6)	12.3 (9.6–14.9)

CI = confidence interval.

the reduced risk for DM-related TB among Africans compared to Asians was not reported.

Duration of diabetes and calendar time

The rapid decrease in the risk of TB during the first years after DM diagnosis may be explained by acute hyperglycaemia at the time of DM diagnosis. Glucose tolerance may be reversible following adequate treatment.[25] The association between metabolic control and risk of progression from latent tuberculous infection (LTBI) to TB disease is not yet fully established, although some studies have linked poor glucose control to increased risk of TB.[24] As DM facilitates progression from LTBI to TB disease, this mechanism could rapidly 'exhaust' the reservoir of persons with LTBI among those who develop DM.

A Danish study by Leegaard et al. found no association with metabolic control;[11] however, a decrease in risk of TB with increasing calendar time was observed. In our study, the decrease was most pronounced after 2005. This decline may reflect the general improvement in DM management, particularly in glycaemic control,[26,27] and indicates a substantial increase in DM incidence in Denmark, which may be due in part to intensified diagnostic activity, resulting in more low-risk DM patients being included in the DM register. This could therefore result in reduced DM-related risk of incident TB. However, the strongly elevated TB risk observed immediately after DM diagnosis and the marked decrease during the first 2 years may also indicate the presence of an ascertainment bias: when diagnosing TB, screening and diagnosis of DM is more likely, and vice versa.

Study limitations

We did not have access to nationwide data on glycaemic control, HIV status, nutritional status, substance intake (e.g., alcohol/*khat*), recent TB vs. LTBI or socio-economic factors. Furthermore, entry of DM individuals into the register may have been delayed.

Addressing the dual disease burden

Questions remain about the strength of the DM-TB association in different settings.[28,29] Differences in the risk of DM-related TB between individuals born in different geographic regions could suggest that non-DM-related risk factors for TB such as HIV, malnutrition during pregnancy/intra-uterine programming, etc., act as effect-modifiers on the DM-TB association, resulting in reduced risk among African-born individuals. It would be interesting to see if these results could be reproduced in different geographic and socio-economic settings. In low TB burden settings, our findings are not likely to change recommended practices, i.e., screening for TB in migrants from high TB burden countries with symptoms suggestive of TB, recent exposure, poor DM control or other TB risk factors;[29] however, our findings should create increased awareness about DM as a risk factor for TB.

For low- and middle-income countries with an increasing dual burden of disease but limited NCD management, our findings suggest that optimising DM management might reduce the risk of TB; however, no clinical trials support this hypothesis.[30]

CONCLUSION

Our study confirms a higher DM-associated risk of TB, except in African-born individuals. As no association between DM and incident TB was found with longer duration of DM and after 2005, these results do not support systematic bidirectional screening. Although our data suggest that early diagnosis of DM and improved metabolic control may be beneficial in the control of TB, such recommendations should be based on clinical trials rather than on observational data.

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RESUME

CONTEXTE : L'association entre diabète (DM) et tuberculose (TB) a été établie à partir d'études transversales, mais seules quelques études longitudinales ont été réalisées, avec des résultats inconstants.

OBJECTIF : A partir d'un suivi de 15 ans de toute la population du Danemark, étudier l'effet de l'ethnicité et de la présence et de la durée d'un DM sur le risque de TB.

SCHÉMA ET MÉTHODES : En liant les registres nationaux DM et TB au niveau du registre national civil pour chaque cas, nous avons estimé l'incidence de la TB chez des sujets diabétiques par rapport à des sujets non diabétiques grâce à l'analyse de régression de Poisson.

RÉSULTATS : Le ratio de la TB a été de 1,9 chez les sujets atteints de DM comparés aux non diabétiques, indépendamment du pays de naissance, sauf pour ceux nés en Afrique, avec un taux de 0,5. Le risque a diminué considérablement au cours des 2 années suivant le diagnostic du DM, et pour des durées de DM plus longues, aucune association n'a été trouvée. Le risque a également diminué si le DM était plus tardif.

CONCLUSION : L'étude a confirmé le DM comme facteur de risque de la TB, sauf pour les personnes nées en Afrique. Les autres facteurs de risque de TB, hormis le DM, pourraient jouer le rôle de modificateurs d'effet sur l'association DM-TB. Mettre en œuvre un diagnostic plus précoce du DM et améliorer le contrôle du syndrome métabolique pourraient diminuer le risque de TB liée au DM.

RESUMEN

MARCO DE REFERENCIA: Algunos estudios transversales han establecido la asociación entre la diabetes (DM) y la tuberculosis (TB), pero existen pocos estudios longitudinales y sus resultados han sido contradictorios.

OBJETIVO: Analizar el efecto de la etnia y la presencia y la duración de la DM sobre el riesgo de aparición de un caso nuevo de TB a partir de un seguimiento de 15 años de toda la población danesa.

MÉTODOS: Se vincularon los registros nacionales de DM y TB con el Registro Civil Nacional a escala de los casos y mediante un análisis de regresión de Poisson se calculó la incidencia de TB en las personas con diagnóstico de DM, en comparación de las demás personas.

RESULTADOS: El cociente de riesgos de TB fue 1,9 en las personas con diagnóstico de DM en comparación con las personas sin esta enfermedad, sin tener en cuenta el país de nacimiento, con la excepción de las personas nacidas en África, cuyo cociente de riesgos fue 0,5. El riesgo de padecer TB disminuyó notablemente durante los 2 primeros años después del diagnóstico de DM y en los casos de mayor duración de la DM, no se observó ninguna asociación. El riesgo también disminuyó cuando el diagnóstico de DM se establecía más tardíamente.

CONCLUSIÓN: El estudio confirmó que la DM constituye un factor de riesgo de contraer la TB, excepto en las personas nacidas en la región de África. Otros riesgos de padecer TB, diferentes a la DM, podrían actuar como modificadores del efecto de la asociación de estas dos enfermedades. El establecimiento más temprano del diagnóstico de DM, con una mejor regulación del equilibrio metabólico, podría contribuir a disminuir el riesgo de padecer TB que se asocia con la DM.