Original Article

Risk of having pulmonary tuberculosis in type 2 diabetes: A hospital-based matched case-control study

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Background and Objectives: Diabetes mellitus (DM) leads to nearly 3-fold higher risk of pulmonary tuberculosis (TB), indicating an increasing challenge to public health in low-to-middle income countries. Till now, the risk factor is still uncertain. We carried out this study with the main purpose to identify the risk factors of having TB in DM patients. **Methods and Study Design:** A hospital-based matched case-control study was conducted in Qingdao, China from March, 2016 to January, 2018. Cases were DM patients with concurrent TB (DM-TB). Each case was matched with two controls, patients with DM only of similar age, sex and DM course. Cox regression of conditional logistic analysis was used to define the risk factors for having TB in DM, and then sensitivity analysis was carried out. **Results:** We identified 315 patients, including 105 cases and 210 controls. Smokers had a higher risk of having TB with a multivariable adjusted odds ratio (aOR) of 12.45 than non-smokers. Poor glycemic control (aOR=2.66), frequency of DM re-examination <1 time/year (aOR=3.39), as well as TB contact history was also independently related with higher risk, while BMI ≥24 (aOR=0.42), education level ≥ college (aOR=0.11) showed a negative association. **Conclusions:** Poor glycemic control, smoking, low frequency of reexamination was associated with higher risk of having TB in DM, while overweight and obesity, high education levels showed a negative association. These findings provide clues to target DM populations prone to TB, which may be of help to halt the epidemic of TB in high burden countries.

Key Words: clinical epidemiology, diabetes, poor glycemic control, smoking, tuberculosis

INTRODUCTION

Diabetes mellitus (DM) is a well-known risk factor for pulmonary tuberculosis (TB), tripling the risk of TB,[1,2] whereas about 10~15% of cases is attributable to DM.[3-5] Although a downward trend of TB incidence has been observed since the year 2000, China still accounts for nearly 10% of the world's TB burden, with approximately 0.9 million new cases every year.[6] Also, in this country, due to industrialization, urbanization, extended life expectancy and lifestyle changes, the prevalence of diabetes has increased especially rapidly over the last 10 years.[7] The increasing diabetes and still high burden of tuberculosis may result in aggravated tuberculosis epidemic for a relatively long period of time to come.[8,9]

Some factors are related with higher risk of TB in diabetics, including elderly, male, low education level and socio-economic status, alcohol use and malnutrition,[10-13] as well as poor glycemic control.[12,14] In a 5-year prospective cohort study, DM patients with baseline hemoglobin A1c ≥7% had nearly 3 times higher risk of TB [HR 3.11, 95% CI 1.63~5.92].[15] In accordance, the use of insulin, indicating a sign of poor glycemic control was related to 53% increased risk.[16] However, discrepancies also exist. In a population-based study in Denmark, a country with a low TB-burden, no evidence for any association between TB and dysglycemia was found.[17]

Therefore, we aimed to investigate the possible risk factors for having active TB in diabetes patients by a matched case-control study in China. The results may provide new evidence to define the risk factors for having TB in diabetics, as well as insights to targeting DM populations prone to TB.

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METHODS

Design and participants

A hospital-based 1:2 matched case-control study consisting of 315 participants was carried out from March, 2016 to January, 2018. One hundred and five cases, namely DM patients with concurrent TB (DM-TB) were randomly selected from Qingdao chest hospital. The diagnosis of DM was based on self-reported patients who had already taken anti-diabetic medicines, or the results of fasting plasma glucose (FPG) by using WHO criteria (1990) for the classification of glucose tolerance. The diagnosis of TB followed the National Tuberculosis Guidelines of China[18] based on chest radiography, sputum smear microscopy and clinical manifestations. The inclusion criteria of the cases were (1) aged ≥18 years; (2) DM diagnosed before TB; (3) TB treated for the first time. Patients with (1) local residence <1y; (2) hematogenous disseminated TB, tuberculous pleurisy and other extrapulmonary tuberculosis; (3) other endocrine diseases such as hyperthyroidism, systemic lupus erythematosus, rheumatoid arthritis; (4) diseases that affect the patient's immune function such as AIDS, malignant tumors, chronic hepatitis, etc; (5) hormones and immune-suppressants within 4 months were excluded.

Two hundred and ten controls, namely patients with DM only were concomitantly recruited from unselected inpatients and outpatients DM population in a general hospital in the same city of Qingdao. Each case had two controls, individually matched by sex, age (±3) and DM course (±5). We excluded participants who had any of the following conditions: local residence <1y, pulmonary infection, reported diagnosed tuberculosis or suspected tuberculosis lesions by chest X-ray or CT, any other endocrine diseases and illness that affect the patient's immune function similar as the exclusion criteria previously stated for DM-TB cases. The participants enrolled in this study were limited to those of Chinese Han ethnicity. The Ethics Committee of Qingdao Disease Prevention and Control Centre approved the present study, and informed consent was obtained from all the participants. This study was registered at Chinese Clinical Trial Registry (No. ChiCTR-IPR-15006395).

Sample size calculation

We calculated the number of participants needed in the present 1:2 matched case-control study by using the following formula

$$n = [Z\alpha\,[\sqrt{(1 + 1/r)\,\bar{p}\,(1 - \bar{p})}\,] + [Z\beta\,\sqrt{[(p_1\,(1 - p_1))/r + p_0\,(1 - p_0)\,]^2}] / (p_1 - p_0)^2$$

$$p_1 = p_0\,OR / [1 + p_0\,(OR - 1)];\ \bar{p} = (p1 + rp_0) / (1 + r)$$

p_1, p_0 is the exposure rate of the main risk factor in case group and control group respectively. In the present study, $\alpha = 0.05$, $\beta = 0.10$, $Z_\alpha = 1.96$, $Z_\beta = 1.28$, $r = 2$

Based on the report that poor glycemic control was a main risk factor of TB with an odds ratio nearly to three,[15] and the prevalence of poor glycemic control in Chinese DM patients was nearly 60%,[19] the number of DM-TB cases needed was 81, and 162 for DM control. An estimated drop-out rate of 10% was taken into account, and finally 90 cases and 180 controls were needed.

Questionnaire and anthropometric measurements

Structured questionnaires were used by trained interviewers to collect information on demographic and socioeconomic characteristics, as well as living habits including smoking and secondary smoking,[20] alcohol drinking and exercise. Immunity condition was evaluated based on accumulated infection in the last year by using the questionnaire adapted from the self-reporting immune system assessment questionnaire by university medical center Freiburg, Germany.[21] Incidence of upper respiratory tract infection (cold, sinusitis, tonsillitis, tympanitis, pharyngitis, laryngitis); bronchitis or pneumonia; infection of skin or mucosa (herpes, wart, furuncle, abscess); urinary tract infection was investigated.

Diabetes-related features included DM family history, treatment of DM, compliance on diet control, etc. were collected. We inquired potential influencing factors of TB including TB contact history, dust contact history, etc. Height and weight were measured by using standard procedure.

Laboratory analyses

After a 10-h overnight fasting, venous blood samples were collected for separation. FPG, albumin and lipid profiles including total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDLC) were detected by Hitachi auto-analyzer 7180. Automatic hematology analyzer (SYSMEX XE-2100) was used to analyze hemoglobin, lymphocyte count (TLC), etc.

Glycemic control of the participants was evaluated based on FPG[22] at admission due to the missing data in HbA1c of nearly 20%. Hypoproteinemia, lymphocytopenia was defined as reported.[23]

Statistical analysis

T test or non-parametric Mann-Whitney U test was used for continuous variable and chi-square test for categorical variables. Due to matched case-control design of the present study, Cox proportional hazards regression analysis (Forward LR) was constructed to calculate the OR and 95% CIs of existing DM-TB to fit conditional logistic regression. Possible confounders, the variables which have significant association with the risk of having TB in DM in univariable analysis were included in the multivariable model. For certain variables with internal relations such as poor glycemic control, treatment of DM and compliance on diet control, we chose poor glycemic control to include in the final model due to its best representative of glycemic control. To avoid the possible lowered statistical efficiency and bias, multiple imputation based on 5 replications were used to handle the missing data.[24] Then, a sensitivity analysis was carried out and the results were consistent in the imputed and raw data, indicating that the missing data had little effect on the results. In addition, considering a possible long duration before TB was diagnosed in some patients, we excluded all the participants with a DM course <2 years (n=55, 17.4%) for the TB risk analysis to test the possibility of reverse causality. The results also remained consistent. Analyses were performed with SPSS version 21.0 software (IBM SPSS Statistics 21); statistical significance was defined as $p<0.05$ (2-tailed).

RESULTS

Flow diagram of the enrollment of the participants was shown in Figure 1. Initially, 557 eligible patients were enrolled. Then, 71 participants with local residence <1 year, other endocrine diseases, other diseases that affect the patient's immune function were excluded, and 486 participants remained. Finally, 105 DM-TB cases and 210 DM controls were included by using individual matching based on sex, age (±3) and DM course (±5).

Baseline characteristics of the study population

As shown in Table 1, the cases had lower percentage of married (86.7 vs 95.2%), hypertension (44.8 vs 62.4%), BMI ≥24 (38.1 vs 64.5%), regular exercise (40.0 vs 61.0%) and kitchen ventilator using (61.9 vs 82.9%), but a higher prevalence of hypoproteinemia (24.2 vs 11.4%), lymphocytopenia (14.4 vs 6.5%), accumulated infections in the past year ≥1 time (70.5 vs 53.8%), TB contact history (21.0 vs 6.7%), current smoking (49.5 vs 22.8%) and current drinking (39.0 vs 18.1%).

DM related traits

Compared with DM controls, DM-TB cases had higher prevalence of poor glycemic control (77.9 vs 56.5%), while a lower frequency of DM reexamination ≥1 time/year (13.3 vs 47.6%). Also, treatment on DM, as well as compliance on diet control differed between the two groups. A marginal significant difference was found in regular glucose monitor between the two groups (p=0.06). See in Table 2.

Risk factors of having TB in DM patients

Possible factors related to TB risk in DM such as marriage status, education level, poor glycemic control, BMI and frequency of reexamination were defined in the univariable conditional logistic regression. Further, in multivariable analysis, besides TB contact history, smoking, DM reexamination <1 time/year, poor glycemic control was independently associated with increased risk of having TB in DM patients, while education level ^{3}college, and BMI ≥24 was associated with decreased odds ratio of TB in DM (Table 3).

DISCUSSION

In the present hospital-based study we found that smoking, poor glycemic control, DM reexamination <1 time/year as well as TB contact history was independently related to increased risk of having active TB in diabetic patients; while BMI ≥24, education level ≥college was associated with decreased odds ratio of TB in DM.

We carried out a 1:2 matched case-control study. DM-TB cases were recruited from a city level TB hospital, which is the largest specialist hospital for TB treatment with a catchment area of about 9 million people and the average number of hospitalized patients per year is about two thousand. DM controls were recruited from a large size tertiary comprehensive hospital in the same city. Besides age and sex, DM course was matched in the recruitment due to its close correlation with the severity of the disease. Other major socio-economic factors such as residence, monthly income level, health insurance status distributed in a balanced way between the two groups. Therefore, the included study populations as representative for their source populations as well as the comparability between the case and control can be assured.

Current smoking was related with nearly 12-fold higher risk of having TB in DM, as well as nearly 7-fold higher risk in ex-smokers. Similarly, smoking was reported to be associated with TB risk in prospective cohort studies in general population.[25,26] From mechanistic perspective, smoking may damage the cilia of airway epithelial cells, impair phagocytosis of macrophages, reduce the expression of surface proteins associated with antigen presentation by macrophages, and finally reduce the body's ability

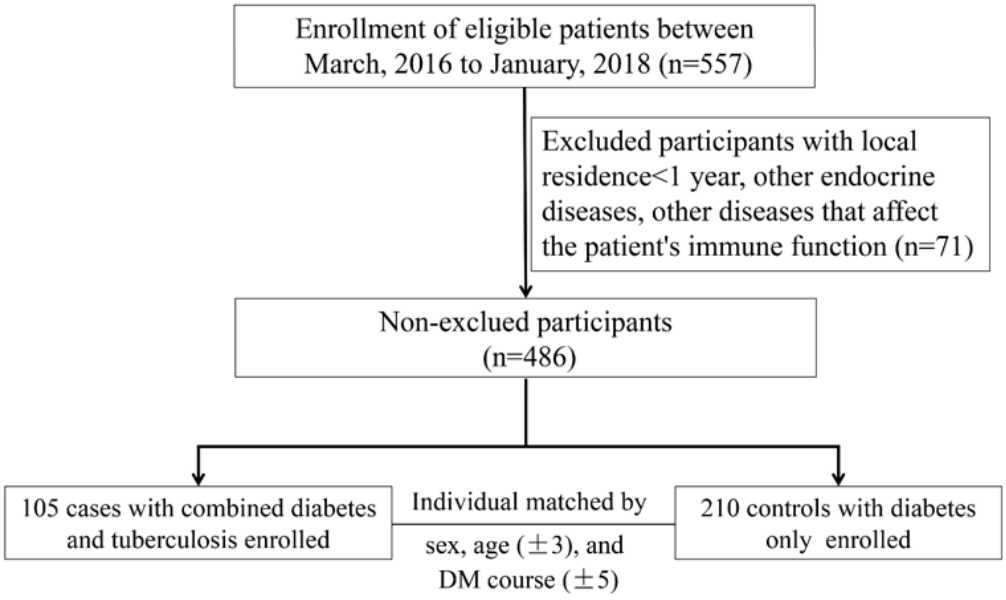

Figure 1. The numbers of individuals enrolled at each stage and the case-control selection. From March, 2016 to January, 2018, totally 557 eligible patients were enrolled. After exclude participants with local residence <1 year, other endocrine diseases and other diseases that may affect the patient's immune function, 486 participants were left. Among them, 105 patients who had combined diabetes and tuberculosis were defined as the cases. 1:2 individually matching based on sex, age (±3) and DM course (±5) was used for the non-TB controls, and finally 210 patients with diabetes only were enrolled.

Table 1. Characteristics of the study populations by concurrent TB (mean±SD)

	DM-TB cases	DM controls	*p*
Accumulated infections in the past year			
0	31 (29.5)	97 (46.2)	<0.05
1~2 times	57 (54.3)	93 (44.3)	
≥3 times	17 (16.2)	20 (9.5)	
TB contact history, n (%)	22 (21.0)	14 (6.7)	<0.01
Dust contact history, n (%)			
often	7 (6.7)	14 (6.7)	0.34
seldom	5 (4.8)	20 (9.5)	
never	93 (88.6)	176 (83.8)	
Ventilation of the house, n (%)			
>2 hours/d	77 (73.3)	158 (75.2)	0.08
≤2 hours/d	20 (19.1)	47 (22.4)	
no	8 (7.6)	5 (2.4)	
Ventilation in the kitchen, n (%)			
kitchen ventilator	65 (61.9)	174 (82.9)	<0.01
other equipment	24 (22.9)	16 (7.6)	
no	16 (15.2)	20 (9.5)	
Contact with other person			
fixed population	19 (18.1)	65 (31.0)	<0.05
shifting population	24 (22.9)	36 (17.1)	
seldom	62 (59.0)	109 (51.9)	
Per capita living space (m^2), n (%)			
<25	19 (18.1)	39 (18.6)	0.83
25~	32 (30.5)	54 (25.7)	
35~	24 (22.9)	50 (23.8)	
50~	30 (28.6)	67 (31.9)	

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; TC: total cholesterol; TG: triglyceride; HDLC: high density lipoprotein cholesterol; LDLC: low density lipoprotein cholesterol; TB: tuberculosis.

†Missing data, 10 in BMI, 41 in Hypoproteinemia and 34 in lymphocytopenia

‡Other health insurances included rural cooperative medical insurance, commercial insurance, poverty relief insurance, free medical service, self-paid medical service and other social insurance.

§Participants who smoked≥100 cigarettes in previous years and continued smoking were defined as current smokers; those who smoked more than 100 cigarettes previously while ceased in the last year were defined as ex-smoker; secondary smoker referred to those who did not smoke themselves but exposed to cigarette smoking in the environment frequently.

¶Those who consumed alcohol at least once a week and 25 g hard liquor (≥42°), 50 g light liquor (<42°), a pint of beer or 150g wine or 40g spirits each time in the past and continued drinking alcohol were considered as current alcohol drinker. Ex-drinkers were defined as drinking alcohol in the past but ceased ≥one year.

††Regular exercise was defined as ≥3 times/wk physical activities such as running, jogging, walking, swimming, bicycling, and at least 10 minutes each time during the last 6 months.

‡‡skewed distribution was observed and median, inter-quartile range were used for the description

§§Hypoproteinemia was defined as serum albumin ≤35g/L.

¶¶lymphocytopenia was defined as TLC<1.0×10^9/L.

to clear inhaled *M. tuberculosis* (MTB).[27] Greater effect size of smoking with TB was found in our study. The possible explanation was that diabetic patients, especially those with chronic hyperglycemia had impaired immune function with respect to macrophage and T lymphocyte that play a key role in the defense against MTB,[28-32] and there was a synergistic effect between smoking and diabetes. Nevertheless, a wide 95% confidence intervals were noticed, indicating larger sample size in future studies is needed to verify the finding.

Poor glycemic control was found to be related with about 2.5-fold higher risk of having TB. Fasting plasma glucose (FPG) was used to evaluate glycemic control due to the missing data of HbA1c. Also, HbA1c was used with similar purpose in recent studies.[22,33] Our results were in line with previous findings from prospective study that suggested the increased possibility of developing TB among those with increasing diabetes severity,[34] although there were certain discrepancies.[35] DM patients with chronic hyperglycemia were more prone to develop hypoxia, resulting in elevated pressure of the venous system and favor the growth of MTB.[36] By using a murine model, a reduced production of Th1-related cytokines and NO were observed to account for the hampered host defense against MTB infection under diabetic condition, of which insulin therapy resulted in a significant improvement.[37] In addition, we found low frequency of reexamination of DM was associated higher risk of having TB. Further analysis found a significantly lower proportion of basic medical insurance for urban employees in patients with low reexamination frequency, 26.4% lower than their counterpart. The establishment of basic medical insurance system for urban employees, started in 1999 in China is an important strategy to ensure basic medical care for the general population. Lack of a guaranteed health insurance may hinder the patients from frequent reexamination. Also, a marginal significantly lower education level was observed in the participants with sparse reexamination. These findings indicate that comprehensive measures are highly needed in the individual management of DM.

Table 2. DM related traits of the study populations by concurrent TB (mean±SD)

	DM-TB cases	DM controls	*p*
N	105	210	
DM family history, n (%)	31 (29.5)	77 (36.7)	0.21
DM course (year)	6.8±5.7	7.4±5.7	0.39
<1	15 (14.3)	25 (11.9)	0.76
1~	29 (27.6)	52 (24.8)	
5~	27 (25.7)	53 (25.2)	
10~	34 (32.4)	80 (38.1)	
FPG (mmol/L)	10.7±4.2	8.5±3.4	<0.01
Poor glycemic control[†], n (%)	74 (77.9)	100 (56.5)	<0.01
Treatment of DM, n (%)			
oral medicine	48 (45.7)	92 (43.8)	<0.05
insulin	22 (21.0)	30 (14.3)	
oral medicine+ insulin	11 (10.5)	52 (24.8)	
diet control only	17 (16.2)	24 (11.4)	
Irregular treatment	7 (6.6)	12 (5.7)	
Compliance on diet control, n (%)			
good	29 (27.6)	53 (25.3)	<0.05
moderate	30 (28.6)	91 (43.3)	
no	46 (43.8)	66 (31.4)	
Frequency of DM reexamination, n (%)			
never	43 (41.0)	62 (29.5)	<0.01
<1 time/year	48 (45.7)	48 (22.9)	
≥ 1 time/year	14 (13.3)	100 (47.6)	
Regular glucose monitor[‡], n (%)			
fasting and postprandial	8 (7.6)	32 (15.2)	0.06
fasting or postprandial	27 (25.7)	37 (17.6)	
no	70 (66.7)	141 (67.1)	

DM: diabetes mellitus; TB: tuberculosis; FPG: fasting plasma glucose.
[†]FPG>130 mg/dL (7.22 mmol/L) was defined as poor glycemic control.
[‡]Regular blood glucose monitor refers to detecting glucose at least once a month.

We observed a negative association of BMI ≥24 with TB in DM, with a decreased odds ratio of nearly 60%. In agreement, BMI was recently reported to be negatively associated with the risk of TB in another case-control study in DM population.[33] In general populations, prospective cohort studies have reported the negative correlation between BMI and risk of TB[38,39] with BMI in the range of 18.5 and 30.0 kg/m^2.[40] Although more evidence is needed, an obviously decreased body weight may be an early sign of active TB in diabetes populations.

There are several strengths in our study. To our knowledge, this is the first time to carried out a matched case control study with the main purpose to define the risk factor of having TB in diabetes patients. There are a few studies with similar purpose with certain limitations. Ji Y[33] reported a 1:4 matched case control study with similar findings as our study. However, the sample size was relatively small with only 22 TB cases included. In other two studies, [17,41] the design differs from the present study with TB patients and non-TB controls as the subjects. We used 1:2 matched case control study, which may increase the study efficacy. And DM was diagnosed before the explicit TB in DM-TB cases to make the results more reliable. In addition, due to the consideration of possible long duration in some TB patients before the definite diagnosis, we carried out a sensitivity analysis by excluding all the participants with a DM course <2 years, and the results remained consistent. Therefore, we are confident of the internal validity of the present study.

However, our study has several limitations. First, cautions must be taken when infer the possible causality between identified factors and TB in DM because of the case-control design. Second, the potential selection bias might result from different hospitals for the recruitment of the participants, although it is understandable that we could not include DM-TB and DM only patients from the same setting. Neither did we adopt a population based controls mainly because of the consideration of the compliance of the participants, since we preferred to investigate immune status based on both clinical laboratory test and questionnaire. Nonetheless, the controls were recruited from a large size tertiary comprehensive hospital in the same city as the cases, and there was no significant difference in main socio-economic traits such as residence, income level and insurance status. Therefore, we think the potential selection bias was minimized in our study. Finally, despite adjustment for possible confounders, residual confounding cannot be completely ruled out.

Conclusions

Our study demonstrates that smoking, poor glycemic control, low frequency of DM reexamination as well as TB contact may increase the risk of having TB in diabetic patients, while BMI ≥24 and high education level showed a negative association with TB in DM. Our results provide insights to targeting DM populations prone to TB, which may be of great significance in halting TB epidemic in countries with the double burden of TB and DM. Further studies are warranted to confirm our findings, especially in prospective design and elucidate the potential mechanisms.

Table 3. Conditional logistic regression of risk factors of TB in DM

	Univariable OR (95% CI)	*p*	Multivariable OR (95% CI)†	*p*
Married	0.29 (0.12-0.73)	<0.01	/	/
Education level, n (%)				
≤ primary school	Ref.	--	Ref.	--
middle school	0.48 (0.24-0.95)	<0.05	0.36 (0.10-1.29)	0.12
≥ college	0.26 (0.10-0.64)	<0.01	0.11 (0.02-0.51)	<0.01
Poor glycemic control‡	2.36 (1.32- 4.22)	<0.01	2.66 (1.19-5.96)	<0.05
Hypertension	0.51 (0.32- 0.82)	<0.01	/	/
BMI†				
<24	Ref.		Ref.	
≥24	0.37 (0.23-0.61)	<0.01	0.42 (0.19-0.88)	<0.05
Frequency of reexamination				
≥1 time/year	Ref.		Ref.	--
<1 time/year	5.97 (3.09-11.5)	<0.01	3.39 (1.40-8.21)	<0.01
Lymphocytopenia§	2.36 (1.10-5.09)	<0.05	/	/
Hypoproteinemia¶	2.51 (1.16-5.41)	<0.05	/	/
Accumulated infections in the last year				
0	Ref.		/	/
1~2 times	1.84 (1.11-3.05)	<0.05	/	/
≥3 times	2.64 (1.22-5.73)	<0.05	/	/
TB contact history	4.49 (1.97-10.2)	<0.01	11.7 (2.39-56.9)	<0.01
Ventilation in the kitchen				
no	Ref.			
kitchen ventilator	0.47 (0.23-0.98)	<0.05	/	/
Smoking††				
no smoking	Ref.		Ref.	
ex-smoker	4.05 (1.52-10.8)	<0.05	6.95 (1.55-31.1)	<0.05
current smoker	7.10 (3.34-15.1)	<0.01	12.5 (3.91-39.6)	<0.01
Drinking‡‡				
no drinking	Ref.		/	/
ex-drinker	0.42 (0.12-1.49)	0.18	/	/
current drinker	3.04 (1.66-5.58)	<0.01	/	/
Regular exercise§§	0.39 (0.24-0.66)	<0.01	/	/

DM: diabetes mellitus; TB: tuberculosis; BMI: body mass index.
†Estimate of risk factor of TB in DM patients after multiple imputation.
‡FPG>130 mg/dL (7.22 mmol/L) was defined as poor glycemic control.
§lymphocytopenia was defined as TLC<1.0×10^9/L.
¶Hypoproteinemia was defined as serum albumin ≤35g/L.
††Participants who smoked ≥100 cigarettes in previous years and continued smoking were defined as current smokers; those who smoked more than 100 cigarettes previously while ceased in the last year were defined as ex-smoker; secondary smoker referred to those who did not smoke themselves but exposed to cigarette smoking in the environment frequently.
‡‡ Those who consumed alcohol at least once a week and 25 g hard liquor (≥42°), 50 g light liquor (<42°), a pint of beer or 150g wine or 40g spirits each time in the past and continued drinking alcohol were considered as current alcohol drinker.
§§Regular exercise was defined as ≥3 times/wk physical activities such as running, jogging, walking, swimming, bicycling, and at least 10 minutes each time during the last 6 months.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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