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# Diabetes is a risk factor for tuberculosis in the Inuit population of Greenland

*To the Editors*:

Diabetes is a known risk factor for tuberculosis (TB), and studies across populations and geographic regions suggest substantial increased risks of developing TB ranging from 1.16 to 7.83 with co-existing diabetes [1]. It is suggested that the risk is due to latent TB infections being activated by the hyperglycemia associated with diabetes. The evolving epidemiology of concurrent diabetes and TB in settings where both diseases are frequent is therefore looked upon with special concern. The prevalence of diabetes among the Greenland Inuit is high (10%) and increasing [2]. Meanwhile, the TB incidence remains high with an estimated 180 cases per 100,000 suggesting ongoing TB transmission [3]. The aim of this study was to quantify the effect of diabetes on TB development among the Greenland Inuit.

We conducted a retrospective cohort study. Study participants comprised ethnic Inuit who participated in two previously conducted cross-sectional studies where diabetes status were assessed; Inuit Health in Transition Study (IHIT) [4] and the Greenland Population Study (B99) [2]. All study participants in IHIT and B99 were randomly selected from the Civil Registration System (CRS) in order to represent the entire Greenlandic population. The CRS provides all citizens of Greenland with a unique identification number at birth, facilitating tracing of persons through all public registries. The CRS identifier enabled follow-up of study participants in the National TB register. The study was approved by the Ethics Review of Greenland.

Participants not previously diagnosed with diabetes (98%) underwent a standard oral glucose tolerance test (OGTT). Participants were categorised with diabetes if previously diagnosed with diabetes or if fasting and 2-h blood glucose levels were $\geqslant 7$ mmol·L$^{-1}$ and $\geqslant 11.1$ mmol·L$^{-1}$, respectively. Weight and height were measured and body mass index (BMI) calculated. Age and sex of participants were determined from CRS data. Place of residence, divided into town or settlement, was likewise derived from the CRS registry.

TB is a mandatory notifiable disease in Greenland and all incident cases diagnosed by a medical doctor are recorded in the National TB register [5]. For the present study, all incident

**TABLE 1** Incidence rate ratio (RR) of tuberculosis with co-existing diabetes

| | RR | 95% CI |
|---|---|---|
| **Crude** | | |
| Diabetes | 2.66 | 0.41–10.3 |
| Non-diabetes | 1 | |
| **Adjusted#** | | |
| Diabetes | 11.7* | 1.48–65.9 |
| BMI kg·m$^{-2}$ | 0.67* | 0.51–0.84 |
| Age yrs | 0.93* | 0.88–0.97 |
| Sex | | |
| Males | 1 | |
| Females | 0.16* | 0.02–0.63 |
| Place of residence | | |
| Town | 1 | |
| Settlement | 1.82 | 0.47–6.11 |

BMI: body mass index. #: adjusted for age, sex, place of residence and BMI. *: $p<0.05$.

TB cases recorded among the study participants were retrieved from the National TB register; however, only TB cases recorded after diabetes assessment were included in the study.

Diabetes status, age, sex, place of residence and BMI retrieved from B99 and IHIT were linked to the National TB register and the death register by the CRS number. Participants were followed from entry into either B99 or IHIT until TB diagnosis, death/emigration or December 31 2010, whichever came first. The incidence rate ratios (RRs) for developing TB according to diabetes status were estimated by log-linear Poisson regression, using the logarithm of person years as offset. The RRs were adjusted for BMI, age, sex and place of residence in a multivariate regression analyses. To evaluate the robustness of our results, we also estimated the crude estimate using exact Poisson regression with mid-p confidence intervals (CIs). This only led to a minor widening of the confidence interval. Level of significance was set at 5%. All analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC, USA).

A total of 3,012 study participants were identified as Inuit and registered in CRS, of these 276 were excluded from further analysis for not meeting the inclusion criteria (prior TB (n=257) and missing sample dates (n=19)). 2,736 were included in the analyses. Mean follow-up was 4.97 yrs. Approximately 44% were males (49% in Greenland as a whole), and the median age was 45 yrs (interquartile range: 37–56 yrs) (40 yrs in Greenland (interquartile range: 30–50 yrs)). Median BMI was 25.6 kg·m$^{-2}$ (interquartile range: 22.5–29.5 kg·m$^{-2}$) and 74% lived in towns.

A total of 281 (10.3%) participants had diabetes and 11 (0.4%) were registered with TB during follow-up. The unadjusted TB incidence rate was 2.66 times higher in participants with diabetes compared with participants without diabetes (table 1). Adjusting for age, sex, BMI and place of residence, however, entailed a significantly increased RR of 11.7 ($p<0.01$). High BMI and female sex had a protective effect on the risk of developing TB.

The present study is, to our knowledge, the first study to explore and quantify the effect of diabetes on the risk of developing TB in an Inuit population. The present study found the TB incidence rate to be 11.7 times higher among Inuit with diabetes relative to Inuit without when adjusting for age, sex, place of residence and BMI. The results of the present study are overall in accordance with similar studies assessing the link between diabetes and TB. However, the magnitude of the RR in this study is higher than the risk identified in most studies. Thus, a prospective study from Mexico found a seven-fold increase in TB rates among persons with diabetes relative to persons without diabetes [6]. The link between diabetes and TB was also explored in indigenous populations; thus MORI *et al*. [7], found diabetes to be more frequent in Oglala Sioux Indians diagnosed with TB compared with Indians without TB (odds ratio 5.2).

Surprisingly, a study of TB risk factors recently conducted in Greenland, could not identify diabetes as a risk factor for TB [8]. However, diabetes was self-reported in the study and therefore subject to major under-reporting as an estimated 70% of people with diabetes in Greenland are unaware of their diabetes [2]. Additionally, the study population comprised mixed Inuit/Danish ethnicity. A study from Denmark found an odds ratio of 1.18 (95% CI 0.96–1.45) of active TB with a prior diagnosis of diabetes [9]; the discrepancy to our study is most likely due to the low risk of latent TB in Denmark compared with Greenland [10].

Adjusting for age, sex, BMI and place of residence entailed a dramatic increase in the RR due to the strong association between BMI and TB, and between sex and TB. The apparent strengthening of risk estimates after confounder adjustment has been found in similar studies [1, 7]. The seemingly protective effect of a higher BMI is in accordance with studies suggesting underweight to be a substantial risk factor for active TB [8]. Nonetheless, it is also plausible that persons with advanced TB symptoms (*e.g.* extensive weight loss) are more likely to seek medical attention and, therefore, more often registered with TB. However, a low BMI may also be an expression of more advanced diabetes and hence, longer duration of unknown diabetes. It is well known that the TB incidence is lower among females, which is also in accordance with the finding in this study [8]. Likewise, participants living in towns had lower RR of developing TB than participants living in settlements, consistent with one study, where living in settlements was a risk factor for TB [8].

A major strength of the present study is the longitudinal study design allowing the calculation of RR and thus assessing the temporal order of the association of diabetes and TB. Furthermore, as diabetes is unknown in an estimated 70% of diabetes cases in Greenland [2], the assessment of diabetes from OGTT is a substantial strength. Likewise, TB cases are diagnosed by a medical professional and microbiologically confirmed before registration in the National TB register.

Furthermore, as assessment of diabetes is made at point of study entry in IHIT and B99, the duration of diabetes exposure, is not taken into account. Hence, unknown diabetes may have facilitated the occurrence of TB before a confirmed diabetes diagnosis, underestimating the effect of diabetes on the risk of TB development. Additionally, it is possible that unmeasured confounders, not adjusted for in the present study may account for some of the effect of diabetes on the risk of developing TB.

The contribution of diabetes is still widely overlooked in TB prevention efforts [1]. In this sample of Greenland Inuit where both HIV and undernutrition remain uncommon, the risk of developing TB was markedly higher in persons with co-existing diabetes than in persons without. The very high risk associated with diabetes suggests potential reduction in the Greenland TB incidence rates through incorporating diabetes control and prevention in TB prevention schemes. However, the validity of the results should be confirmed in a larger sample size, preferentially by applying longer follow-up time to the study cohort.

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# Outcomes of a tuberculosis contact investigation programme in Italy

*To the Editors:*

*Mycobacterium tuberculosis* transmission is affected by several key factors, such as contagiousness of the index tuberculosis (TB) case, immune status and susceptibility of the exposed TB contact, duration and patterns of contact between the index TB case and the exposed TB contact, and characteristics of the environment within which such contact occurs [1–3]. Tracing strategies that allow the early identification and appropriate treatment of TB contacts with latent TB infection (LTBI) or active TB should be a priority of TB control programmes with adequate resources [3, 4].

In agreement with the guidelines laid out by the Italian Ministry of Health, the Piedmont Region has activated and regularly updated TB contact investigation procedures [5]. We used data from the Piedmont Region TB contact investigation programme to assess the role of selected risk factors for TB infection (TBI) among TB contacts in the city of Turin, Italy. For each suspected or confirmed pulmonary TB case, active contact investigation was conducted among household members, close contacts and regular contacts, defined according to the stone-in-the-pond method [6]. Passive investigation was used for occasional contacts [5].

The Piedmont TB notification systems were used to identify pulmonary TB cases between January 2002 and December 2008. TB cases were classified into three categories of contagiousness: 1) sputum smear-positive and culture-positive (acid-fast bacillus positive (AFB+)); 2) sputum smear-negative but culture-positive (CULT+); and 3) sputum smear-negative and culture-negative or not examined, *i.e.* other than defined (OtD). Interviews were conducted with each TB case to identify TB contacts, defined as anyone having shared air with an active TB case. All traced TB contacts were screened for active TB or LTBI using the tuberculin skin test (TST). The TST was performed using tuberculin purified protein derivative (5 IU) according to the Mantoux method [3]. TB contacts were classified as infected either if the induration was $\geqslant$5 mm in diameter regardless of any prior bacille Calmette–Guérin (BCG) vaccination [3] or if clinical, bacteriological or radiological signs or symptoms of manifest disease were present. If the TST was negative, a second