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Incident rate and risk factors for tuberculosis among patients with type 2 diabetes: retrospective cohort study in Shanghai, China

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Abstract

OBJECTIVE To examine the incident rate of tuberculosis (TB) and its associates among adults with type 2 diabetes in Shanghai, China.

METHODS We conducted a retrospective cohort study among 170 399 patients with type 2 diabetes aged ≥18 years who were registered in Shanghai community-based diabetes management system between 2004 and 2009. Their TB status was tracked until 31 December 2014. Cox regression was performed to identify the risk factors for TB.

RESULTS We documented 785 new TB cases during 654 977 person-years of follow-up. The incident rate of TB was 224.20 (206.69, 243.16) per 100 000 person-years among men and 51.34 (44.75, 58.92) per 100 000 person-years among women. A 1-unit increase of BMI was associated with a risk reduction in 16% ($P < 0.01$) for men and a 14% ($P < 0.01$) reduction for women. TB cases were more likely to be insulin-dependent [men: hazard ratio = 2.13 (1.29, 3.53); women: 3.28 (1.28, 8.39)] and had a poor glucose level initially [men: 1.21 (1.15, 1.27); women: 1.27 (1.18, 1.37)]. The risk factor for TB specific to men was a young age at diagnosis of diabetes, and the protective factor specific to women was actively engaging in physical activity.

CONCLUSIONS TB incident rate among patients with type 2 diabetes was substantially higher among men than among women. The risk of TB was reversely associated with initial BMI. The severity of poor glucose control among patients with diabetes was also linearly associated with the risk of TB.

keywords diabetes, tuberculosis incidence, China

Introduction

An ageing population, rapid urbanisation and the associated lifestyle have propelled a rapid increase in non-communicable diseases (NCD) worldwide, and among these, diabetes mellitus (DM) has been emerging as the most urgent global challenge [1]. People with diabetes are at increased risk of developing a number of health problems; consistently high blood glucose levels lead to serious damage of heart and blood vessels, eyes, kidneys, nerves and teeth, and confer a higher risk for developing infections, among which *Mycobacterium tuberculosis* (TB) infection is a major one [2, 3]. TB is re-emerging as one of the significant communicable diseases worldwide. In 2013, about 9 million people fell ill with TB and 1.5 million died from it globally. The comorbidity of TB and diabetes presents an eminent threat to global public health especially in major developing countries [4]. The dual burden of TB and DM has attracted much attention in the past decade as DM prevalence has increased dramatically worldwide [5]. In India, patients with DM accounted for 14.8% of pulmonary TB cases and 20.2% of smear-positive (i.e. infectious) TB cases in 2000 [6]. A good estimate of TB incident rate and identifying predictors of TB prognosis among patients with diabetes are needed to align the priority of health care development in resource-limited countries and regions.

Chinese people account for a quarter of all patients with diabetes worldwide [7]; 10% of Chinese adults are diabetic, and the prevalence of diabetes among adults in China is climbing without any sign of stopping in the foreseeable future. Meanwhile, in developed countries, the population-attributable fraction of diabetes for pulmonary TB is higher for Asian populations than other ethnicities [8]. The heavy burden of TB and DM among the Chinese population and the high comorbidity between TB and DM among Asian populations call for

[Correction added on 02 June 2017, after first online publication: The first author's name has been corrected in this version].

an extensive effort to investigate the unique comorbidity between TB and DM among Chinese.

As diabetes has been considered as a significant risk factor for TB, Shanghai faces a great challenge in controlling and preventing TB as the prevalence of diabetes in this megacity reached 17.6% in 2013. Thus, the care and control of TB among patients with diabetes should be highlighted in implementing the END TB Strategy launched by WHO.

Therefore, we conducted a population-based retrospective cohort study among DM cases in Shanghai, China. Its specific aim was to longitudinally assess the risk of developing TB among adults with diabetes. We also evaluated factors associated with an increased risk of TB, including body mass index (BMI), DM complications, medication status and lifestyle among adults with diabetes.

Methods

Data sources

The data used were from Shanghai community-based diabetes management system (SCDMS), a diabetes register operated by the Shanghai Municipal Centers for Disease Control and Prevention (Shanghai-CDC). SCDMS covers more than 25% of confirmed DM cases in Shanghai identified through community-based DM screenings, routine physical examinations and self-reporting. Regardless of how DM cases were identified, as part of the initial assessments, the diagnosis must be verified by physicians in Community Health Centers (CHCs) using 1999 World Health Organization (WHO) criteria [9] before being registered. For confirmed DM cases, in-person interviews were conducted every 3 months after the initial assessment by CHC physicians to collect data on physical examination (including BMI and fasting blood glucose), complications, treatment modalities (categories and forms of medications used) and lifestyle factors (including duration and intensity of physical activity in leisure time).

By linking SCDMS database with Shanghai Municipal TB Surveillance System (SMTSS), a mandatory TB reporting system managed by all CDCs at city and district level in Shanghai [10, 11], we were able to trace DM participants' TB status.

Study population

We started by excluding participants who were HIV-positive and registered in the HIV Surveillance System, which was also managed by Shanghai-CDC. The study populations started with 185 684 HIV-negative DM patients living in 18 districts of Shanghai who were registered in SCDMS between 1 January, 2004 and 31 December 2009 roughly 5 years for most of the study participants (210 losses of follow-up of 185 684, Figure 1), if loss of follow-up did not occur. After exclusions, the records of 170 399 patients with diabetes were retained for the present analyses. The exclusion steps of study participants were summarised in Figure 1. Data completion for each variable was greater than 96.0%. A full set of information was available for 163 062 participants, 95.7% of the study population used in the main analyses of the current report. The Ethical Review Committee at Shanghai-CDC approved the study protocols and waived the need for obtaining patient consent forms due to the retrospective nature of the study.

Initial assessment

Basic sociodemographic information was collected during the initial assessment by physicians from CHCs; and diagnoses of diabetes were also verified at the initial assessment if the cases were self-reported, and the diagnoses were made before community-based screening or routine physical examination. A single phlebotomy after 8-14 h fasting was performed during the initial assessment. The individual's weight and height were recorded, and BMI was calculated as weight in kilograms divided by height in metres squared and then rounded to two decimal places. We grouped patients with DM into three groups (no complication, one complication and more than one complication) according to the number of DM complications reported at the initial assessment. Complications of DM comprised of kidney lesions, nervous lesion, vasculopathy, skin infection and retinopathy, which were diagnosed in medical institutions prior to or at the initial assessment performed by a physician from a CHC.

Follow-up assessment

Follow-ups took place every 3 months by face-to-face interview (90%) or a phone call (10%) if no mutually convenient times were available. With medical records transferred electronically within SCDMS, patients relocated to other districts of Shanghai city were followed-up by staff from the CHC near his or her new address using standardised protocols. Patients were censored as lost to follow-up if they moved to a location outside of Shanghai city. The individual's weight and height were recorded at each follow-up assessment, and we subtracted the BMI measured at the initial assessment from the mean of the values measured in the following-up assessment. Fasting

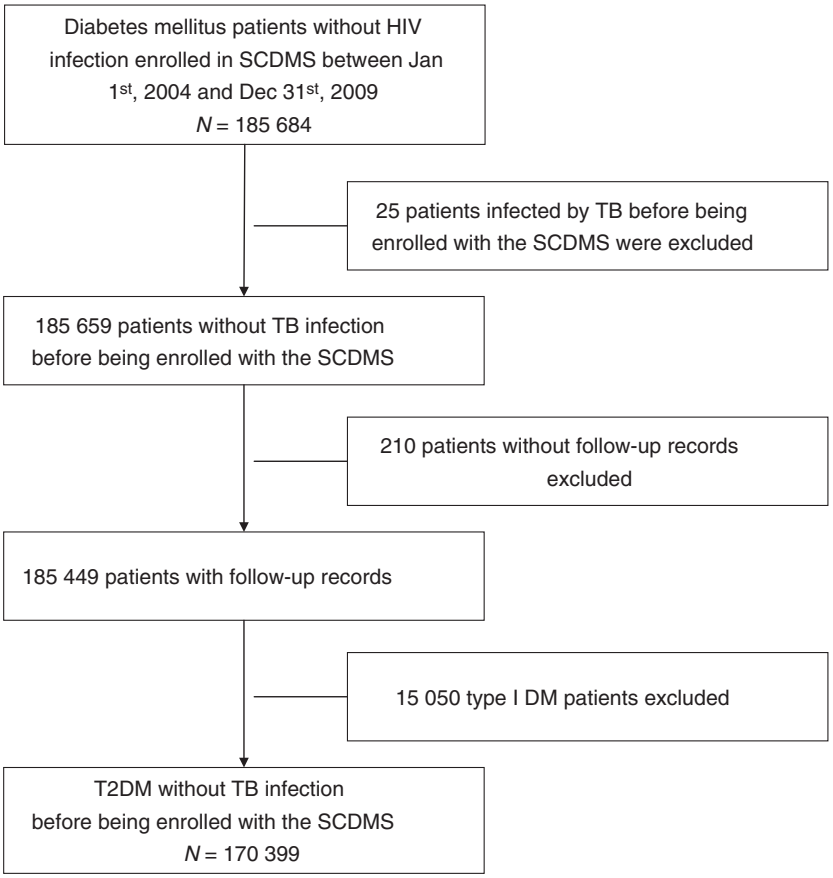

Figure 1 Flow chart of the study population of adults aged ≥18 years from Shanghai community-based diabetes management system (SCDMS).

phlebotomy was also performed for each face-to-face follow-up interview. Participants' venous blood glucose was assessed (self-tested if a phone call follow-up was conducted) and recorded by physicians from CHCs. We calculated the overall trend of fasting glucose across the study period in a similar manner as we did with BMI. We also categorised patients with DM into four groups according to the antidiabetes medications used, no medication, oral drug only, insulin only, both oral drug and insulin. The medication use status was based on the most recent status immediately before TB diagnosis was made. In each follow-up interview, a CHC physician asked about details of leisure-time physical activities (LTPA) the patients with diabetes had engaged in over the preceding 3 months, such as activity type and average hours per day. Activity types were categorised into three groups: sedentary (e.g. watching TV and reading newspapers), mildly active (e.g. gardening and household activities), moderately and vigorously active (e.g. jogging, dancing, playing badminton, weight lifting). The values most frequently appearing were used to proxy the LTPA pattern for the analysis.

Outcome ascertainment

All TB diagnoses were confirmed by laboratory-based diagnostic tests using the China National TB Diagnostic Guidelines, including acid-fast bacilli (AFB) smear and culture test, purified protein derivative (PPD) skin test and serological test for *Mycobacterium tuberculosis* infection (Mtb) [12].

Statistical analyses

For patients with TB, follow-up assessments ended at the time when TB diagnosis was confirmed. For non-TB patients, follow-up assessments continued until the end of study, that is 31 December 2014 unless the patients went missing or died. Missing data were handled by multiple imputation approaches designed to allow the inclusion of patients with incomplete data into analysis to increase the power of the analysis and produce models that were statistically more reliable [13]. In this study, every missing value based on the assumption of missing completely at random was imputed by the chained equation method five times,

to attain a relative efficiency of at least 95%. The incident rate of TB and its 95% confidence interval (CI) were estimated based on a Poisson distribution. Kaplan–Meier survival curves for TB infection were obtained, and their difference was assessed by the log-rank test.

Person-years contributed by each participant were calculated as the interval between the date of initial assessment and the date of TB diagnosis or last follow-up interview. Estimates of the crude and the adjusted hazard ratios (HRs) of being diagnosed with TB were derived from Cox proportional hazard regression models for individuals with different levels of risk factors. The proportional hazards assumption was checked by visual inspection of plots of log [−log (S)] against time, where S was the estimated survival function. The presence of multicollinearity was also checked by examining the tolerance. To assess the impact of missing value on the estimates, we conducted sensitivity analyses and repeated the steps described above with the participants who had a full set of data (n = 163 062). As the literature repeatedly demonstrated a sex difference in risk factors for TB incident rate [14], we stratified our analysis by sex. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina), and all hypothesis tests were two-sided, and $P \leq 0.05$ was considered statistically significant.

Results

Baseline demographic and other characteristics for the T2DM cohort were shown in Table 1 by sex after multiple imputations. About 14% of men and 16% of women had at least one DM complication reported. Specifically, 1.25% of men and 1.05% of women reported retinopathy, 1.69% of men and 1.68% of women reported kidney lesions, 1.59% of men and 1.76% of women reported nervous lesion, and 5.01% of men and 6.56% of women reported skin infection (data not shown in tables). The most common complication was vasculopathy, reported by 7.98% of men and 8.15% of women. All the characteristics listed in the table were significantly different between men and women.

By the end of follow-up, a total of 16 363 deaths were documented with an overall mortality of 9.6%. With an average following-up period of 3.8 year (range: 0.25–10.96 years), 785 TB cases were recorded among 170 399 patients with T2DM from 654 977 person-years follow-up. The overall incident rate of TB was 119.85 (95% CI: 111.76–128.54) per 100 000 person-years (Table 2), with 224.20 (95% CI: 206.69–243.16) per 100 000 person-years for men and 51.34 (95% CI: 44.75–58.92) per 100 000 person-years for women. There was a clear separation of Kaplan–Meier survival curves; men had a higher probability of being infected with TB than women (Figure 2). The log-rank test revealed a significant sex difference in incident rates (P of log-rank test <0.001). The separation started at the beginning of the follow-up, and the diverging trend accelerated in the third year of follow-up.

Both men and women tended to have a higher risk of TB infection if they had a lower BMI or poor blood glucose control at initial assessment (Table 3). A 1-unit increase in BMI was associated with a 16% reduction of risk of TB infection in men [HR = 0.84 (95% CI: 0.81 to 0.86)] and a 14% reduction in women [HR = 0.86 (95% CI: 0.82–0.90)]. Those with poor glucose control initially were more likely to be infected by TB [men: 1.21 (95% CI: 1.15–1.27); women: 1.27 (95% CI: 1.18–1.37)]. Those infected with TB were also more likely to be insulin-dependent; patients who used insulin had a higher risk of being infected with TB [men: 2.13 (95% CI: 1.29–3.53), women: 3.28 (95% CI: 1.28–8.39)] than their counterparts who did not use insulin.

Several factors associated with TB infection were sex-specific in patients with T2DM. The risk factor specific to men was young age at diagnosis of T2DM. Increasing BMI during the study period was associated with a decreased risk of TB in men but not in women. Actively engaging in mild physical activity, such as housework, gardening and walking for more than 2 h daily, was significantly associated with a low risk of being infected with TB for women. No significant interaction was observed between either BMI and baseline fasting glucose level or BMI and change of fasting glucose levels, in neither men nor women (data not shown).

When the analysis was repeated among 163 062 patients with T2DM who had a set of complete information, the directions and magnitudes of estimated effects described above remained unchanged. For example, the HR of TB infection for baseline BMI in men was 0.84 (95% CI: 0.81–0.86) in the main analyses, and the corresponding estimates in the sensitivity analyses were 0.83 (95% CI: 0.81–0.86). However, due to the reduced sample sizes, the 95% CI for some estimates became wider, and the estimates lose their statistical significance. For example, physical activity intensity and activity time duration became insignificant in female patients in the sensitivity analyses.

Discussion

Our study was the first large population-based longitudinal study performed in a developing country to examine the incident rates of TB and associated factors among

Table 1 Characteristics of 170 399 patients with type 2 diabetes from Shanghai community-based diabetes management system, 2004-2009

Initial characteristics	Mean (SD) or no. (%)		*P*-value
	Men (*N* = 69 986)	Women (*N* = 100 413)	
Sociodemographics†			
Age at diagnosis of DM (years)	58.98 (11.31)	59.45 (11.17)	<0.001
Clinical parameters†			
Initial BMI (kg/m^2)	24.00 (3.00)	24.30 (3.50)	<0.001
BMI changed (kg/m^2)‡	−0.09 (1.55)	−0.01 (1.68)	<0.001
Initial fasting glucose (mmol/l)	7.14 (1.21)	7.16 (1.23)	<0.001
Fasting glucose change (mmol/l)§	−0.58 (2.06)	−0.51 (1.95)	<0.001
Complications of DM†			
No	60 030 (85.77%)	84 778 (84.43%)	<0.001
One	8 071 (11.53%)	12 608 (12.56%)	
More than one	1 885 (02.69%)	3 027 (03.01%)	
Antidiabetic medication††			
No	4 698 (06.71%)	6 944 (06.92%)	<0.001
Insulin used	8 178 (11.69%)	10 654 (10.61%)	
Oral drug used	48 445 (69.22%)	70 058 (69.77%)	
Oral drug and insulin used	8 665 (12.38%)	12 757 (12.70%)	
Exercises‡‡			
Intensity of physical activity§§			<0.001
Inactive	10 403 (14.86%)	15 642 (15.58%)	
Mild	52 627 (75.20%)	77 810 (77.49%)	
Moderate & vigorous	6 956 (09.94%)	6 961 (06.93%)	
Activity of time duration			<0.001
Less than 1 h	21 388 (30.56%)	31 787 (31.66%)	
1~2 h	41 252 (58.94%)	59 033 (58.79%)	
More than 2 h	7 346 (10.50%)	9 593 (09.55%)	

BMI, body mass index.
†Measured at the enrolment to the SCDMS unless indicated otherwise.
‡BMI change was estimated by subtracting the initial values from the means of follow-up.
§Fasting glucose change was estimated by subtracting the initial values from the means of follow-up.
††The medication use status was based on the most recent status before TB diagnosis was made.
‡‡The values most frequently appearing in follow-up were used to proxy the LTPA pattern and time duration for the analyses.
§§Leisure-time physical activities (LTPA) were categorised into three groups: sedentary (i.e. watching TV and reading newspapers), mildly active (e.g. gardening and household activities), moderately and vigorously active (e.g. jogging, dancing, playing badminton, weight lifting).

adults with type 2 diabetes. With a relatively large sample size, we found that the TB incidence rate among men was four times than that among women. The risk of TB infection was inversely associated with initial BMI. The severity of poor glucose control among patients with T2DM was also linearly associated with the risk of TB attack. These associations were more salient among men than women.

Consistent with the literature, we found that the TB incident rate among patients with T2DM is substantially higher than in the general population. In 2015, Shanghai had population of 24 million, and 6,851 new TB cases were reported by SMTSS. Thus the incident rate was 28.5 per 100 000 people. The TB incidence rate ratios between population with type 2 DM and the general population can be roughly estimated as 4.21 (119.85/28.5), which is close to the estimates from urban settings in South Korea (RR = 3.49) [15] and Indonesia (RR = 4.7) [16], but lower than that observed among the patients admitted into a large teaching hospital in Karachi, Pakistan [17].

The second main finding emerging from the current report is that the initial BMI was linearly and inversely associated with the risk of TB infection. An early cohort study using the 1971–1975 national survey as the baseline assessment observed that the TB incident rate increased inversely with body weight among adults from the general population; the adjusted hazard ratios were

Table 2 The number of TB cases and incident rate of TB attack among 170 399 patients with type 2 diabetes, Shanghai Diabetes Control and Prevention Cohort, 2004-2009

	Total Person-year	TB Cases	TB incident rate (cases/100 000 person-years)	
			Estimate	95% CI
Men (N = 69 986)	259 601	582	224.20	(206.69, 243.16)
Women (N = 100 413)	395 376	203	51.34	(44.75, 58.92)
Total (N = 170 399)	654 977	785	119.85	(111.76, 128.54)

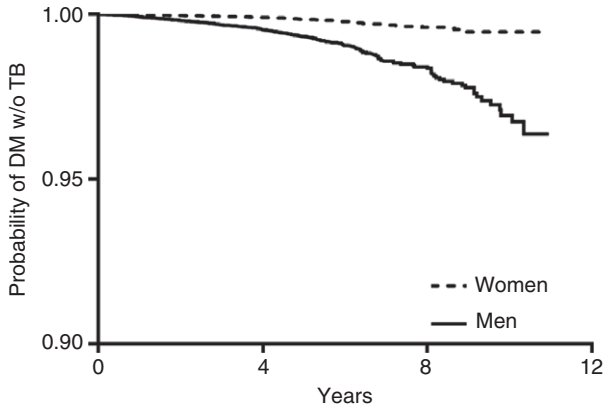

Figure 2 Kaplan–Meier plot for TB infection between men and women in patients with T2DM, 170 399 patients with type 2 diabetes from Shanghai community-based diabetes management system, 2004-2009. ($P < 0.01$).

12.43, 1.00 (reference), 0.28 and 0.20, for adults with underweight, normal weight, overweight and obesity respectively after controlling for demographic, socioeconomic and medical characteristics [18]. Our study extends the observation from the general population to the population with diabetes, and observations from older populations with diabetes [19] to relative young populations with diabetes. Underweight, defined as BMI <18.5 kg/m^2, is a well-established marker of malnutrition [20] and has been linked to an increased susceptibility to develop tuberculosis biologically [21–23] and epidemiologically [24], especially in low- and middle-income countries [14, 25, 26]. The biological plausibility to explain the protective role against TB from excessive body weight remains unclear. This is especially relevant for the current report because diabetes is overwhelmingly associated with excessive body weight in developed countries, and obesity is rising globally. Unpuzzling this paradox may offer new insights on how to address the global challenges associated with the re-emergence of TB and increasing prevalence of obesity, too.

Insulin dependence is a reliable indicator of the severity of diabetes; and active TB was more common in patients with insulin-dependent diabetes than patients with non-insulin-dependent diabetes [27–30]. Similar to these observations, we observed a doubled risk of TB infection among men with insulin-dependent diabetes and tripled risk among women with insulin-dependent diabetes compared to their counterparts who were not insulin-dependent. A dose–response relationship between fasting glucose level and risk of TB was evident. Poorly controlled glucose may impair immune response to Mtb infection and increase the susceptibility of Mtb infection. However, we cannot rule out the possibility that poor glucose control was just an indicator of low socioeconomic status, whose association with high risk of TB infection is well-documented. Men with diabetes were at a significantly higher risk of TB infection than women among patients with T2DM. We attribute this sex difference to differences in cigarette smoking between Chinese men and women. The smoking prevalence remains exceptionally high among Chinese men and the interaction between diabetes and tobacco smoking explained a much higher TB burden among men than women and contributed to the wide variation in TB prevalence across 14 high-burden TB countries [24]. Unfortunately, due to data limitation, we cannot test our hypothesis in the current report.

Another interesting finding in the current study is that for female cohort, daily mild activities acted as a protective factor against TB. Moreover, if women with T2DM took part in activities at least 2 h every day, they also had a lower risk of TB. Regular physical activity may improve the metabolic profile and seems to be protective against various metabolic disorders [31, 32]. We found that the beneficial effect may extend to an improved immune response against Mtb.

The major limitations of a retrospective study are evident in the current report. The temporal relationship was difficult to assess as no TB tests were performed for each patients with diabetes at the initial assessment, and we cannot rule out the possibility that some baseline

Table 3 Cox regression for predictors of TB infection, 170 399 patients with type 2 diabetes from Shanghai community-based diabetes management system, 2004-2009

	Men (N = 69 986)			Women (N = 100 413)		
Variable	Adjusted HR	95% CI	P-value	Adjusted HR	95% CI	P-value
Sociodemographics†						
Age at diagnosis of DM (years)	0.99	(0.98,1.00)	<0.01	1.00	(0.99,1.01)	0.94
Clinical parameters†						
Initial BMI (kg/m^2)	0.84	(0.81,0.86)	<0.01	0.86	(0.82,0.90)	<0.01
BMI changed (kg/m^2)‡	0.92	(0.86,0.97)	<0.01	0.91	(0.83,1.01)	0.07
Initial fasting glucose (mmol/L)	1.21	(1.15,1.27)	<0.01	1.27	(1.18,1.37)	<0.01
Fasting glucose change (mmol/L)§	1.17	(1.11,1.24)	<0.01	1.27	(1.16,1.40)	<0.01
Complications of DM†						
No	1.00	(ref)	(ref)	1.00	(ref)	(ref)
One	0.85	(0.66,1.08)	0.19	0.91	(0.61,1.35)	0.64
More than one	0.69	(0.42,1.14)	0.14	0.67	(0.30,1.53)	0.35
Antidiabetic medication††						
No	1.00	(ref)	(ref)	1.00	(ref)	(ref)
Insulin used	2.13	(1.29,3.53)	<0.01	3.28	(1.28,8.39)	0.01
Oral drug used	1.75	(1.09,2.81)	0.02	1.94	(0.79,4.76)	0.15
Oral drug and insulin used	1.48	(0.88,2.47)	0.14	2.52	(0.98,6.44)	0.05
Exercises‡‡						
Intensity of physical activity§§						
Inactive	1.00	(ref)	(ref)	1.00	(ref)	(ref)
Mild	0.83	(0.65,1.08)	0.16	0.87	(0.81,0.93)	0.02
Moderate & heavy	0.94	(0.66,1.34)	0.73	1.07	(0.45,2.52)	0.88
Activity of time duration						
Less than 1 h	1.00	(ref)	(ref)	1.00	(ref)	(ref)
1~2 h	0.87	(0.71,1.07)	0.20	0.75	(0.54,1.05)	0.09
More than 2 h	1.21	(0.90,1.61)	0.21	0.55	(0.30,1.00)	<0.05

HR, hazard ratio; BMI, body mass index.
†Measured at enrolment in SCDMS unless indicated otherwise.
‡BMI change was estimated by subtracting the initial values from the means of follow-up.
§Fasting glucose change was estimated by subtracting the initial values from the means of follow-up.
††Medication use status was based on the most recent status before TB diagnosis was made.
‡‡The values most frequently appearing in follow-up were used to proxy the LTPA pattern and time duration for the analyses.
§§Leisure-time physical activities (LTPA) were categorised into three groups: sedentary (e.g. watching TV and reading newspapers), mildly active (e.g. gardening and household activities), moderately and vigorously active (e.g. jogging, dancing, playing badminton, weight lifting).

characteristic or measurements might be the results of undiagnosed TB infections. A typical retrospective study cannot control exposure but instead relies on others for accurate recordkeeping; we cannot assess the comparability of the records kept by the Centers of Disease Control and Prevention from various administrative units, ending with potential misclassifications. The data on potential risk factors such as family income, cigarette smoking status and alcohol consumption were not available. Information on glycosylated haemoglobin test, a more reliable biomarker of prognosis of diabetes, was unavailable. Nevertheless, the relative large sample size of our study with an average follow-up of 3.8 years and repeated measurements may capture the objective glucose trend of the individuals. The large sample size and the utilisation of administrative data routinely collected using a standardised protocol made it possible to stratify study participants by sex and clinical characteristics. Shanghai's GDP per capita is exceptionally high and close to that of many advanced economies, so caution should be exercised in generalising the current report's conclusion to other districts in China.

The findings of this report call for a closer collaboration between communicable disease and non-communicable disease control and prevention. Such a collaboration presents an opportunity for a comprehensive and integrated approach to address diabetes and TB, two leading public health challenges in China. Standard treatment

guidelines which incorporate the core issues in the bidirectional screening and cost-effective management of TB and diabetes need to be developed and enforced [5, 33]. Screening can be conducted in those with T2DM to maximise the cost-effectiveness of TB screening, especially young cases with poorly controlled glucose levels and low body weight.

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