Glycemic Control and the Risk of Tuberculosis: A Population-based Cohort Study

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Abstract

**Background:** Although diabetes, low body mass index (BMI) and high blood lipid are established risk factors for active tuberculosis, the joint effect of diabetes, BMI and blood lipid is unclear.

**Methods:** We conducted a population-based census in eastern China including 40,311 individuals. We investigated risk factors for incident tuberculosis by excluding tuberculosis at baseline and linking all participants to the Infectious Disease Reporting Management System and Tuberculosis Management Information System of Nanjing City. Follow-up for incident tuberculosis occurred ten years. We matched participants using unique health identity card numbers, name, age, birthdate, and address. We constructed Cox Proportional hazard models adjusting for age, sex, smoking, alcohol use.

**Results:** After ten years follow-up, 143 individuals progressed to tuberculosis. In participants with BMI>24 kg/m², diagnosed diabetics with fasting blood-glucose (FBG)≥7.0mmol/L showed nearly three-fold increased risk of active TB (HR=3.78, 95%CI: 1.32-10.79, *P*=0.007), and FBG ≥7.0mmol/L was associated with more than three-fold higher risk of active TB (HR=3.16, 95%CI:1.37-7.28, *P*=0.007). Among high blood lipid levels, undiagnosed diabetics was related to increase the high risk of TB (HR=3.04, 95%CI: 1.03-8.95, *P*=0.044) and FBG ≥7.0mmol/L increased nearly two-fold higher risk of TB (HR=2.66, 95%CI: 1.13-6.30, *P*=0.026). In the linear dose-response analysis, the hazard of TB increased with FBG (with a 1-unit (1-mmol/L) increase in FBG, the hazard of TB increased by 15% (95% CI, 3%–29%).

**Discussion:** In this large population-based cohort study in a medium tuberculosis burden region, we found that diabetes increases the hazard of tuberculosis disease and diabetics with poor glycemic control aggravated this relationship especially in individuals with high level of blood lipid.

Introduction

Nutritional status has long been thought to be a major determinant of active tuberculosis (TB). Diabetes mellitus (DM) is a well-known risk factor for TB [1, 2]. High body mass index (BMI) is a major determinant of DM, however, high BMI is a protective factor for TB[3, 4]. It followed that high BMI should have increased the risk of TB, but this is inconsistent with available epidemiological data. In addition, BMI is positively correlated with cholesterol and cholesterol increases the risk of active TB [5, 6]. This inverse association between BMI and TB showed a “paradox” with regard to DM.

Two recently published retrospective cohort studies conducted in Taiwan, China, showed that overweight individuals with DM had similar risk of TB as normal-weight healthy people without DM. The increased risk of DM to TB may be offset by the protective effect of obesity[7]. A recent cohort study including 63,257 participants (the Singapore Chinese Health Study) identified that DM and lower BMI levels were independent risk factors for active TB, and individuals with low BMI diabetes had an 8.3 times higher risk of developing TB than obese people without DM[8]. It's common in Western populations that obesity is a major determinant of DM, however, a significant proportion of DM cases globally especially in Asians may not due to increase BMI, and were not overweight[7]. Furthermore, DM is often related to severe dyslipidemia as a result of high dietary fat intake and deregulated hepatic lipid metabolism [9]. DM-associated high insulin levels stimulate de novo lipogenesis in hepatocytes while cannot suppress lipolysis in insulin-resistant adipocytes of DM patients [10]. A cohort of 63,257 Chinese from the Singapore Chinese Health Study demonstrated dietary intake of cholesterol increased
the risk of TB [6]. The complex relationship between BMI and DM in Asian populations has increased the complexity of the interaction between BMI, DM and TB. It is still unclear that whether there is a joint effect of DM and BMI in regard to active TB, modulating TB risk independently or jointly.

To evaluate the association between BMI, blood lipid level, DM and active TB, we conducted a population-based cohort study in eastern China.

Method

Study design and participants

Between January 1, 2011 and 30 April, 2020, we conducted a population-based cohort study in eastern China. First, we conducted a baseline survey in seven districts in Nanjing city of Jiangsu Province from January 1, 2011 and January 1, 2012. We used cluster random sampling to conduct household surveys and enroll participants ≥ 18 years old and permanent residents. For eligible participants, we used structured sociodemographic and clinical questionnaires in-person interview collecting information such as age, sex, BMI (calculated as the formula: Weight/Height²), smoking status, alcohol use and history of diabetes. We then completed blood glucose, total cholesterol and triglyceride screening. Permanent residency was defined as continuous habitation in local district for at least six months. We excluded active TB at baseline or pregnancy. BMI was categorized as underweight (< 18.5), normal weight (≥ 18.5 to 24.0), overweight (≥ 24.0 to 28.0) and obese (≥ 28.0) [11][11].

Ascertainment of Diabetes and High blood lipid.

We defined diabetes and high blood lipid according to guidelines by the World Health Organization and a recent China diabetes prevalence survey [12–14]. Self-reported clinical diagnosis, medical records and a fasting blood glucose (FBG) test were used to diagnose the diabetes. During the first baseline visit, we collected venous blood. After an overnight fast of over 10 hours, participants were given the fasting test between 6:00 and 8:00 am. Greater than or equal to 7.0 mmol/L of the fasting blood glucose test was defined as diabetes [12].

We divided diabetic patients into four groups: (i) nondiabetics; (ii) diagnosed diabetics with FBG < 7.0 mmol/L; (iii) undiagnosed diabetics; (iii) and diagnosed diabetics with FBG ≥ 7.0 based on the recommendation of the American Diabetes Association [15]. Diagnosed diabetics with FBG < 7.0 mmol/L was defined as participants self-reporting or through medical records for a clinical diagnosis or confirmation of diabetes with this < 7 mmol/L, which was same diagnosed diabetics with FBG ≥ 7.0 mmol/L except for this fasting blood glucose. These diabetics were thought to have poor control of blood sugar; undiagnosed diabetics was defined as participants had a positive fasting plasma glucose test result without evidence of a prior diabetes. High blood lipid level was defined as participants with serum total cholesterol > 5.72 mmol/L or serum triglyceride > 1.70 mmol/L.

Measurement of active tuberculosis

TB is a reportable disease in China and, due to this, all cases were confirmed by Infectious Disease Reporting Management System and Tuberculosis Management Information System of Nanjing city. We linked two datasets: (a) a dataset with study participant information and (b) records of all tuberculosis patients notified to the Infectious Disease Reporting Management System and Tuberculosis Management Information System of Jiangsu province from January 1 2011 to 30 April 2020. We used several variables available including first and
last name, identity card number, date of birth, age, sex, and address. In both datasets to link participants from our cohort and patients in TB patients’ database.

| **Statistical analysis** |
|--------------------------|

We used standard 2 × 2 contingency tables and interquartile ranges (IQRs) to summarize categorical and continuous variables. Pearson χ² and Fisher exact tests were used to compare the frequency of categorical variables as appropriate. Cochran-Armitage test were used to positive or increasing linear trends.

Kaplan-Meier curves was used to compare the time to incident TB among the different DM groups. We used a binary, univariable Cox proportional-hazards analysis to evaluate the risk of active TB. We included all measured characteristics within this univariable analysis and produced hazard ratio (HR) and 95% confidence intervals (CIs). Variables demonstrating a suggestive relationship with TB (P < 0.1) in univariable analysis were included one at a time when building a multivariable model. Sex, age, and smoking, drinking and diabetes status were included in the multivariable logistic model regardless of P value. Considering relationship among the BMI, blood lipid and the diabetes, we did two subgroup analyses by both BMI (with cutoff value of 24 kg/m²) and blood lipid.

We calculated tuberculosis incidence in cases per 100,000 person-years for participants with the following test results: (1) nondiabetics, (2) diabetics, (3) diagnosed diabetics with FBG < 7.0 mmol/L, (4) undiagnosed diabetics, (5) diagnosed diabetics with FBG ≥ 7.0 mmol/L, (6) FBG < 7.0 mmol/L, and (7) FBG ≥ 7.0 mmol/L. We calculated 95% Poisson confidence intervals (CIs) around these estimates and used two-sample Poisson tests to compare tuberculosis incidence rates. Data were analyzed by using SPSS software (version 23.0, IBM Corporation, Armonk, NY).

**Results**

Demographic Characteristics.

After excluding 12 active TB at baseline, a total of 40,311 were finally included in the baseline survey (Fig. 1). At enrollment, median age was 50 years old (IQR, 37–61) and only 16.7% (N = 6,722) of participants were older than 65 years of age; About half of participants were female (54.7%; N = 22,067); 15,661 (39.0%) were overweight or obesity; About a quarter of participants reported ever smoking (21.7%, N = 8,745) or use of alcohol (N = 6,394, 15.9%); 3,382 (8.4%) were diabetes. Diabetes were more likely to have high blood glucose level (43.1% Versus.26.0%) (Table 1).
Table 1
Demographic characteristics 40311 participants, overall and by test status.

| Characteristic          | All       | Non-diabetes | Diabetes   |
|-------------------------|-----------|--------------|------------|
|                         | (N, %)    | (N, %)       | (N, %)     |
| Sex                     |           |              |            |
| Female                  | 22067(54.7)| 20258(54.9)  | 1809(53.5) |
| Male                    | 18244(45.3)| 16671(45.1)  | 1573(46.5) |
| Median Age (IQR)        |           |              |            |
|                         | 50(37–61) | 49(35–60)    | 59(50–67)  |
| BMI                     |           |              |            |
| <18.5                   | 1880(4.7) | 1738(4.7)    | 142(4.2)   |
| ≥18.5–<24               | 22566(56.3)| 20818(56.6)  | 1748(52.1) |
| ≥24–<28                 | 12449(31.0)| 11312(30.8)  | 1137(33.9) |
| ≥28                     | 3212(8.0) | 2884(7.8)    | 328(9.8)   |
| Smoking status          |           |              |            |
| Never smoked            | 31566(78.3)| 28966(78.4)  | 2600(76.9) |
| Ever smoked             | 8745(21.7)| 7963(21.6)   | 782(23.1)  |
| Alcohol drinking        |           |              |            |
| No                      | 33917(84.1)| 31092(84.2)  | 2825(83.5) |
| Yes                     | 6394(15.9)| 5837(15.8)   | 557(16.5)  |
| High blood glucose level|           |              |            |
| No                      | 22577(72.4)| 20953(74.0)  | 1624(56.9) |
| Yes                     | 8606(27.6)| 7375(26.0)   | 1231(43.1) |
| Blood lipid level (IQR) |           |              |            |
|                         | 5.1(4.6–5.6)| 5.0(4.6–5.4) | 7.2(6.1–8.5) |

BMI = Body Mass Index

†We grouped diabetic by whether the participant with diabetes. Participants who self-reporting a clinical diagnosis, through medical records and for a diagnosis of diabetes and with a positive fasting blood glucose test ≥ 7.0 mmol/L were regarded as diagnosed diabetes.

Risk of development of tuberculosis.

During ten years of follow-up with a median of 8.6 y, 143 individuals progressed to tuberculosis (incidence rate, 41.4 per 100,000 person-years, 95% CI, 35.0-48.6), among whom 19 (13.3%) were diabetes (incidence rate, 65.5 per 100,000 person-years, 95% CI, 40.6-100.4), and the 7 (4.9%) were with FBG ≥ 7 mmol/L (incidence rate, 94.7 per 100,000 person-years, 95% CI, 41.4-187.3). Diagnosed diabetics with FBG ≥ 7.0 mmol/L showed the highest incidence rate compared with nondiabetics diagnosed diabetics with FBG < 7.0 mmol/L and undiagnosed diabetics (P_trend=0.092)(Fig. 2). Among BMI > 24, the overall incidence rate of TB were 26.8 per 100,000 person-
years (95% CI: 18.3–38.0) and 93.8 per 100,000 person-years (95% CI: 41.0–185.6) in FBG < 7.0 mmol/L and FBG ≥ 7.0 mmol/L, respectively. And in individuals with high blood lipid level, the overall incidence rate of TB among FBG < 7.0 mmol/L and FBG ≥ 7.0 mmol/L were 31.8 per 100,000 person-years (95% CI: 20.2–47.7) and 94.7 per 100,000 person-years (95% CI: 41.4–187.3) (Table 2).
## Table 2
Tuberculosis incidence among participants according to baseline diabetic, BMI and blood lipid status.

|                          | Events (n) | Observation Time (Person-Years) | Rate per 100 Thousand Person-years | 95% Confidence Interval |
|--------------------------|------------|---------------------------------|-----------------------------------|-------------------------|
| **All Participants**     | 143        | 345,793                         | 41.4                              | 35.0-48.6               |
| **Diabetic status**      |            |                                 |                                   |                         |
| Nondiabetics             | 124        | 316,802                         | 39.1                              | 32.7-46.5               |
| Diabetics                | 19         | 28,991                          | 65.5                              | 40.6-100.4              |
| **Diabetic status**      |            |                                 |                                   |                         |
| Nondiabetics             | 124        | 316,802                         | 39.1                              | 32.7-46.5               |
| Diagnosed diabetics with FBG < 7.0 | 6    | 12,338                          | 48.6                              | 19.7-101.1              |
| Undiagnosed diabetics   | 6          | 8,919                           | 67.3                              | 27.3-139.9              |
| Diagnosed diabetics with FBG ≥ 7.0 | 7    | 7,734                           | 90.5                              | 40.0-179.0              |
| **BMI ≤ 24**             |            |                                 |                                   |                         |
| FBG < 7.0                | 76         | 160,442                         | 47.4                              | 37.6-59.0               |
| FBG ≥ 7.0                | 6          | 9,062                           | 66.2                              | 48.4-182.3              |
| **BMI > 24**             |            |                                 |                                   |                         |
| FBG < 7.0                | 29         | 108,272                         | 26.8                              | 18.3-38.0               |
| FBG ≥ 7.0                | 7          | 7,462                           | 93.8                              | 41.0-185.6              |
| **Normal blood lipid level** |         |                                 |                                   |                         |
| FBG < 7.0                | 77         | 186,562                         | 41.3                              | 32.8-51.3               |
| FBG ≥ 7.0                | 3          | 7,732                           | 38.8                              | 9.9-105.6               |
| **High blood lipid level** |         |                                 |                                   |                         |
| FBG < 7.0                | 21         | 66,059                          | 31.8                              | 20.2-47.7               |
| FBG ≥ 7.0                | 7          | 7,394                           | 94.7                              | 41.4-187.3              |

BMI = Body Mass Index, kg/m², FBG = fasting blood-glucose, mmol/L

& Diagnosed diabetics with FBG < 7.0 mmol/L was defined as participants self-reporting or through medical records for a clinical diagnosis or confirmation of diabetes with this < 7 mmol/L, which was same diagnosed diabetics with FBG ≥ 7.0 mmol/L except for this fasting blood glucose. These diabetics were thought to have poor control of blood sugar; undiagnosed diabetics was defined as participants had a positive fasting plasma glucose test result without evidence of a prior diabetes. High blood lipid level was defined as participants with serum total cholesterol > 5.72 mmol/L or serum triglyceride > 1.70 mmol/L.
Factors contributing to the risk of tuberculosis.

In univariate analysis (Table 3), we found that factors associated with the progression to TB were male (HR = 2.12, 95%CI: 1.51–2.98, \(P<0.0001\)), increasing age (HR = 1.01, 95%CI = 1.00–1.02, \(P=0.019\)), smoking (HR = 1.50, 95%CI = 1.05–2.16, \(P=0.026\)), diabetics (HR = 1.67, 95%CI = 1.03–2.71, \(P=0.037\)).
Table 3
Univariable Cox Proportional hazard model analysis of the risk of active tuberculosis.

| Characteristic          | Active tuberculosis | Hazard Ratio (95% CI), P-value |
|-------------------------|---------------------|-------------------------------|
|                         | N incident/N total  | (%) in subcategory             |
|                         |                     |                               |
| Sex                     |                     |                               |
| Female                  | 52/22067 (0.2%)     | Reference                      |
| Male                    | 91/18244 (0.5%)     | 2.12 (1.51–2.98), P < 0.0001  |
| Age (Continuous)        |                     | 1.01 (1.00–1.02), P = 0.019    |
| BMI                     |                     |                               |
| <18.5                   | 5/1880 (0.3%)       | Reference                      |
| ≥18.5–<24               | 95/22566 (0.4%)     | 1.58 (0.64–3.89), P = 0.317   |
| ≥24–<28                 | 35/12449 (0.3%)     | 1.06 (0.41–2.70), P = 0.910   |
| ≥28                     | 8/3212 (0.2%)       | 0.94 (0.31–2.86), P = 0.908   |
| Smoking status          |                     |                               |
| Never smoked            | 101/31566 (0.3%)    | Reference                      |
| Ever smoked             | 42/8745 (0.5%)      | 1.50 (1.05–2.16), P = 0.026   |
| Alcohol drinking        |                     |                               |
| No                      | 119/33917 (0.4%)    | Reference                      |
| Yes                     | 24/6394 (0.4%)      | 1.08 (0.70–1.67), P = 0.736   |
| Diabetic status         |                     |                               |
| Nondiabetics            | 124/36929 (0.3%)    | Reference                      |

BMI = Body Mass Index, kg/m², FBG = fasting blood-glucose, mmol/L
| Characteristic                                           | Active tuberculosis |
|---------------------------------------------------------|---------------------|
|                                                         | N incident/N total  |
|                                                         | (% in subcategory)  |
|                                                         | Hazard Ratio (95% CI), P-value |
| Diabetics                                               | 19/3382 (0.6%)     | 1.67 (1.03–2.71), P = 0.037 |
|                                                                                                       |
| Diabetic status                                         |                     |                               |
| Nondiabetics                                            | 124/36929 (0.3%)   | Reference                      |
|                                                                                                       |
| Diagnosed diabetics with FBG < 7.0                      | 6/1434 (0.4%)      | 1.24 (0.55–2.81), P = 0.607 |
|                                                                                                       |
| Undiagnosed diabetics                                   | 6/1045 (0.6%)      | 1.71 (0.76–3.89), P = 0.198 |
|                                                                                                       |
| Diagnosed diabetics with FBG ≥ 7.0                      | 7/903 (0.8%)       | 2.31 (1.08–4.94), P = 0.032 |
|                                                                                                       |
| Blood glucose level                                     |                     |                               |
| FBG < 7.0                                               | 105/31436 (0.3%)   | Reference                      |
|                                                                                                       |
| FBG ≥ 7.0                                               | 13/1948 (0.7%)     | 2.00 (1.12–3.56), P = 0.018 |
|                                                                                                       |
| High blood lipid level                                  |                     |                               |
| No                                                      | 80/22577 (0.4%)    | Reference                      |
|                                                                                                       |
| Yes                                                     | 28/8606 (0.3%)     | 0.92 (0.60–1.42), P = 0.709  |

Table 4. Multivariable Cox Proportional hazard model analysis of risk of active tuberculosis.

BMI = Body Mass Index, kg/m², FBG = fasting blood-glucose, mmol/L
| Characteristic          | Active tuberculosis |                      |                      |                      |
|------------------------|---------------------|----------------------|----------------------|----------------------|
|                        | N incident/N total  | Hazard Ratio (95% CI), | P-value              |                      |
|                        | (% in subcategory)  | P-value              |                      |                      |
|                        |                     |                      |                      |                      |
|                        |                     | Hazard Ratio (95% CI), |                      |                      |
|                        |                     | P-value              |                      |                      |
|                        |                     |                      |                      |                      |
| Sex                    |                     |                      |                      |                      |
| Female                 | Reference           | Reference            | Reference            | Reference            |
| Male                   | 2.26(1.53–3.33),    | 2.27(1.54–3.35),     | 2.00(1.30–3.09),     | 2.00(1.30–3.09),     |
|                        | P<0.0001            | P<0.0001             | P=0.002              | P=0.002              |
| Age (Continuous)       | 1.01(1.00-1.02),    | 1.01(1.00-1.02),     | 1.01(1.00-1.02),     | 1.01(1.00-1.02),     |
|                        | P=0.034             | P=0.033              | P=0.110              | P=0.095              |
| BMI                    |                     |                      |                      |                      |
| <18.5                  | Reference           | Reference            | Reference            | Reference            |
| ≥18.5–<24              | 1.45(0.59–3.56),    | 1.44(0.59–3.55),     | 2.95(0.72–12.00),    | 2.99(0.73–12.17),    |
|                        | P=0.423             | P=0.425              | P=0.131              | P=0.126              |
| ≥24–<28                | 0.89(0.35–2.27),    | 0.89(0.35–2.26),     | 1.73(0.41–7.26),     | 1.75(0.42–7.34),     |
|                        | P=0.802             | P=0.799              | P=0.454              | P=0.445              |
| ≥28                    | 0.82(0.27–2.50),    | 0.82(0.27–2.49),     | 1.64(0.34–7.91),     | 1.66(0.34–7.98),     |
|                        | P=0.724             | P=0.720              | P=0.536              | P=0.528              |
| Smoking status         |                     |                      |                      |                      |
| Never smoked           | Reference           | Reference            | Reference            | Reference            |
| Ever smoked            | 1.03(0.68–1.56),    | 1.03(0.68–1.56),     | 1.18(0.75–1.87),     | 1.18(0.75–1.87),     |
|                        | P=0.903             | P=0.909              | P=0.480              | P=0.479              |

BMI = Body Mass Index, kg/m², FBG = fasting blood-glucose, mmol/L
| Characteristic | Active tuberculosis |
|---------------|---------------------|
|               | N incident/N total  | Hazard Ratio (95% CI), P-value |
|               | (% in subcategory)  |                               |

**Alcohol drinking**

|   | Reference | Reference | Reference | Reference |
|---|-----------|-----------|-----------|-----------|
| No |           |           |           |           |
| Yes | 0.78(0.49–1.25), P = 0.305 | 0.78(0.48–1.24), P = 0.288 | 0.72(0.42–1.23), P = 0.228 | 0.71(0.42–1.22), P = 0.211 |

**Diabetic status**

|   | Reference |
|---|-----------|
| Nondiabetics | Reference |
| Diabetics    | 1.51(0.92–2.47), P = 0.104 |

**Diabetic status**

|   | Reference |
|---|-----------|
| Nondiabetics | Reference |
| Diagnosed diabetics with FBG < 7.0 | 1.07(0.47–2.45), P = 0.871 |
| Undiagnosed diabetics | 1.67(0.73–3.81), P = 0.222 |
| Diagnosed diabetics with FBG ≥ 7.0 | 2.04(0.94–4.40), P = 0.070 |

**Blood glucose level**

|   | Reference |
|---|-----------|
| FBG < 7.0 | Reference |
| FBG ≥ 7.0 | 1.91(1.07–3.42), P = 0.030 |
| Blood glucose level(Continuous) | 1.10(1.02–1.20), P = 0.020 |

BMI = Body Mass Index, kg/m², FBG = fasting blood-glucose, mmol/L

In multivariable analysis stratifying diabetic status as nondiabetics, diagnosed diabetics with FBG < 7.0 mmol/L, undiagnosed diabetics, and diagnosed diabetics with FBG ≥ 7.0, there was a nonsignificant trend towards a risk association with diagnosed diabetics with FBG ≥ 7.0 mmol/L but it was near the borderline (P = 0.070). When grouping blood glucose level with the cutoff of 7.0 mmol/L, compared with FBG < 7.0 mmol/L, participants with
FBG ≥ 7.0 mmol/L had 91% increase in tuberculosis hazard (HR = 1.91, 95%CI: 1.07–3.42, P = 0.030). With a 1-unit (1 mmol/L) increase in blood glucose, the hazard of tuberculosis increased by 10% (95% CI: 2–20%, P = 0.020)(Table 4).

In the stratified analysis, in participants with BMI ≤ 24 kg/m², there was no statistically significant with diabetics or blood glucose and tuberculosis (P = 0.940, 0.610, 0.690 and 0.505, respectively). In participants with BMI > 24 kg/m², diagnosed diabetics with FBG ≥ 7.0 mmol/L showed nearly three-fold increased risk of active TB (HR = 3.78, 95%CI: 1.32–10.79, P = 0.013), and FBG ≥ 7.0 mmol/L was associated with more than three-fold higher risk of active TB(HR = 3.16, 95%CI:1.37–7.28, P = 0.007)(Table 5) (Fig. 3).
Table 5
Multivariable Cox Proportional hazard model analysis of risk of active tuberculosis by MBI status

| Characteristic          | Active tuberculosis |   |   |   |
|-------------------------|---------------------|---|---|---|
|                         | BMI ≤ 24            | BMI > 24 |   |   |
|                         | Hazard Ratio (95% CI), P-value | Hazard Ratio (95% CI), P-value | Hazard Ratio (95% CI), P-value | Hazard Ratio (95% CI), P-value |
| Sex                     | Female              | Reference | Reference | Reference | Reference |
|                         | Male                | 2.04(1.29–3.21), P = 0.002 | 1.84(1.11–3.07), P = 0.019 | 3.30(1.50–7.23), P = 0.003 | 2.64(1.14–6.11), P = 0.023 |
| Age (Continuous)        | 1.01(1.00-1.02), P = 0.175 | 1.01(0.99–1.02), P = 0.370 | 1.02(1.00-1.04), P = 0.038 | 1.02(1.00-1.05), P = 0.088 |
| Smoking status          | Never smoked        | Reference | Reference | Reference | Reference |
|                         | Ever smoked         | 1.06(0.63–1.78), P = 0.836 | 1.17(0.66–2.07), P = 0.593 | 0.99(0.49–1.99), P = 0.979 | 1.25(0.57–2.73), P = 0.574 |
| Alcohol drinking        | No                  | Reference | Reference | Reference | Reference |
|                         | Yes                 | 0.57(0.30–1.08), P = 0.086 | 0.61(0.30–1.23), P = 0.167 | 1.24(0.60–2.56), P = 0.554 | 0.95(0.41–2.21), P = 0.909 |
| Diabetic status         | Nondiabetics        | Reference | Reference | Reference | Reference |
|                         | Diagnosed diabetics with FBG < 7.0 | 1.04(0.38–2.86), P = 0.940 | 1.14(0.27–4.81), P = 0.858 |
|                         | Undiagnosed diabetics | 1.35(0.43–4.29), P = 0.610 | 2.35(0.72–7.69), P = 0.157 |
|                         | Diagnosed diabetics with FBG ≥ 7.0 | 1.27(0.40–4.04), P = 0.690 | 3.78(1.32–10.79), P = 0.013 |
| Blood glucose level     | FBG < 7.0           | Reference | Reference | Reference | Reference |
|                         | FBG ≥ 7.0           | 1.33(0.57–3.09), P = 0.505 | 3.16(1.37–7.28), P = 0.007 |

BMI = Body Mass Index, kg/m², FBG = fasting blood-glucose, mmol/L

In another stratified analysis by high blood lipid level, in normal high blood lipid level, there was no statistic difference between the diabetics and TB, however, among high blood lipid levels undiagnosed diabetics was
related to increase the high risk of TB (HR = 3.04, 95% CI: 1.03–8.95, \( P = 0.044 \)) and FBG \( \geq 7.0 \text{ mmol/L} \) nearly two-fold higher risk of TB (HR = 2.66, 95% CI: 1.13–6.30, \( P = 0.026 \)) (Table 6) (Fig. 3). In the linear dose-response analysis, the hazard of TB increased with FBG (with a 1-unit (1-mmol/L) increase in FBG, the hazard of TB increased by 15% (95% CI, 3–29%) (Table 7) (Fig. 3).
Table 6
Multivariable Cox Proportional hazard model analysis of risk of active tuberculosis by blood lipid status.

| Characteristic               | Active tuberculosis | Normal high blood lipid level | Hazard Ratio (95% CI), P-value | High blood lipid level$ | Hazard Ratio (95% CI), P-value | Normal high blood lipid level | Hazard Ratio (95% CI), P-value | High blood lipid level$ | Hazard Ratio (95% CI), P-value |
|-----------------------------|---------------------|-------------------------------|--------------------------------|-------------------------|--------------------------------|-------------------------------|--------------------------------|-------------------------|--------------------------------|
| Sex                         | Male                | 1.89(1.12–3.18), P = 0.017   |                                | 1.89(1.12–3.19), P = 0.017 |                                | 2.03(0.84–4.94), P = 0.117   |                                | 2.05(0.84–4.97), P = 0.114 |                                |
| Age (Continuous)            | 1.00(0.99–1.02), P = 0.819 |                                | 1.00(0.99–1.02), P = 0.728   |                         | 1.04(1.01–1.07), P = 0.011 |                                | 1.03(1.01–1.07), P = 0.009 |                                |
| Smoking status              | Never smoked        | Reference                      | Reference                      | Reference                | Reference                      | Reference                      | Reference                      | Reference                | Reference                      |
|                             | Ever smoked         | 1.10(0.62–1.94), P = 0.743   |                                | 1.10(0.62–1.93), P = 0.748 |                                | 1.42(0.56–3.63), P = 0.459   |                                | 1.42(0.56–3.62), P = 0.464 |                                |
| Alcohol drinking            | No                  | Reference                      | Reference                      | Reference                | Reference                      | Reference                      | Reference                      | Reference                | Reference                      |
|                             | Yes                 | 1.07(0.57–1.98), P = 0.843   |                                | 1.06(0.57–1.97), P = 0.863 |                                | 0.25(0.06–1.09), P = 0.064   |                                | 0.25(0.06–1.09), P = 0.064 |                                |
| Diabetic status             | Nondiabetics        | Reference                      |                                | Reference                | Reference                      |                                |                                | Reference                | Reference                      |
|                             | Diagnosed diabetics with FBG < 7.0 | 1.43(0.52–3.96), P = 0.491   |                                | 1.47(0.34–6.41), P = 0.609 |                                |                                |                                |                        |
|                             | Undiagnosed diabetics | 0.65(0.09–4.70), P = 0.670 |                                | 3.04(1.03–8.95), P = 0.044 |                                |                                |                                |                        |
|                             | Diagnosed diabetics with FBG ≥ 7.0 | 1.30(0.32–5.36), P = 0.716 |                                | 2.46(0.72–8.40), P = 0.150 |                                |                                |                                |                        |
| Blood glucose level         | FBG < 7.0           | Reference                      |                                | Reference                | Reference                      |                                |                                | Reference                | Reference                      |
|                             | FBG ≥ 7.0           | 0.95(0.30–3.04), P = 0.934   |                                | 2.66(1.13–6.30), P = 0.026 |                                |                                |                                |                        |

BMI = Body Mass Index, kg/m$^2$; FBG = fasting blood-glucose, mmol/L; $ High blood lipid level was defined as participants with serum total cholesterol > 5.72 mmol/L or serum triglyceride > 1.70 mmol/L.
Table 7
Multivariable Cox Proportional hazard model analysis of risk of active tuberculosis by blood lipid status.

| Characteristic       | Active tuberculosis |                      |                      |
|----------------------|---------------------|----------------------|----------------------|
|                      | Normal high blood lipid level | High blood lipid level‡ |
|                      | Hazard Ratio (95% CI), $P$-value | Hazard Ratio (95% CI), $P$-value |
| Sex                  | Reference           | Reference            |
| Female               |                     |                      |
| Male                 | 1.87(1.11–3.16), $P = 0.019$ | 1.74(0.72–4.20), $P = 0.217$ |
| Age (Continuous)     | 1.00(0.99–1.02), $P = 0.532$ | 1.04(1.02–1.07), $P = 0.002$ |
| Smoking status       | Reference           | Reference            |
| Never smoked         |                     |                      |
| Ever smoked          | 1.10(0.62–1.94), $P = 0.744$ | 1.19(0.47–3.02), $P = 0.712$ |
| Alcohol drinking     | Reference           |                      |
| No                   |                     |                      |
| Yes                  | 1.09(0.59–2.04), $P = 0.781$ |                      |
| Blood glucose level (Continuous) | 0.84(0.64–1.10), $P = 0.202$ | 1.15(1.03–1.29), $P = 0.011$ |

‡High blood lipid level was defined as participants with serum total cholesterol > 5.72 mmol/L or serum triglyceride > 1.70 mmol/L.

Another factor that increased the hazard of TB were male sex and increasing age. Male sex had two to three-fold higher risk of TB and every unit increase in age was associated with 1–4% increase in TB risk.

Discussion

In this large population-based cohort study of over 40,000 participants from a medium tuberculosis burden region in Eastern China, we found that DM, especially in DMs with poor glycemic control, increased the TB disease and that disease severity was associated with increasing risk. However, the TB risk was not unified across all DM patients. In DM with BMI > 24 kg/m$^2$, compared to those without DM, the hazard of TB was higher (near 4-fold) in patients with poor glycemic control ($FBG \geq 7.0$ mmol/L) but was familiar with those with good glycemic control ($FBG < 7.0$ mmol/L) and undiagnosed diabetics. In addition, in DM with high blood lipid level, compared with nondiabetics, undiagnosed diabetics increased the hazard of developing TB disease, but was not significantly different in diagnosed DM with poor glycemic control.

The dual prevalence of DM and TB in China is alarming. The prevalence of DM in China is estimated to be 12%, with more than 100 million DM patients[16, 17]. The DM burden in China has been increasing across the past 20 years and is expected to continue to increase [16–18]. Several cohort studies had shown that patients with
DM were associated with approximately 2–3 times increased TB risk [1, 19]. China has been carrying out TB screening among DM, but has little effect. Therefore, it is particularly important to identify the high-risk population to TB in DM individuals. Better understanding correlation between BMI, blood lipid level, DM and TB will make it more effectively to identify more TB patients in DMs.

Two recently published retrospective cohort studies conducted in Taiwan, China, showed that overweight individuals with DM had similar risk of TB as normal-weight healthy people without DM. The increased risk of DM to TB may be offset by the protective effect of obesity [7]. A recent cohort study including 63,257 participants (the Singapore Chinese Health Study) identified that DM and lower BMI levels were independent risk factors for active TB, and individuals with low BMI diabetes had an 8.3 times higher risk of developing TB than obese people without DM [8]. However, in our study, although the undiagnosed diabetics and diagnosed diabetics with poor glycemic control had the highest incident rate, after adjusting covariables, the result was opposite to these studies that in BMI > 24 kg/m², diagnosed diabetics with poor glycemic control increased the hazard of developing active TB. The reason maybe that DM in our study were more likely to have high blood glucose level (43.1% Versus.26.0%). High cholesterol was the well-known risk factor increasing the hazard of TB. A cohort of 63,257 Chinese from the Singapore Chinese Health Study demonstrated dietary intake of high cholesterol increased the risk of TB, and was in accordance with strong experimental evidence [6]. Mycobacterium tuberculosis (Mtb) possessed a molecule with epitopes structurally, which was semblable to the human cholesterol specific receptor-Ck, and interactions between the receptor-Ck–like molecule of Mtb and cholesterol-rich domains of the plasma membrane create a steady junction between the plasma membrane and Mtb before the bacteria can be internalized with effect [20–22]. Moreover, cholesterol was associated with coronin, a protein that could prevent lysosomal delivery of the phagosome. Hence cholesterol-mediated sequestration of Mtb led to acoronin-coated phagosome be resistant to phagosome–lysosome fusion, helping the mycobacteria to resist host eradication [20, 21]. Furthermore, hypercholesterolemia may also imped the priming of adaptive immune responses to increase TB susceptibility [23]. A diet with rich cholesterol could also provide more energy source that can be used by Mtb, and thus ensure its survival and growth in activated macrophages [6].

The hazard leading DM to develop into TB depending varied from the levels of glycemic control. In a Taiwan study, a cohort enrolling 123,546 individuals demonstrated that DM patients with poor glycemic control had a significantly higher hazard of TB compared to nondiabetics. The hazard of TB in DM patients with good glycemic control were familiar with in nondiabetic individuals [24]. Another cohort study in Hong Kong, DM patients with FBG ≥ 7.0 mmol/L had a higher risk of developing TB than those without DM (aHR = 2.56), while the risk among individuals with FBG < 7.0 mmol/L was not elevated [25]. However, in other two studies in the UK and Denmark, the level of FBG was not related to the risk of TB [26, 27]. Of note, several factors including BMI in Denmark study were not adjusted, and high BMI was more likely to be under poor glycemic control. Thus, In the UK study, nearly two-thirds of DM patients having FBG < 7.0 mmol/L that most of them had generally good glycemic control. The reasons that poor glycemic control increased the risk of TB may be that: (i) The phagocytic function was impaired in non-insulin-dependent DM patients with FBG ≥ 7 mmol/L, and when improving the glycemic control, the phagocytic function was significantly elevated [28]. (ii) The granulocyte adherence function was lower in patients with poor glycemic control, and was recovered after 1–2 weeks of antidiabetic treatment [29]. (iii) Metformin, a main drug used to treat DM, may inhibit the intracellular growth of Mtb in human monocytic cell line and can also improve the treatment effect of TB patients [30]. (iii) Diabetic mice had lower expression of in response to Mycobacterium tuberculosis infection, and Insulin treatment could significantly
improve the synthesis of Th1-related cytokines which was impaired in diabetic mice with TB infection [31]. Poor glycemic control could also increase the hazard of TB infection [32, 33].

There are limitations to our study. First, we just collected the FBG at baseline, and it failed to reflect the long-term level of individuals’ glycemic status and may underestimate the proportion of undiagnosed DM. However, if existed, this bias would lead the association between active TB and DM toward the null. Second, we failed to evaluate the relationship between DM and TB infection for this reason we didn’t perform interferon gamma release assays and tuberculin skin tests, two most commonly used test for TB infection in our study. Another limitation of our method was that we referred only to CDC databases from Nanjing city and therefore participants that moved out of the Nanjing developing to TB would not be identified. Furthermore, we did not collect information on human immunodeficiency virus infection in our screening survey, therefore, we could not adjust this strong risk factor for TB disease. However, Nanjing was a city with low prevalence of HIV infection, we expect that it had little effect on the hazard.

In summary, in this large population-based cohort study in a medium tuberculosis burden region, we found that DM increases the hazard of TB disease and DM with poor glycemic control aggravated this relationship especially in individuals with high level of blood lipid level.

Abbreviations

TB
tuberculosis; DM:diabetes mellitus; BMI:high body mass;
FBG
fasting blood glucose; IQR:interquartile range; HR:hazard ratio;
MtbtMycobacterium tuberculosis

Declarations

Ethics approval and consent to participate

Center for Disease Control and Prevention of Nanjing City reviewed and approved this study. All eligible participants signed the written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to some of datasets derived from tuberculosis patients management information system, which is confidential in China.

Competing interests
The authors declare that they have no competing interests.

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**Authors’ contributions**

Peng Lu, Chen Li and Xin Hong designed the research, analyzed the data and drafted the manuscript; Limei Zhu, Wen Kong, Xiaoyan Ding conducted the research; Songning Ding and Hao Yu implemented the field investigation; Qiao Liu and Wei Lu participated in the study design and helped draft the manuscript. Peng Lu and Qiao Liu had primary responsibility for final content. All authors contributed to the study and have read and approved the final manuscript.

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Not applicable

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Figures

After excluding 12 active TB at baseline, a total of 40,311 were finally included in the baseline survey.
Diagnosed diabetics with FBG $\geq$ 7.0mmol/L showed the highest incidence rate compared with nondiabetics diagnosed diabetics with FBG $< 7.0$mmol/L and undiagnosed diabetics (P$_{trend}$=0.092)
In the linear dose-response analysis, the hazard of TB increased with FBG (with a 1-unit (1-mmol/L) increase in FBG, the hazard of TB increased by 15% (95% CI, 3%-29%).