The Effect of Diabetes and Prediabetes on *Mycobacterium tuberculosis* Transmission to Close Contacts

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40-word summary of the article's main point: Diabetes is a risk factor for tuberculosis, but its association with *Mycobacterium tuberculosis* transmission is unclear. We performed a prospective study demonstrating that close contacts of pulmonary tuberculosis patients with dysglycemia had an increased risk of *M. tuberculosis* infection.

ABSTRACT

Background: It is unknown whether dysglycemia is associated with *M. tuberculosis* transmission.

Methods: We assessed epidemiological and clinical characteristics of patients with culture-confirmed pulmonary TB and their close contacts, enrolled in a multicenter prospective cohort in Brazil. Contacts were investigated at baseline and 6 months after enrollment. QuantiFERON positivity at baseline and conversion (from negative to positive at month 6) were compared between subgroups of contacts according to glycemic status of persons with tuberculosis (PWTB) as diabetes mellitus (DM) or prediabetes. Multivariable mixed-effects logistic regression models were performed to test independent associations with baseline QuantiFERON-positive and QuantiFERON-conversion.

Results: There were 592 PWTB (153 DM, 141 prediabetes, 211 normoglycemic) and 1784 contacts, of whom 658 were QuantiFERON-positive at baseline and 106 converters. Multivariable analyses demonstrated that TB-prediabetes cases, acid-fast bacilli-positive, pulmonary cavities, and living with someone who smoked, were independently associated with QuantiFERON-positive in contacts at baseline. DM, persistent cough, AFB-positive and pulmonary cavities in TB source cases were associated with QuantiFERON-conversion.

Conclusion: Contacts of persons with pulmonary TB and dysglycemia were at increased risk of being QuantiFERON-positive at baseline or month 6. Increased focus on such close contacts could improve TB control.

Keywords: Diabetes; Prediabetes; Quantiferon; Interferon-gamma releasing assay; *Mycobacterium tuberculosis*.

INTRODUCTION

Understanding factors associated with *Mycobacterium tuberculosis* (Mtb) transmission is an important component for tuberculosis (TB) control. Mtb is transmitted via aerosols generated by people with active pulmonary TB, through speaking, coughing or sneezing [1]. Individuals with more severe pulmonary TB may emit higher numbers of infectious droplet nuclei. Vigorous and persistent cough, as well as cavitary lung lesions, may increase the emission of infectious droplets [2]. Other drivers of Mtb transmission include biological characteristics of Mtb [3], the number of contacts, the proximity and duration of contact, delays in TB diagnosis in the source case, and environmental factors such as closed indoor spaces with low air circulation and no ultraviolet light [2]. Other factors are associated with higher risk of developing TB, such as HIV infection, diabetes mellitus (DM), smoking, alcohol abuse, and malnutrition [2, 3]. Although DM is associated with an increased risk of developing active disease once infected with Mtb [4], the effect of DM on Mtb transmission has not been evaluated.

Previous studies have found that persons with DM (PWDM) and TB more frequently present with extensive or cavitary pulmonary TB than normoglycemic patients [5]. Furthermore, PWTB with DM exhibit a higher bacillary load in sputum [6, 7], more persistent cough [8] and delayed mycobacterial clearance compared to persons without DM [7, 8]. Although DM has the potential to increase Mtb transmission, to our knowledge no studies have directly investigated this hypothesis. We therefore investigated whether contacts of persons with pulmonary TB and dysglycemia were at increased risk of Mtb infection compared to contacts of normoglycemic PWTB.

MATERIALS AND METHODS

Ethics Statement

The study was conducted according to the principles of the Declaration of Helsinki. The RePORT-Brazil protocol was approved by the institutional review boards at each study site and at Vanderbilt University Medical Center. Participation in RePORT-Brazil was voluntary, and written informed consent was obtained from all participants.

Study design

This was a multicenter prospective observational cohort study of individuals ≥18 years old with culture-confirmed pulmonary TB and their close contacts. Description of RePORT sites and data collection is presented in **Supplementary Methods** and in [9].

For this protocol, close contacts were defined as having ≥4 hours of contact/week with the TB index case at any time in the previous 6 months [10]. Contacts identified who agreed to participate in the study were evaluated at two visits: baseline and 6 months after enrollment. They were also contacted by phone at months 12, 18, and 24, to see if they developed active TB. At the baseline visit QuantiFERON (QTF) testing was performed, and at month 6 a repeat QTF was performed if the initial QTF result was negative. Individuals whose QTF result was indeterminate (at either the baseline or month 6 visit) or who did not have a second QTF performed at month 6 (if negative at baseline) were excluded from the analysis. For TB index

cases for whom close contacts were excluded from this study, data from the index case were not included in the statistical analyses.

Study definitions

In PWTB , DM was defined according to baseline HbA1c, following American Diabetes Association (ADA) guidelines [11]. Patients were classified as having DM (HbA1c≥6.5%), prediabetes (PDM; HbA1c=5.7-6.4%) or normoglycemia (HbA1c<5.7%). HbA1c≥5.7% was classified as dysglycemia. For TB close contacts, DM status was obtained by self-report, or by HbA1c when available. To investigate Mtb transmission, we considered a positive result of the first (baseline) or second QTF (month 6) test an indicator of Mtb infection.

Data analysis

Categorical variables were presented as proportions and compared using a two-sided Pearson's chi-square test (with Yates correction) or Fisher's two-tailed test. Continuous variables were presented as median and interquartile range and compared using the Mann Whitney *U* (between 2 groups) or Kruskal Wallis test (between ≥2 groups). To evaluate independent associations between clinical characteristics of pulmonary TB index cases and presence of diabetes and/or prediabetes, we used unadjusted and multivariable-adjusted binomial logistic regression models. Variables were selected using the stepwise method (Wald) with backward selection criteria. We additionally assessed associations between clinical characteristics of PWTB and contacts and QuantiFERON (QTF) results (positive at baseline or QTF conversion, compared to contacts who were QTF negative at both baseline and month 6) using unadjusted

and multivariable-adjusted mixed-effects logistic regression models [12]. The "TB case" variable was included as the random effect term to address clustering of TB cases with more than one contact. Parameters with p-values ≤0.2 in univariate analyses were included in multivariable models. For the analysis of clinical characteristics of PWTB and contact QTF result, we also used bootstrapping to estimate a bias-corrected coefficient, addressing potential bias due to small sample size [13]. Over 1000 bootstrap iterations, we sampled with replacement from the data and estimated coefficients within the bootstrap sample (the unit of resampling was "the contacts from the same TB case". The distribution of those coefficient estimates over the 1000 bootstrap iterations were used to estimate the mean and 95% confidence intervals of the bias-corrected coefficient estimates. P-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS 24.0 (IBM statistics), Graphpad Prism 6.0 (GraphPad Software, San Diego, CA) and R 3.1.0 (R Foundation, Austria).

RESULTS

Characteristics of study participants

RePORT-Brazil enrolled 1,038 patients with culture-positive pulmonary TB during the study period, of whom 592 had close contacts who enrolled in the study. Of the 1,038, 643 (62%) had dysglycemia at baseline (**Figure 1**). Additional information is provided in Supplementary **Table 1**. Among all dysglycemic PWTB, 61.1% had PDM (n=393, 37.9% of all PWTB) and 38.9% had DM (n=250, 24.1% of all PWTB). Details are in **Supplementary Table 2 and Supplementary Table 3**. Among PWTB, 446 (43%) did not have a close contact enrolled into our study. Of the 592 PWTB who reported contacts, an average of 3 contacts per PWTB were enrolled. PWTB who had

contacts were stratified according to glycemic status at the time of diagnosis: TB-dysglycemia (n=381, 64.4%) and TB-normoglycemia (n=211, 35.6%) (**Figure 1**).

There were 609 contacts of 211 normoglycemic PWTB and 1186 close contacts of 381 dysglycemic PWTB. There were 47 contacts with indeterminate QTF results either at baseline or at the month-6 visit, who were excluded. There were an additional 175 contacts considered lost to follow up because they missed the second QTF test; they were also excluded. The sample size with which all further analyses were performed was 1573 close TB contacts: 537 close contacts of 198 normoglycemic PWTB and 1036 contacts of 294 dysglycemic PWTB (DM=153 and PDM=141) (**Figure 1**).

Characteristics of TB close contacts

TB close contacts were next grouped according to the glycemic status of their TB index case. Contacts of normoglycemic PWTB more frequently had DM (p=0.011) and reported illicit drug use than contacts of PWTB with diabetes or prediabetes (**Figure 2A**). Other detailed comparisons among the subgroups of TB close contacts are shown in **Supplementary Table 3**. The Sankey diagram shown in **Figure 2B** describes the QTF results, the number of TB close contacts with QTF conversion from negative to positive and active TB incidence. Close contacts of normoglycemic PWTB more frequently exhibited a positive QTF at the baseline visit than contacts from PWDM or PDM (**Figure 2C**). The different groups of TB close contacts could be distinguished by frequency of QTF conversion (**Figure 2D**). The highest TB incidence values were

found in QTF positive individuals who were close contacts of TB index cases with PDM or normoglycemia (0.44 and 0.38 persons-years, respectively).

The final set of analyses stratified TB close contacts into three groups according to the final QTF test result: (i) those who tested positive at the baseline visit (QTF-positive, n=658), (ii) those who tested negative at both baseline and month 6 visit (QTF-negative, n=809) and (iii) those who tested negative at the baseline visit and positive at the month-6 visit (QTF-conversion, n=106). Comparisons of characteristics of these study subgroups of TB contacts are described in **Supplementary Table 4**. The frequency of smokers was significantly higher in positive QTF group (29.5%) vs. negative QTF (22.9) (p=0.001). Individuals with QTF-conversion were more frequently contacts of PWTB with DM, whereas those with a negative QTF more commonly were contacts of prediabetic PWTB (**Figure 3A**). QTF-positive participants were generally contacts of normoglycemic PWTB (**Figure 3A**). Additional analyses revealed that HIV-infection was more frequently detected in TB index cases who had QTF-negative contacts (p<0.001; **Figure 3B**). Of note, TB index cases who had AFB positive sputum smears and exhibited cavitary lung lesions were more likely to have contacts who were QTF-positive or converted the QTF result at month 6 visit (p<0.001; **Figure 3B**). Moreover, QTF-positive contacts were on average older than those who were QTF-negative and those who experienced QTF conversion (p<0.001; **Figure 3C**). The subgroup of TB contacts with QTF-conversion more frequently reported smoking. No participant from this latter group had DM.

A multivariable mixed-effects logistic regression with a random effect per "TB case" tested associations between characteristics of PWTB, or of TB contacts and positivity of the QTF test at baseline or conversion of the QTF in TB contacts. The results demonstrated that PDM (adjusted

odds ratio [aOR]:1.54, 95%CI:1.25-1.65, p=0.002), passive smoking (aOR:1.44, 95%CI:1.25-1.82, p=0.003), AFB smear positive (aOR:1.54, 95%CI:1.19-1.99, p=0.001) and cavitary lung lesions (aOR:1.68, 95%CI:1.32-2.13, p<0.001) and age (aOR:1.01, 95%CI:1.01-1.03, p<0.001) were important characteristics of PWTB associated with positive QTF in contacts, independent of other confounding factors (**Figure 3D**, left panel). Interestingly, this model also revealed characteristics of TB index cases which were independently related with QTF-conversion in contacts, such as DM (aOR:1.21, CI:1.01-1.98, p=0.046), persistent cough (aOR:1.67, 95%CI:1.00-2.45, p=0.0049) AFB positive (aOR:1.99, 95%CI:1.17-3.40, p=0.012) and cavitary lung lesions (aOR:1.94, 95%CI:1.23-3.05, p<0.001) (**Figure 3D**, right panel). When evaluating the same model using 1000 bootstrap iterations, the association between DM and QTF-conversion was slightly increased, yet similar to the original model, indicating relatively low bias due to small sample size (OR=1.77, 95%CI:1.05-2.98; p=0.031) **(Figure 4).**

DISCUSSION

Identifying whether DM affects Mtb transmission is important to guide TB control strategies. Previous studies have found that dysglycemia in TB contacts can make them more susceptible to infection [4, 14-16] but to date it had not been investigated whether TB-DM increases the risk of contacts acquiring Mtb infection. In the current study, 62% of PWTB presented with dysglycemia (PDM or DM), and 37.9% had DM. This prevalence is higher than recently reported in Ethiopia[17], Peru[18] and India [19], as well as in a previous study of our group, from a smaller subpopulation from Northeastern Brazil [20], In the previous study, we observed a 63.1% prevalence of dysglycemia, which is comparable to the present study, but the DM

prevalence was lower (25%). This difference could be explained by the heterogeneity of the population in the country. The current cohort is larger and includes individuals from different regions of the country (five sites of RePORT Brazil, located in three states), while the previous cohort included individuals from just one state. That said, the cohort in the present study is more representative of Brazilian PWTB [21]. In spite of the different frequency of PWDM, the present work had findings consistent with the previous one, such as higher BMI and higher prevalence of cough and weight loss in patients with dysglycemia, particularly in PWDM [20].

TB-DM patients exhibited similar characteristics to those in a large cohort of 709,000 Brazilians with TB from 2007 to 2014: mostly men, mean age >40 years, self-reported black or *pardo,* and low frequency of HIV-infection [22]. [23],

TB-DM patients more frequently reported smoking and alcohol consumption, which are shared risk factors for both diseases [3, 24, 25]. This corroborates the relationship described in populations from Peru, Mexico and South Africa [6, 18]. where PWTB with DM and PDM were older and had an increased BMI compared to normoglycemic PWTB.

There were 1573 contacts followed up in this study. Only 1% (n=16) of the close contacts had a confirmed diagnosis of TB at the baseline visit, while 42% (n=658) were diagnosed with LTBI. The findings are comparable with what has been reported in low to middle-income countries, including Brazil, where the prevalence of active TB in contacts was 1.4%, while the prevalence of LTBI was 51.5% [26].

Only 81 (5%) of TB contacts were diagnosed with DM. This prevalence is 12 times lower than that reported in household TB contacts from India [27], but could be an underestimate, since

HbA1c was not routinely measured in all contacts and many DM diagnoses were self-reported. In our study, these individuals were primarily contacts of normoglycemic PWTB.

Among those who had a negative QTF at baseline, 106 (6.7%) converted to positive QTF at the 6-month visit. An Ethiopian study [28] using QTF-TB Gold to follow TB household contacts for one year demonstrated that nearly half of negative QTF individuals at the first visit became positive after 12 months and for this reason the authors suggested that repeated screening of QTF negative contacts may be needed for early diagnosis of LTBI. Since the second QTF in our study was carried out once, at six months after baseline, this may explain the lower conversion rate.

Regarding factors that could potentially increase Mtb transmission, TB-DM index cases had a significantly higher frequency of positive AFB sputum smears, consistent with previous publications [3, 29]. However, there was no significant difference in presence of cavities between the DM, PDM and normoglycemic TB index cases subgroups. Although this was not expected based on the prior literature, it has been described before in a Brazilian retrospective cohort study [8]. Similarly, persistent cough was unexpectedly more common in the normoglycemic PWTB group. A possible explanation for both findings could be an earlier diagnosis of TB in Brazilian PWDM, self-reported response, other conditions that can stimulate or inhibit cough (use of medications, smoking or neuroperipheral lesions among others) may be related to this result. In fact, most patients were newly diagnosed (156 [62.4%]) and were not taking anti-DM drugs. Brazil has a decentralized public health care system and PWDM, who are already in the system and followed by family medicine teams, may have easier access to healthcare to evaluate symptoms. Furthermore, TB-DM patients had significantly more

symptoms such as weight loss and fatigue, which is associated with earlier healthcare-seeking behavior and diagnosis of TB [20].

When assessing PWTB-related factors associated with baseline positive QTF in contacts, DM was not found to be a significant factor, whereas normal HbA1c, positive AFB and presence of cavities on X-ray were associated with a significantly increased risk of LTBI. While these findings have clinical importance, a positive QTF at baseline may not be the most accurate measure for the purpose of this study, as the positivity can be related to a previous exposure. In this scenario, QTF conversion within six months of follow up may be a better measure of recent exposure and infection. After adjusting for confounders, the following index case-related factors significantly increased the risk of QTF conversion: DM, persistent cough, AFB positive and presence of cavitary lung lesions. Contacts with a TB-DM index case were 1.21 times more likely to be infected with Mtb, compared to contacts of a normoglycemic TB index case. These findings confirm our hypothesis that TB-DM increased Mtb transmission and corroborates previous studies that reported persistent cough, AFB positive and presence of cavitation on chest X-ray increase Mtb transmission risk [2, 30]. The differing results regarding TB index case diabetes and pre-diabetes, and baseline QTF and QTF conversion, require further evaluation in additional cohorts.

After adjusting for confounders, the only individual characteristics of TB contacts significantly associated with an increased risk of QTF conversion was increased age. Other factors previously found to increase the risk of acquiring TB (DM, HIV, smoking and alcohol use) were not confirmed in this study [31].

The present study had some limitations. Dysglycemia was investigated by means of HbA1c levels; we did not perform fasting glucose levels or oral glucose tolerance tests. Although glycated hemoglobin levels have been reliably used to estimate dysglycemia in several studies, it is possible that the final numbers of DM and PDM would have differed if additional laboratory assessments had been used. In this prospective cohort, additional measurements of HbA1c were not performed at other study timepoints. Thus, it was not possible to investigate whether transient vs. persistent dysglycemia over the course of antituberculosis treatment had differential impact on Mtb transmission to close contacts. The TB close contacts were not systematically screened for DM using HbA1c in all study sites, and DM was recorded based only on self-report. The use of anti-DM drugs was not uniformly recorded, and it is possible that patients with dysglycemia receiving medication to lower the glucose levels may have exhibited a differential impact on Mtb transmission. Finally, we did not have data on whether the pulmonary lesions in the TB index case were upper vs. lower lobe; this information could help determine why TB index cases with DM were less likely to have cavitary disease.

The present study adds important knowledge to the field by demonstrating that dysglycemic PWTB were at higher risk of transmitting Mtb to close contacts in a well-characterized, large, multicenter cohort in Brazil. In addition, the follow up of contacts of PWTB with the highest probability of transmitting Mtb can optimize strategies focused on controlling the disease [32]. Actions focused on disease control among contacts [33, 34] is one of the main pillars for reducing TB incidence.

NOTES

Potential conflicts of interest: All No reported conflicts of interest.

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Figures Legends

Figure 1. Study flow chart. The main objective of the study was to compare incident TB infection among contacts from pulmonary TB patients with or without dysglycemia. Data were obtained from 1038 individuals diagnosed with culture-confirmed pulmonary tuberculosis (TB) enrolled into the RePORT Brazil study protocol. Of those, 592 (57%) had close contacts (average of 3 contacts per TB index case) who enrolled and were included in the analyses. During the clinical and laboratory evaluation (HbA1c levels) of the TB index cases, 141 had prediabetes (PDM), 153 had type-2 diabetes (DM) and 211 were normoglycemic. In 609 contacts of 198 TB-normoglycemic and 1186 contacts of 294 TB-dysglycemic was performed the first QTF. The close contacts enrolled of each TB index case, were evaluated, and screening for *M. tuberculosis* infection was performed with clinical and radiographic examination as well as with QuantiFERON (QTF) testing. Those who had negative QTF result at baseline underwent repeat QTF testing at 6 months, to assess for QTF conversion. For the present study, individuals whose QTF result was indeterminate (first or second QTF) or those who did not have a second QTF test performed at month 6 of follow up were excluded from the analysis. Ind: Indeterminate.

Figure 2. Characteristics of contacts of patients with active TB stratified by glycemic status. (A) Characteristics of the close contacts of pulmonary TB patients stratified according to the presence of diabetes or prediabetes were compared with those from patients with normoglycemia using the Fisher's exact test (additional comparisons are displayed in **Supplementary Table 3**). **(B)** Sankey diagram shows number of close contacts of pulmonary TB patients stratified based on QuantiFERON (QTF) result. Number of individuals who developed

incident TB during the follow up is also highlighted (blue type font) in each indicated subgroup. **(C)** Frequency of TB contacts who tested positive in the first QTF result (prevalent latent TB infection), stratified based on the glycemic status of the TB index case. **(D)** Frequency of TB contacts who were QTF negative in the first examination and tested positive in the second evaluation (QTF conversion, incident TB infection), stratified based on the glycemic status of the PWTB. In **(C)** and **(D)**, data were compared using the Fisher's exact test. In the figures 2A, 2C and 2D p-values were adjusted for clustering by index case.

Figure 3. Factors associated with tuberculosis infection in contacts of pulmonary tuberculosis patients with diabetes and prediabetes (A) Characteristics of the close contacts of pulmonary TB patients stratified according to the QuantiFERON (QTF) test result were compared using the Fisher's exact test (additional comparisons are displayed in S3 Table). **(B)** Frequency of indicated characteristics of the pulmonary TB index cases stratified based on the QTF results of the contacts was compared using the Pearson's chi-square test. **(C)** *Left panel*: Scatter plot shows distribution of age (median and interquartile range) among the subgroups of contacts of PWTB based on the QTF result. Data were compared using the Kruskal-Wallis test with Dunn's multiple comparisons ad hoc test. The difference in median age values between the groups of positive QTF and of QTF conversion was statistically significant. *Right panel*: Frequency of close TB contacts with the indicated characteristics was compared between the subgroups based on the QTF result was compared using the Pearson's chi-square test (nd: not detected). **(D)** A multivariable mixed-effects logistic regression with a random effect per "TB case" (to decrease the possible selection bias, because only one "TB case" can have more than one contact and these contacts with different QTF results) was used to test association between indicated

characteristics of pulmonary TB index patients or of the TB close contacts and positivity of the baseline QTF test or conversion of the QTF result in TB contacts. Variables included in the adjusted model exhibited univariate p-values≤0.2 (See **Supplementary Table 4** for details). In the figures 3A, 3B and 3C p-values were adjusted for clustering by index case.

AFB: acid-fast bacilli. NA: Not applicable

Definition of passive smoking: Living with someone who smokes.

Definition of persistent cough: Patients who reported cough at the initial evaluation (month 0) and also at the month 2 visit.

Figure 4. Factors associated with QTF conversion in contacts of pulmonary tuberculosis patients

A multivariable mixed-effects logistic regression with a random effect per "TB case". Estimates are bias-corrected based on 1000 bootstrap iterations to account for the small sample size. Estimates (in terms of odds ratios) reflect associations between indicated characteristics of pulmonary TB index patients or of the TB close contacts and conversion of the QTF result (incident TB infection) in TB contacts. Variables included in the adjusted model exhibited univariate p-values ≤0.2 (See **Supplementary Table 4** for details). AFB: acid-fast bacilli.

Definition of persistent cough: Patients who reported cough in the initial evaluation interview (month 0) and also in the month 2 visit.

Figure_1

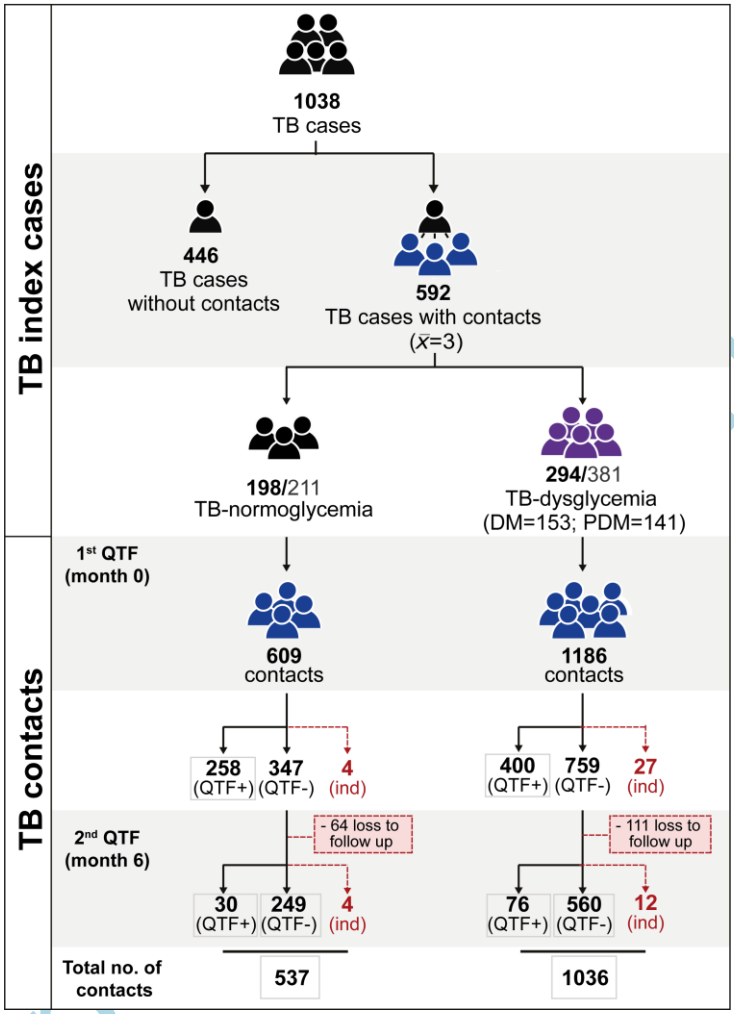

Figure_2

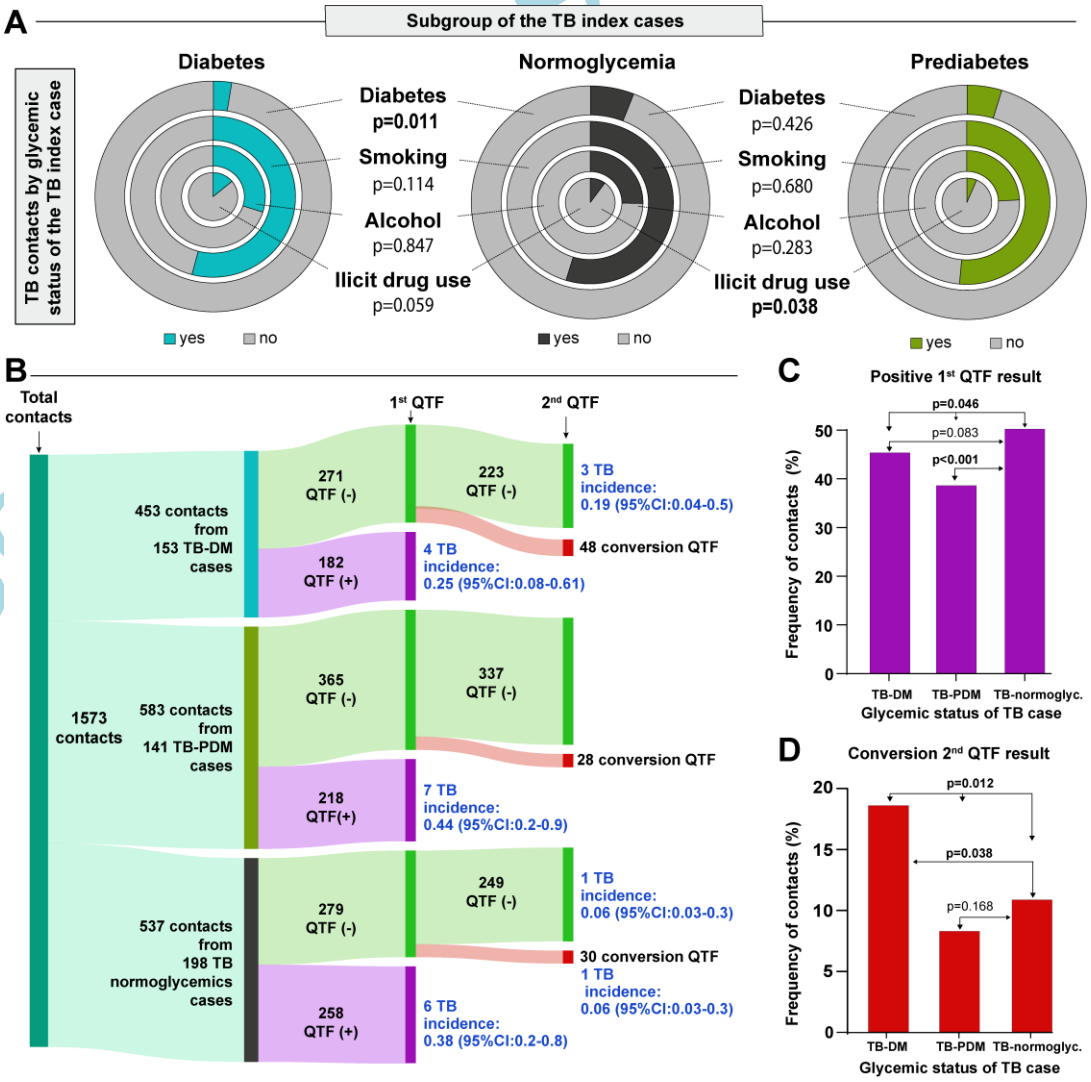

Figure_3

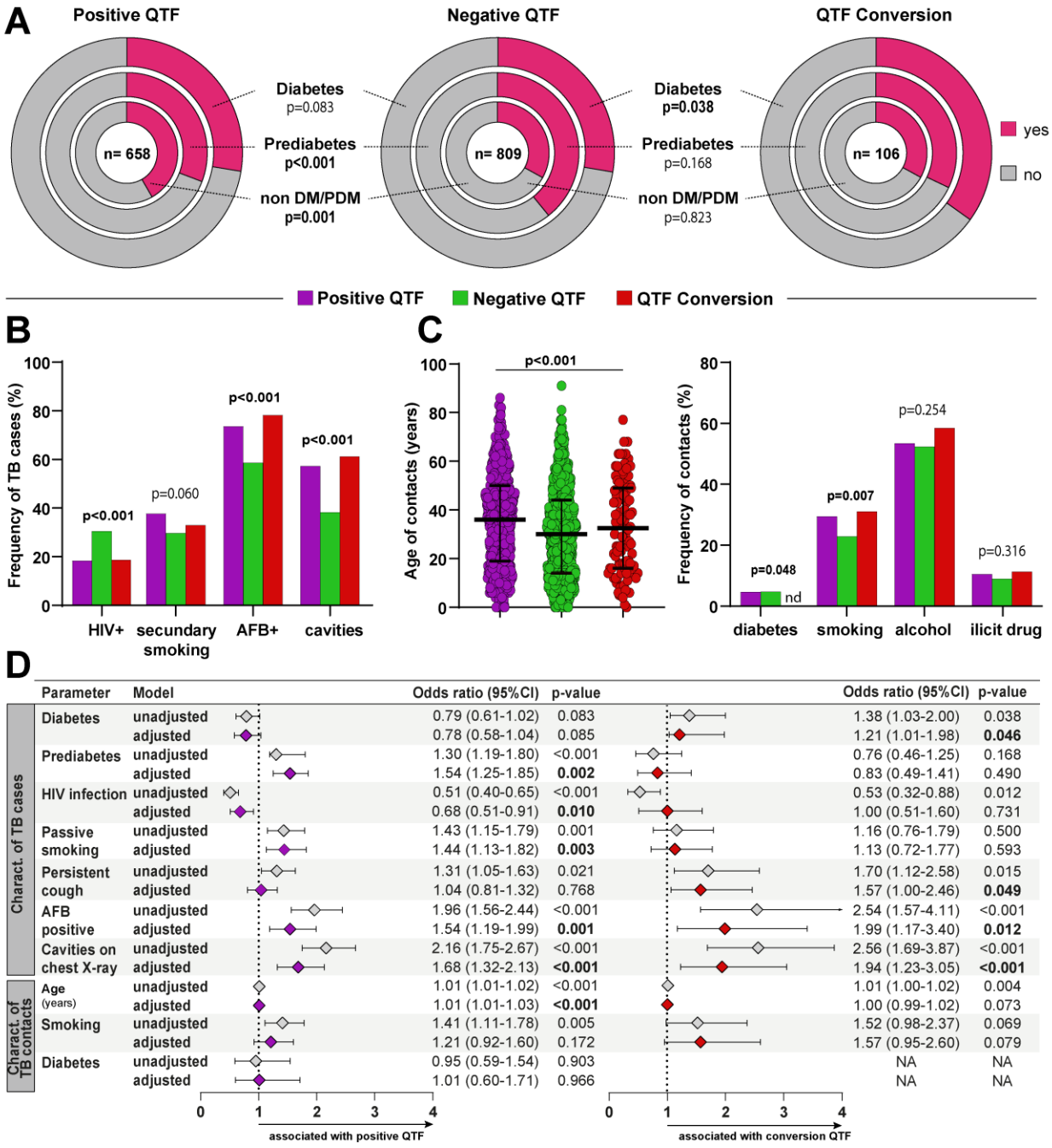

Figure_4