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

Chen Li
Centers for Disease Control and Prevention of Nanjing
Xin Hong
Center for Disease Control and Prevention of Nanjing
Songning Ding
Centers for Disease Control and Prevention of Nanjing
Wen Kong
Jiangsu Center for Disease Control and Prevention
Xiaoyan Ding
Jiangsu Centers for Disease Control and Prevention
Limei Zhu
Jiangsu Centers for Disease Control and Prevention
Wei Lu
Jiangsu Center for Disease Control and Prevention
Qiao Liu
Jiangsu Center for Disease Control and Prevention
Peng Lu (lpjscdc@163.com)
Jiangsu Center for Disease Control and Prevention https://orcid.org/0000-0003-2703-7578

Research article

Keywords: BMI, High blood lipid level, Diabetes, Active tuberculosis, Cohort study

Posted Date: July 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-41181/v1

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/m^2, 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/Height^2), 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; (iiii) 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 χ^2 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/m^2) 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	Observation Time	Rate per 100 Thousand	95% Confidence Interval
	(n)	(Person-Years)	Person-years	
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
Undiagonsed 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/m^2, 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	
	N incident/N total (% in subcategory)	Hazard Ratio (95% CI), *P*-value
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/m^2, 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.

Characteristic	Active tuberculosis

BMI = Body Mass Index, kg/m^2, FBG = fasting blood-glucose, mmol/L

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

BMI = Body Mass Index, kg/m^2, FBG = fasting blood-glucose, mmol/L

Characteristic	Active tuberculosis			
	N incident/N total (% in subcategory)	Hazard Ratio (95% CI), *P*-value		
Alcohol drinking				
No	Reference	Reference	Reference	Reference
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				
Nondiabetics	Reference			
Diabetics	1.51(0.92–2.47), *P* = 0.104			
Diabetic status				
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				
FBG < 7.0			Reference	
FBG ≥ 7.0			1.91(1.07–3.42), *P* = 0.030	
Blood glucose level(Continuious)				1.10(1.02–1.20), *P* = 0.020
BMI = Body Mass Index, kg/m^2, FBG = fasting blood-glucose, mmol/L				

BMI = Body Mass Index, kg/m^2, 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/m^2, 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/m^2, 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	
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
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/m^2, 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 ≥ 7.0 mmol/L nearly than 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		High blood lipid level$	
	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	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
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
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	
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
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		
Female	Reference	Reference
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		
Never smoked	Reference	Reference
Ever smoked	1.10(0.62–1.94), *P* = 0.744	1.19(0.47–3.02), *P* = 0.712
Alcohol drinking		
No	Reference	
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 ≥ 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/m^2, 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]. Mycobacrterium 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]. (iiii) 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;
Mtb
Mycobacrterium 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.

Funding

The work was supported by “Project of Jiangsu commission of health” [grant numbers: Y2015001], “National Science Technology Major Project” [grant numbers: 2018ZX10715002]

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.

ACKNOWLEDGMENTS

Not applicable

References

1. Jeon CY, Murray MB. **Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies**. *PLoS medicine* 2008, 5(7).
2. Al-Rifai RH, Pearson F, Critchley JA, Abu-Raddad LJ: **Association between diabetes mellitus and active tuberculosis**: **a systematic review and meta-analysis**. *PloS one* 2017, **12**(11).
3. Abdullah A, Peeters A, de Courten M, Stoelwinder J. The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. Diabetes Res Clin Pract. 2010;89(3):309–19.
4. Lönnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. Int J Epidemiol. 2010;39(1):149–55.
5. Faheem M, Qureshi S, Ali J, Hameed H, Zahoor Z, Abbas F, Gul AM, Hafizullah M. Does BMI affect cholesterol, sugar, and blood pressure in general population? Journal of Ayub Medical College Abbottabad. 2010;22(4):74–7.
6. Soh AZ, Chee CB, Wang Y-T, Yuan J-M, Koh W-P. Dietary cholesterol increases the risk whereas PUFAs reduce the risk of active tuberculosis in Singapore Chinese. J Nutr. 2016;146(5):1093–100.
7. Lin H-H, Wu C-Y, Wang C-H, Fu H, Lönnroth K, Chang Y-C, Huang Y-T. Association of obesity, diabetes, and risk of tuberculosis: two population-based cohorts. Clin Infect Dis. 2018;66(5):699–705.
8. Soh A, Chee C, Wang Y, Yuan J, Koh W. Diabetes and body mass index in relation to risk of active tuberculosis: a prospective population-based cohort. Int J Tuberc Lung Dis. 2019;23(12):1277–82.
9. Taskinen M-R, BorÚn J. New insights into the pathophysiology of dyslipidemia in type 2 diabetes. Atherosclerosis. 2015;239(2):483–95.

10. Schwenk A, Macallan DC. Tuberculosis, malnutrition and wasting. Current Opinion in Clinical Nutrition Metabolic Care. 2000;3(4):285–91.
11. **Ministry of Health of the People's Republic of China**. **Criteria of weight for adults** (**WS/T428-2013**). **Beijing**: **Ministry of Health of the People's Republic of China**, 2013.
12. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic medicine. 1998;15(7):539–53.
13. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, Wang L, Jiang Y, Dai M, Lu J, et al. Prevalence and control of diabetes in Chinese adults. Jama. 2013;310(9):948–59.
14. Zhu J, Gao R, Zhao S, Zhao G, Zhao D, Li J: **Guidelines for the prevention and treatment of dyslipidemia in Chinese adults** (**revised in** 2016). *Chinese Circulation Journal* 2016, **31**(10):937–953.
15. Association AD. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019;42(Suppl 1):61.
16. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, Wang L, Jiang Y, Dai M, Lu J. Prevalence and control of diabetes in Chinese adults. Jama. 2013;310(9):948–59.
17. Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q. Prevalence of diabetes among men and women in China. New England journal of medicine. 2010;362(12):1090–101.
18. Bragg F, Holmes MV, Iona A, Guo Y, Du H, Chen Y, Bian Z, Yang L, Herrington W, Bennett D. Association between diabetes and cause-specific mortality in rural and urban areas of China. Jama. 2017;317(3):280–9.
19. Stevenson CR, Critchley JA, Forouhi NG, Roglic G, Williams BG, Dye C, Unwin NC. Diabetes and the risk of tuberculosis: a neglected threat to public health? Chronic Illn. 2007;3(3):228–45.
20. Gatfield J, Pieters J. Essential role for cholesterol in entry of mycobacteria into macrophages. Science. 2000;288(5471):1647–51.
21. Pieters J. Entry and survival of pathogenic mycobacteriain macrophages. Microbes infection. 2001;3(3):249–55.
22. Kaul D, Anand P, Verma I. Cholesterol-sensor initiates M. tuberculosis entry into human macrophages. Molecular cellular biochemistry. 2004;258(1–2):219–22.
23. Martens GW, Arikan MC, Lee J, Ren F, Vallerskog T, Kornfeld H. Hypercholesterolemia impairs immunity to tuberculosis. Infect Immun. 2008;76(8):3464–72.
24. Lee P-H, Fu H, Lai T-C, Chiang C-Y, Chan C-C, Lin H-H. **Glycemic control and the risk of tuberculosis: a cohort study**. *PLoS medicine* 2016, 13(8).
25. Leung CC, Lam TH, Chan WM, Yew WW, Ho KS, Leung GM, Law WS, Tam CM, Chan CK, Chang KC. Diabetic control and risk of tuberculosis: a cohort study. Am J Epidemiol. 2008;167(12):1486–94.
26. Pealing L, Wing K, Mathur R, Prieto-Merino D, Smeeth L, Moore DA. Risk of tuberculosis in patients with diabetes: population based cohort study using the UK Clinical Practice Research Datalink. BMC Med. 2015;13(1):135.
27. Leegaard A, Riis A, Kornum JB, Prahl JB, Thomsen V, Sørensen HT, Horsburgh CR, Thomsen RW. Diabetes, glycemic control, and risk of tuberculosis: a population-based case-control study. Diabetes Care. 2011;34(12):2530–5.

28. MacRury S, Gemmell C, Paterson K, MacCuish A. Changes in phagocytic function with glycaemic control in diabetic patients. J Clin Pathol. 1989;42(11):1143–7.
29. Bagdade JD, Stewart M, Walters E. Impaired granulocyte adherence: a reversible defect in host defense in patients with poorly controlled diabetes. Diabetes. 1978;27(6):677–81.
30. Singhal A, Jie L, Kumar P, Hong GS, Leow MK-S, Paleja B, Tsenova L, Kurepina N, Chen J, Zolezzi F. Metformin as adjunct antituberculosis therapy. Science translational medicine. 2014;6(263):263ra159–9.
31. Yamashiro S, Kawakami K, Uezu K, Kinjo T, Miyagi K, Nakamura K, Saito A. Lower expression of Th1-related cytokines and inducible nitric oxide synthase in mice with streptozotocin-induced diabetes mellitus infected with Mycobacterium tuberculosis. Clinical Experimental Immunology. 2005;139(1):57–64.
32. Martinez L, Zhu L, Castellanos ME, Liu Q, Chen C, Hallowell BD, Whalen CC. Glycemic control and the prevalence of tuberculosis infection: a population-based observational study. Clin Infect Dis. 2017;65(12):2060–8.
33. Liu Q, Lu P, Martinez L, Peng H, Zhu T, Zhu L, Wang J, Lu W. Undiagnosed diabetes mellitus and tuberculosis infection: A population-based, observational study from eastern China. Diab/Metab Res Rev. 2020;36(3):e3227.

Figures

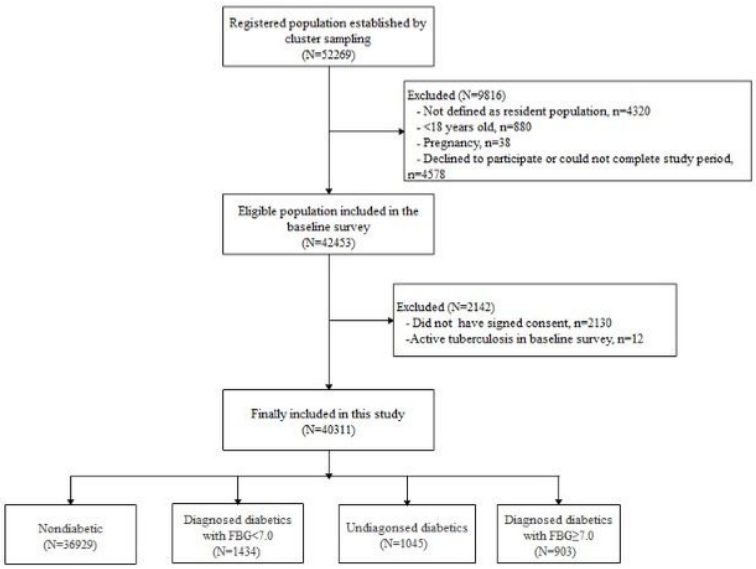

Figure 1. Eligibility and enrollment of included participants.
Abbreviations:FBG,fasting blood glucose

Figure 1

After excluding 12 active TB at baseline, a total of 40,311 were finally included in the baseline survey

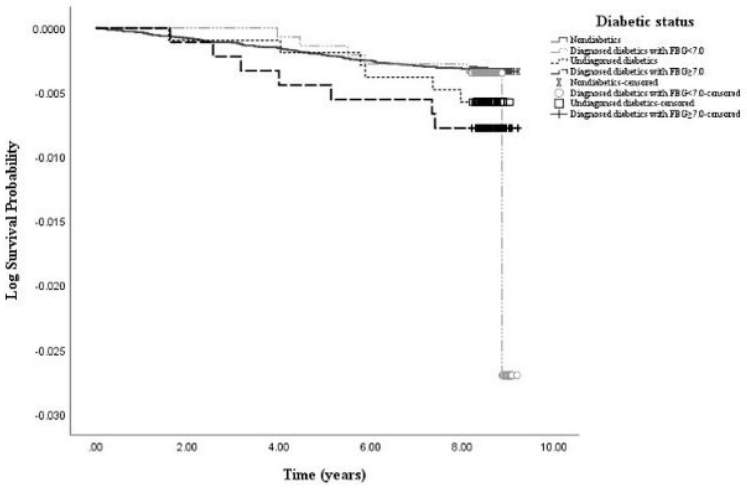

Figure 2. Kaplan-Meier plot of tuberculosis-free survival by diabetes mellitus and glycemic control status.

Figure 2

Diagnosed diabetics with FBG≥7.0mmol/L showed the highest incidence rate compared with nondiabetics diagnosed diabetics with FBG<7.0mmol/L and undiagnosed diabetics (Ptrend=0.092)

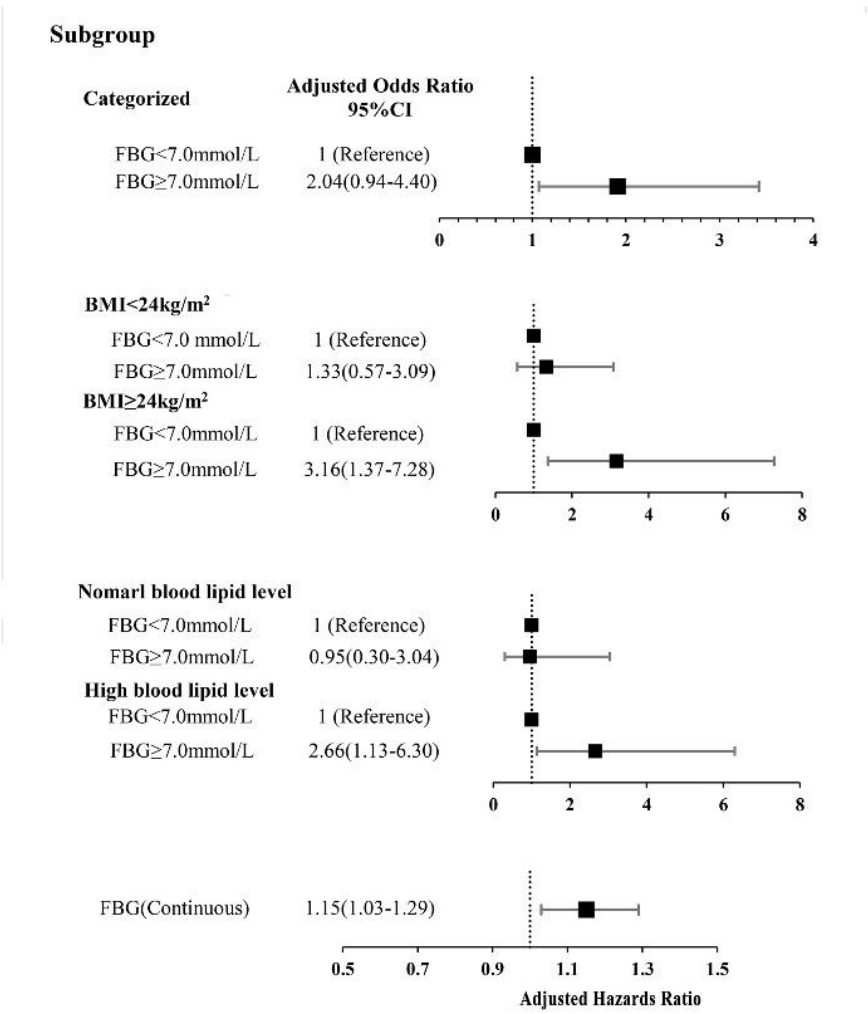

Figure 3. Adjusted Cox regression analysis of tuberculosis infection after stratification by several survey- and laboratory-based proxies of diabetes

Each model is adjusted for participant age, gender, alcohol drinking and smoking.High blood lipid level was defined as participants with serum total cholesterol >5.72mmol/L or serum triglyceride >1.7mmol/L. FPG, fasting plasma glucose; BMI, Body Mass Index.

Figure 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%)