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Risk of active tuberculosis among people with diabetes mellitus: systematic review and meta-analysis

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ABSTRACT

Objective: To assess the risk of active TB in people with DM and the factors associated with this risk.

Methods: Systematic review and meta-analysis. We searched the literature for studies that reported the effect of DM on TB controlled for the effect of age. Studies that had not established the diagnosis of DM prior to detecting active TB were excluded. Study quality was assessed by Newcastle-Ottawa scale and we conducted a meta-analysis using random-effects models.

Results: 14 studies (8 cohort and 6 case-control studies) that involved 22,616,623 participants met the selection criteria and were included in the analysis. There was substantial variation between studies in the estimates of the effect of DM on TB. However, the pooled estimates from 7 high-quality studies showed that diabetic people have a 1.5-fold increased risk of developing active TB versus those without DM (95%CI 1.28-1.76), with relatively small heterogeneity (I2 44%). The increased risk of TB was observed predominantly among DM populations with poor glycaemic control.

Conclusion: There is evidence suggesting an increased risk of developing TB among people with DM, and that improving glycaemic control in DM patients would reduce the risk of developing TB. An integrated approach is needed to control the dual burden of DM and TB.

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INTRODUCTION

Tuberculosis (TB) continues to be a major global health challenge, with an estimated 10.4 million incident cases worldwide in 2016 (1). In addition to improving diagnosis and treatment of active TB, primary prevention through management of risk factors of TB is crucial for reducing the burden of TB because impairment of cell-mediated immunity that occurs in conditions such as HIV infection leads to a dramatic rise in the risk of developing active TB (2).

Diabetes mellitus (DM) can also impair host immunity (3) and the prevalence of DM is increasing all over the world, rising from 4.7% in 1980 to 8.5% in 2014 in the adult population (4). The rise is most remarkable in low- and middle-income countries (LMICs) even though a substantial proportion of people with DM living in LMICs remain undiagnosed. Availability of diagnostic tests and treatment required for management of DM in primary healthcare facilities is not universal in LMICs and this contributes to a high mortality attributable to DM that could be prevented.

Six countries (China, India, Brazil, Indonesia, Pakistan and The Russian Federation) among the ten projected to have the highest numbers of people living with DM by 2035 also have a high TB-burden (1). DM was observed to be a potential risk factor for TB long time ago (5), and the rising prevalence of DM in countries where TB is endemic has revived interest in exploring the relationship between DM and TB. A systematic review published in 2016 reported that DM was associated with an increased risk of latent TB infection (LTBI), with a risk ratio of 4.40 (95% CI; 0.50–38.55) in a cohort study, and a pooled odds ratio of 1.18 (95% CI; 1.06–1.30) from 13 cross-sectional studies (6). However, the latest WHO guideline on the management of LTBI does not recommend systematic testing for LTBI in people with DM based on lack of robust evidence that DM patients have a higher risk for LTBI (7). It is considered that the increased risk of active TB is mainly related to a higher risk of progression from LTBI among people with DM, and a meta-analysis published in 2008 suggests that DM triples the risk of developing active TB (8). However, in this meta-analysis, the pooled effect estimate of DM on TB (rate ratio 3.11, 95% Confidence Interval 2.27–4.26) was based on only three cohort studies, one of which did not control for potential confounders (9) and the other two cohort studies were conducted in renal transplant recipients who were under immunosuppressive therapy (10, 11). Furthermore, 9 of 13 studies included in the review did not establish the diagnosis of DM among participants prior to detecting active TB. Temporal sequence has been one of the major

concerns for investigating the effect of DM on TB risk because TB patients have higher rates of glucose intolerance than community controls (12, 13). Although it is unclear whether the stress of TB infection truly induces glucose intolerance, or whether prevalent DM was newly diagnosed through intensified medical services related to TB treatment, it would be vital to pay attention to this sequence to measure direct effect of DM on developing active TB. More studies of DM and TB infection have been published since 2008, but it remains unclear whether improving glycaemic control in DM patients could mitigate the risk of TB. Thus we conducted a systematic review and meta-analysis of studies investigating the association between DM and active TB.

METHODS

All studies published in English on the association between DM and active TB before April 13th, 2017 were searched through PubMed, EMBASE, MEDLINE, and the Global Health database using a comprehensive search strategy (Supplement file 1). Bibliographies of identified articles were reviewed for additional relevant studies. Studies were screened and selected for full-text review if they met the following inclusion criteria: (1) reported a quantitative measure of association between DM and active TB; (2) diagnosis of DM was established prior to detecting TB; (3) TB diagnosis was based on standard diagnostic criteria; (4) diagnosis of DM was based on self-report, medical records, laboratory test or treatment. Systematic reviews and case reports were excluded from the analysis. We assessed the quality of study based on the Newcastle-Ottawa Scale (14) which assigns a maximum of 9 stars (4 for selection of study population, 2 for comparability, 3 for robustness of outcome or exposure). Studies that had a score more than 8 stars were deemed to be high quality. The selection of papers based on *a priori* criteria was done by one author (SH) and the screening process was repeated two months after the first screening to avoid exclusion of eligible articles by mistake. The quality assessment of papers included in the analysis was reached by consensus between both authors.

Data from each study were transcribed in a structured form and key study characteristics were summarized in a table. The reported relative risk (RR) of developing active TB among persons with DM compared to those without DM (rate ratios or odds ratios) was obtained from the model adjusted robustly for the potential confounding factors in each study. For studies that did not report the background TB incidence, data of the closest matching year of the study for the country were obtained from the WHO global tuberculosis database

(http://data.worldbank.org/indicator/SH.TBS.INCD). A meta-analysis was performed using Der Simonian-Laird random effects model and weighting method, accounting for the variation in the true effect of DM on TB in different populations. It was assumed that the odds ratio reported from case-control studies was a reasonable approximation of rate ratio since background TB incidence rates in the included studies were sufficiently low and none employed concurrent sampling (15). Thus, pooled estimates of relative risk were computed using either rate ratio or odds ratio. The observed relative risk of TB among persons with DM versus those without DM was stratified by the severity of DM, age, and sex within each study and presented in forest plots. In addition, other potential effect modifiers on the association between DM and TB were explored. Meta-regression was performed to explore between-study heterogeneity in effect estimates related to characteristics of the study population (region, background TB incidence, and median age of participants) and study characteristics (design, quality, median follow-up time, sample size, method of DM diagnosis, type of TB, and factors included in the regression models). Potential publication bias was assessed by visual interpretation of funnel plots of relative risks and their standard errors. All statistical analyses were done with Stata (version 14.2).

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42017060873 (http://www.crd.york.ac.uk/PROSPERO/). The results are presented in accordance to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (16).

RESULTS

Initially 4859 titles and abstracts were identified through comprehensive search of the databases. After the removal of duplicates, 3637 abstracts were screened, and 71 potential eligible articles were identified (Figure 1). After reading the full text, 57 studies were excluded for various reasons mentioned in Figure 1. Thus, 14 studies (8 cohort studies and 6 case-control studies), published between 1992 and 2017, which involved 22,616,623 participants, met the eligibility criteria for this analysis (9, 10, 17-28).

The key characteristics of the studies included in this analysis are shown in Table 1. Among the 8 cohort studies, 6 were conducted in general populations while one (South Korea) was done in civil servants (9), and one (India) was in renal transplant patients (10). Median follow-up time in the

cohort studies ranged from one to five years. Of the 6 case-control studies, 1 (Denmark) was nationwide (24) and 1 (Romania) was hospital-based (27). All studies had adjusted the rate ratio or odds ratio at least for age, and some studies had adjusted for a variety of potential confounders, such as sex, ethnicity, body mass index (BMI), or socio-economic status. Six of 8 cohort studies and 1 of 6 case-control studies were of high quality (17, 18, 21, 23-25, 28).

There was substantial heterogeneity in the estimates of the effect of DM on the risk of active TB between the studies in both cohort and case-control studies; between-study variance accounted for 89.7% of the total variance among cohort studies and 90.1% of the total variance among case-control studies. However, all studies showed an increased risk of TB among persons with DM and the effect estimates reported by 12 of 14 studies were statistically significant. The pooled rate ratio estimated from the cohort studies showed that people with DM have a 1.95-fold (95%CI 1.38-2.76) increased risk of TB, and the pooled odds ratio from the case-control studies showed a 3.98-fold (95%CI 1.53-10.37) increased risk of TB. When low-quality studies were excluded, between-study heterogeneity decreased (I^2=44.1%) and combining the estimates from 7 high-quality studies showed that people with DM had a 1.5-fold higher risk of developing active TB than people without DM (95%CI 1.28-1.76).

The estimates of effect of DM on the risk of TB stratified by level of control of DM, age, and sex are presented in Figure 3. Six studies that compared the risk of TB by the severity of DM had used a variety of markers to define the level of control of DM such as plasma glucose level, haemoglobin A1c level, types of complications, and use of insulin. However, poorly controlled diabetes patients had a higher TB risk than patients with mild and well-controlled diabetes in all studies (Figure 3a). Age-stratified analysis in each study showed that the effect of DM on TB was stronger among younger than older people although this association was statistically significant in only 2 of 5 studies (Figure 3b). Sex was not found to be an effect modifier of the association between DM and TB (Figure 3c). Three large population-based studies had conducted stratified analysis by ethnicity, country of origin, indigenous status, and TB incidence in country of origin. None of these studies showed an effect of these factors modifying the association between DM and TB (26, 28, 31).

Figure 4 shows the potential source of heterogeneity in the magnitudes of the association between DM and TB observed in the studies, grouped by population characteristics and study characteristics. Overall, heterogeneity in relative risk was reduced when the studies were grouped

according to background TB incidence and study quality. There was a linear trend in the association between background TB incidence and the effect of DM on TB, with the relative risk rising from 1.46 in low TB incidence countries (<15/100,000 person-years) to 3.96 in high TB incidence countries (>100/100,000 person-years) (p=0.036). However, this trend became statistically non-significant when controlled for the quality of studies (p=0.72). Effect of DM on TB differed by region, but regions except Asia and Europe included only one or two countries, which led to a large confidence interval. Studies in younger populations (median age <40) showed higher effect of DM on TB than studies in older populations (median age ≥40). Although this difference was not statistically significant, this is consistent with the results of age-stratified analyses. The strength of the association between DM and TB was lower in high-quality studies than that in low-quality studies (RR: 1.54 vs 3.83, p=0.001). This association remained statistically significant when adjusted for the effect of background TB incidence (RR 1.48 vs 3.39, p=0.04). Studies with shorter follow-up time, smaller sample size, and those that used self-report for diagnosis were associated with larger effect estimates of DM on TB risk. The funnel plot (Figure 5) shows an asymmetry of the reported effects of DM on TB. This is partly due to smaller studies showing larger effect estimates.

DISCUSSION

In comparison with the previous meta-analysis that was mainly based on one large cohort study that adjusted only for age, this study included six population-based large cohort studies that adjusted for the effect of several potential confounders. By excluding studies that did not establish DM diagnosis prior to developing TB, this study minimised potential reverse causality on the association between DM and TB, which made each study more comparable. This review also addressed the question of whether the risk of TB depends on the severity of DM.

Most studies demonstrated a dose-response association between the severity of DM and TB risk although a pooled estimate of this effect could not be calculated because each study used different markers for DM control level. Aside from DM markers presented in Figure 3, type 1 DM (T1DM) could be considered as a marker of severity since it often represents a more severe form of DM (29). Only two studies had investigated TB risk among people with T1DM (24, 28) and the relative risks observed in these studies were imprecise because the number of patients classified as T1DM was very small. A population-based historical cohort study in Taiwan that included 5195 T1DM patients showed that TB risk was 4.36 (95%CI; 2.43–7.36) times greater among T1DM than

general population controls matched by age, sex, and other comorbidities (30). This association was much stronger than the risk of TB in persons with T2DM compared to non-DM people (adjusted RR; 1.31 95%CI; 1.23–1.39) observed in a similar cohort study using the same database in Taiwan (31). Four of six studies included in this meta-analysis suggest that people with well-controlled DM were at lower risk than their non-DM counterparts (21, 23-25).

In a study that investigated the relationship between blood glucose levels and TB in HIV positive cohort of 12 western Pacific countries (32), there was a U-shaped relationship between glucose level and TB incidence, with the highest risk at both extremes. These findings may reflect the complicated role of BMI on the association between DM and TB. People with low glucose who are more likely to have a low BMI may be at higher risk of TB than people with well-controlled T2DM who are more likely to have a high BMI, in line with the evidence that higher BMI is an independent protective factor against TB (33, 34). In terms of age, there was a consistent trend of increasing TB risk in younger people with DM compared to older people with DM. It could be explained by higher proportion of younger diabetic people having T1DM (8). However, Kuo et al found a similar trend in a cohort study excluding T1DM, in which a stronger association of T2DM and TB were observed in people under the age of 40 years and a declining rate ratio in those over 40 years old. They suggested that elderly controls may have had an increased TB risk than younger ones, and this may dilute the apparent effect of DM. None of the other potential effect modifiers, such as sex, ethnicity, a country of origin, other comorbidities, and duration of DM were found to have a significant effect on the association between DM and TB. HIV status is another important factor strongly associated with TB, yet none of the studies included in this review investigated the effect of HIV status on the DM-TB association. In an HIV positive cohort (32), people whose glucose levels were >7 mmol/L had 1.34-fold risk of TB (95%CI 1.01-1.79) compared to those with a glucose level <7 mmol/L after adjusting for potential confounders. A systematic review that investigated the effect of HIV on DM-TB association in Africa (35) concluded that there have been very few studies and the data were disparate.

The heterogeneity in the observed DM-TB association among studies was mainly explained by differences in three factors: study quality, region, and background TB incidence. Among these, study quality was the key explanatory factor for the between-study variability in the estimates of effect of DM on TB. Although TB incidence was likely to be lower in countries where high-quality

studies were conducted, the effect of DM on TB differed by study quality after adjusting for TB incidence. Large cohort study design with minimum bias, longer follow-up period, and adequate adjustment for confounders showed modest effect estimates of DM on TB. Although the strength of the DM-TB association varies between regions, ethnic difference is unlikely to be a main determinant for heterogeneity, considering the results that ethnicity and a country of origin did not modify the effect of DM on TB in any of the studies. Alternatively, difference in health systems or health utilisation patterns may explain the regional heterogeneity. In this analysis, there is no strong evidence that background TB incidence affects the strength of the DM-TB association. In addition to the quality of studies, high TB incidence setting may be indirectly related to larger disparities in TB susceptibility or exposure between DM and non-DM populations. Since there is evidence that poverty is associated not only with TB but also with a higher incidence of DM, poorer glycaemic control, and more diabetic complications (36-38), a lower-income setting is more likely to have poorly controlled DM patients. Based on these results, we developed an explanatory model illustrating the relationships between factors and the strength of the effect of DM on TB (Figure 6). In this model, lower-income setting is a common factor related to higher TB incidence, younger age distribution, lower study quality, and poorer DM control; consequently, it can lead to a stronger effect of DM on TB risk.

One explanation for the asymmetric distribution of the study results in the funnel plots would be that smaller studies with statistically insignificant effects were not published in English-language journals. However, it is essential to evaluate whether the asymmetry was due to true heterogeneity between the studies included in the meta-analysis. The magnitude of association between DM and TB was smaller in high quality studies but higher in low-quality studies (Figure 7a). Similarly, studies conducted in countries with higher annual per-capita health expenditure (a proxy measure to define level of control of DM) tend to show a modest effect of DM on TB (Figure 7b). There was a linear association between study quality and the strength of the association between DM and TB ($p=0.026$) (Figure 8a). There was a weak linear association between health expenditure per capita and the strength of the association between DM and TB ($p=0.10$) (Figure 8b), and this trend was statistically significant when the analysis excluded low-quality studies ($p=0.04$) (Figure 8c). These results support our hypothetical model explaining between-study heterogeneity, and it may also explain the asymmetric distribution of the results shown in the funnel plots.

This study should be interpreted in light of several limitations. First, all studies were observational studies that are inherently at risk of biases. Differential misclassification of outcome (TB) might have occurred if doctors were more likely to screen DM patients for active TB. Selection bias would have occurred in studies that included only pulmonary TB (PTB) patients (9, 19, 22, 27). These studies might overestimate the effect of DM on TB risk since current findings consistently showed DM patients are more likely to develop PTB than extra-pulmonary TB compared to non-DM populations (25, 39-41). This may partly explain the result of meta-regression grouped by TB type: PTB group had a higher effect estimate (RR;3.63) than All-TB group (RR;2.08). Five studies relied exclusively on self-report for the diagnosis of DM (18-20, 22, 27), which could result in differential misclassification of exposure either by under-reporting or under-diagnosis of DM. A previous review reported that nearly half of adult DM patients globally were undiagnosed (42). In fact, meta-regression grouped by DM diagnosis method demonstrated a significantly higher effect estimate among studies based on self-report (RR;4.66, 95%CI;2.47-8.81) than those diagnosed based on laboratory data (RR;1.86 95%CI;0.90-3.86). This may imply that by using self-report, undiagnosed patients with mild asymptomatic DM were misclassified as non-DM while those with explicit symptoms and frequent medical treatment remained in the DM (self-report) group, which led to overestimating the effect of DM on TB. Second, the reported relative risks may have been confounded by unmeasured social and health risk factors such as BCG immunisation, contact with TB patients, or HIV status. Third, as this systematic review is restricted to studies reported in English, the risk of language bias could not be ruled out (43, 44). The asymmetric distribution seen in the funnel plot may suggest that studies showing statistically significant association between DM and TB were more likely to be published in English-language journals. Fourth, only including studies in middle and high-income countries may limit the generalizability of our results to low-income countries. Despite the use of comprehensive terms in several databases and the inclusion criteria allowing self-report as diagnosis of DM, we were unable to include any studies from Africa and South-east Asia where the large burden of TB lies. Studies from those countries were excluded because they did not establish DM diagnosis prior to detecting TB or did not adjust for age. However, most of the excluded studies conducted in low-income countries showed substantial effect of DM on TB risk, and our analyses (Figure 7, 8) in addition to our model (Figure 6) implied that lower-income setting is associated with higher effect of DM on TB risk. Fifth, the results from meta-regression should be carefully interpreted because they are in danger of ecological fallacy as summary data may not always reflect on individual level data. In addition, these analyses were

post-hoc and consequently at risk of over-interpretation. Despite these limitations, however, this meta-analysis showed a robust evidence of the association between DM and TB.

CONCLUSION

Based on this meta-analysis, if we assume there is a causal relationship between DM and TB and the observed RR of 1.5 is generalizable globally, as the global prevalence of DM is estimated as 8.5% (4), DM would account for 33% of active TB cases among people with DM, and 4.1% of all TB cases can be averted by prevention of DM globally. Our review also suggests that glycaemic control for DM patients would have a similar impact on prevention of TB, since people with well-controlled DM have similar risk of TB as non-DM populations. Indeed, Lee et al estimated that 7.5% (95%CI; 4.1%–11.5%) of all TB cases in Taiwan population would have been prevented if all DM patients had achieved good glycaemic control (23). Another option to prevent active TB would be testing for LTBI among DM patients and offering chemo-prevention with isoniazid for those with positive results. Although DM is associated with increased risk of active TB, it is still unclear whether DM increases primary TB infection or reactivation of LTBI, and previous studies did not provide clear evidence on the effectiveness of preventive therapy with isoniazid for DM people having LTBI (45, 46).

Evidence on the link between DM and TB has grown, yet there remain many uncertainties. To inform policy-makers on optimum management strategies for this dual epidemic, our findings suggest that research should continue to explore: (1) effect of DM on TB risk in the general population of LMICs with robust study design, (2) interaction of HIV on DM-TB association in countries with HIV epidemic, (3) interaction of nutritional status on DM-TB association, (4) effect of glycaemic control for DM among TB patients on TB treatment outcomes, (5) efficacy, effectiveness, and cost-effectiveness of LTBI screening for DM patients, followed by chemoprophylaxis for those with positive results.

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Table 1 Summary characteristics of study

Study	Country, Population	Period	Exposure (Diabetes Mellitus)	Outcome (Tuberculosis)	RR [i]	Study Quality[xiii]
Cohort Study						
Kim et al, 1995	South Korea, Civil servants N=839280	1988-1990	RPG [ii] ≥119 mg/dl at screening, followed by FPG [iii] ≥150 mg/dl and PPPG [iv] ≥180 mg/dl	PTB [v] determined by chest X-ray and/or sputum examination	3.58 [vi] (3.08-4.16)	S★★★ C★ O★★ Overall 6
John et al, 2001	India, Vellore, renal transplant recipients, N=1414	1986-1999	FPG>120 mg/dl or PPPG>200 mg/dl ; two elevated levels of either measurement	Clinical diagnosis and/or X-ray, AFB [vii], culture of affected tissue	2.24 (1.38-3.65)	S★★ C★★ O★★ Overall 6
Leung et al, 2008	Hong-Kong, Community-based health program, N=42,116	2000-2005	FPG≥7.0 mmol /litre and/or blood/plasma glucose determinants	microbiological and/or clinical	1.77 (1.41-2.24)	S★★★★ C★★ O★★★ Overall 9
Baker et al, 2012	Taiwan, NHIS [xii] N=17,715	2001-2004	self-report, ICD [viii] code or DM medication	ICD code on NHI [ix] database	2.09 (1.10-3.95)	S★★★★ C★★ O★★ Overall 8
Dobler et al, 2012	Australia, General population N=19855283	2001-2006	Self-report confirmed by health professional	Notification database of active TB case	1.48 (1.04-2.10)	S★★★★ C★★ O★★★ Overall 9
Chen et al, 2013	China, All residents in two rural counties, N=177529	2009-2011	Self-report	All type of TB based on national criterion	2.43 [x] (0.84-7.00)	S★★★★ C★★ O★★ Overall 8
Pealing et al, 2015	United Kingdom, General population, N=1664078	1990–2013	National Health Service (NHS) Read codes.	A list of NHS Read codes for all forms of tuberculosis	1.30 (1.01-1.67)	S★★★★ C★★ O★★★ Overall 9
Lee et al, 2016	Taiwan, Community-based health screening participants, N= 123546	2005-2012	Prescription of hypoglycemic drug or FPG ≥ 126 mg/dl	ICD9 + prescription of anti-TB treatment for ≥90d	1.70 (1.27-2.27)	S★★★★ C★★ O★★★ Overall 9
Case-control study						
Mori et al, 1992	United States, Native Americans in South Dakoda, N=92	1983-1989	FPG>7.8mmol/L or any glucose level >11.1 mmol/L or received diabetic treatment	Indian Health Service hospital and clinics charts	5.2 (1.22-22.1)	S★★★★ C★ E★★ Overall 7
Coker et	Russia, Residents in Samara	2003	Self-report	culture confirmed PTB	7.83	S★★★ C★★

al, 2006	N=668				(2.37- 25.89)	E★ Overall 6
Leegaard et al, 2011	Denmark, People in northern Denmark, N= 17224	1980-2008	DNRP[xi] validated algorithm, Prescription Database and Danish NHIS[xii] Registry	First time TB diagnosis in hospital records based on ICD	1.18 (0.96-1.45)	S★★★★ C★★ E★★ Overall 8
Jurcev-S et al, 2013	Croatia, People in seven randomly selected counties, N=600	2006-2008	Self-report	Culture positive PTB	2.38 (1.05-5.38)	S★★★ C★★ E★ Overall 6
Davis et al, 2017	Kazakhstan, People in four disperse regions, N=1600	2012-2014	Self-report	microbiological and/or clinical	13.96 (6.37-30.56)	S★★★ C★★ E★ Overall 6
Ndishimye et al, 2017	Romania, Patients in a clinical hospital, N=300	2014-2015	Self-report	PTB confirmed by WHO and national guideline	3.32 (1.36-8.08)	S★★ C★★ E★ Overall 5

[i] Relative Risk (Adjusted rate ratio in cohort studies and adjusted odds ratio in case-control studies on developing active TB comparing DM vs no DM), [ii] RPG; Random plasma glucose, [iii] FPG; Fasting plasma glucose, [iv] PPPG; Postprandial plasma glucose, [v] PTB; Pulmonary tuberculosis, [vi] Original article presented only crude RR; therefore, age-adjusted RR was calculated using Mantel-Haenszel weighting method, [vii] AFB; Acid-fast bacilli stain, [viii] ICD; International classification of diseases, [ix] NHI; National health insurance, [x] A pooled estimate was calculated using Mantel-Haenszel weighting method from the original data (Xiangtan: 1.31 (0.17-9.97), Danyang: 3.05 (0.88-10.55)), [xi] DNRP; Danish national registry of patients, [xii] NHIS; National health insurance service, [xiii] Study quality- S; Selection, C; Comparability, O; Outcome, E; Exposure, Overall score 8-9; high -7; low

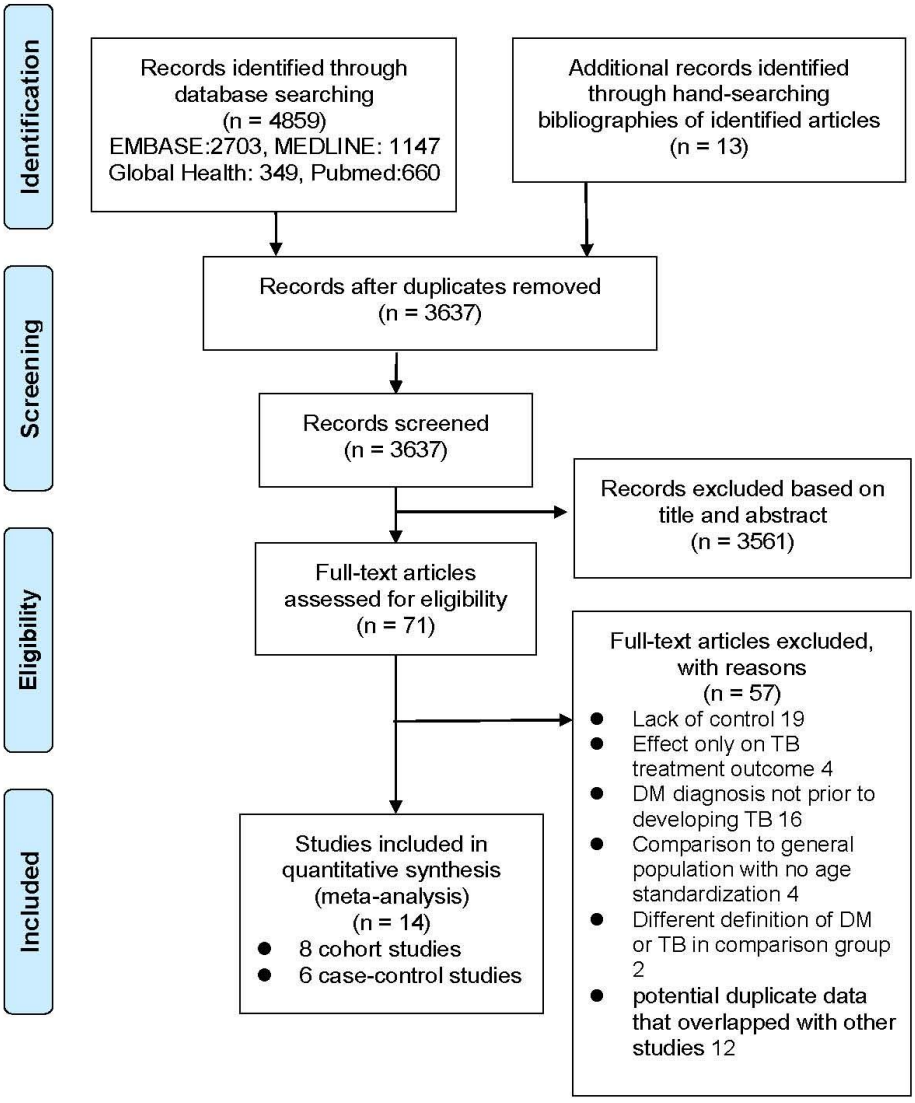


Figure 1 Study selection process

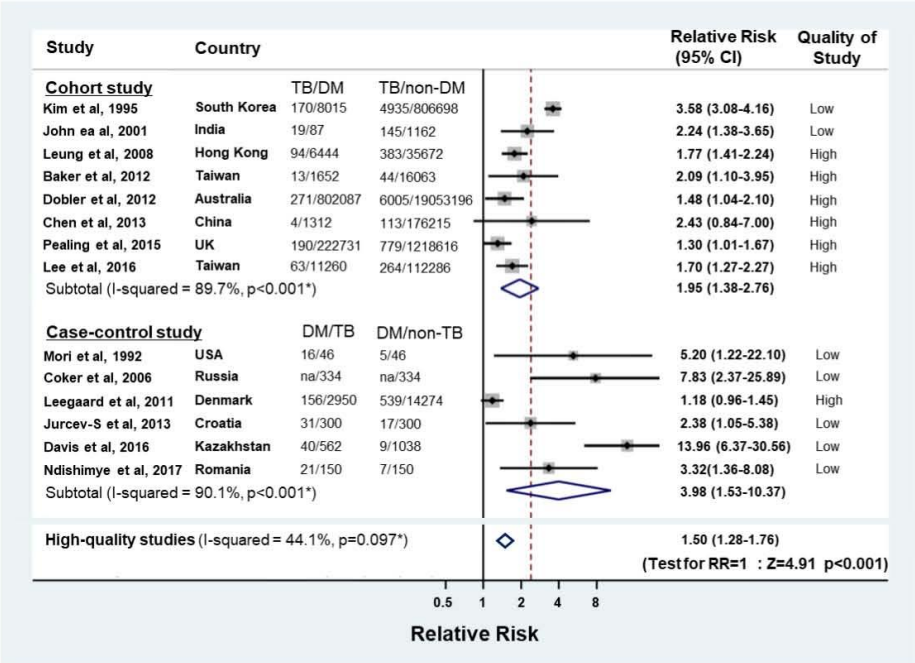


Figure 2 Estimates of effect of DM on active TB in each study and pooled relative risk in cohort studies, case-control studies, and high-quality studies

Relative Risk: Rate ratio in cohort studies and odds ratio in case-control studies, 95% CI: 95% confidence interval, P value*: Test of heterogeneity, na: data not available

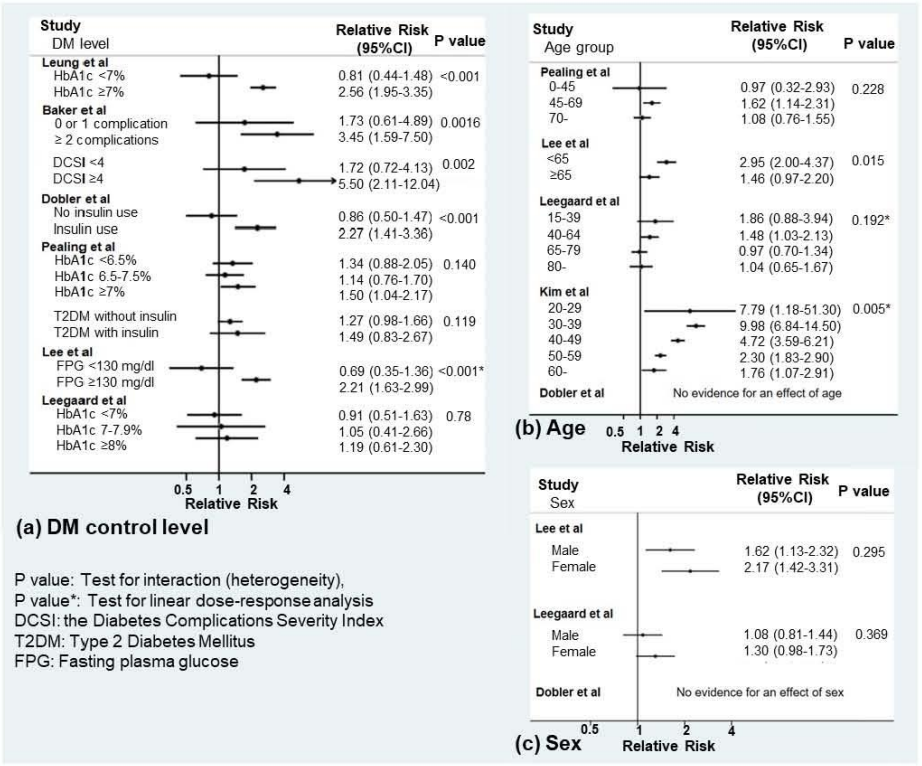


Figure 3 Stratum-specific association between DM and TB: level of control of DM (a), Age (b), and Sex (c)

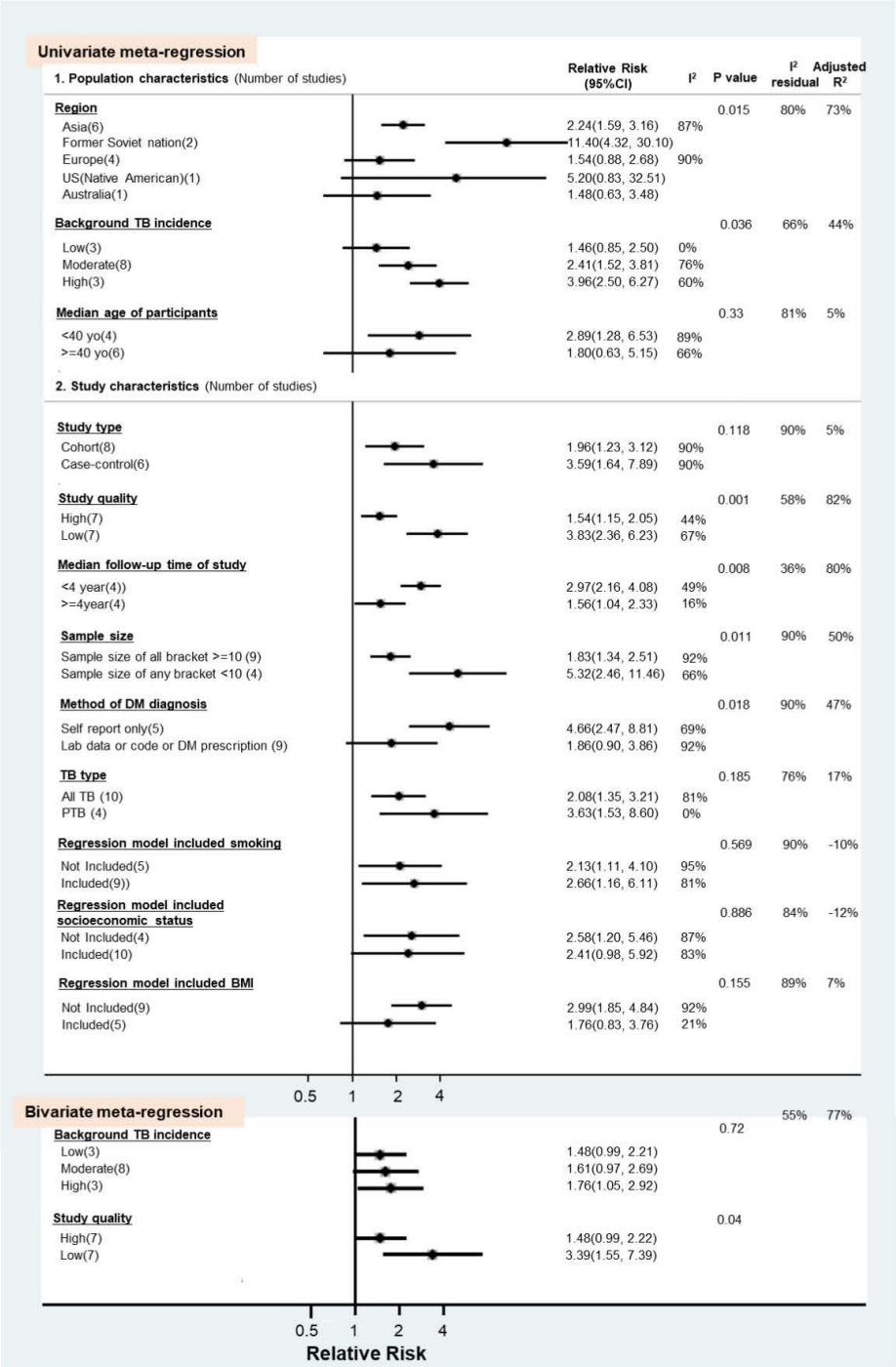
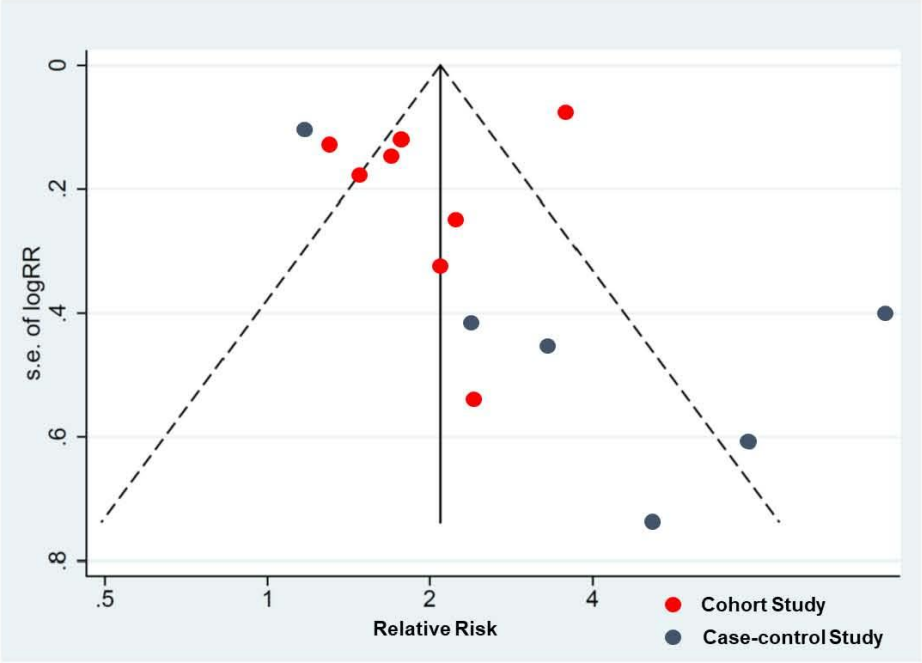


Figure 4 Estimated effect of DM on TB stratified by population characteristics and study characteristics

Background TB incidence (per 100,000 person-years): low <15, moderate 15-100, high >100, Study quality: high 8-9, low -7 (the numbers of stars in Newcastle-Ottawa Scale), I^2: % variation due to between-study heterogeneity in group computed from Der Simonian-Laird random effect model, P value: test of linear trend (meta-regression), I^2 residual: % residual variation due to heterogeneity, Adjusted R^2: Proportion of between-study variance, Bivariate meta-regression included only the background TB incidence and study quality in the model.



s.e of logRR: standard error of log(Relative Risk)

Figure 5 Funnel plot with pseudo 95% confidence limits of the studies included in meta-analysis

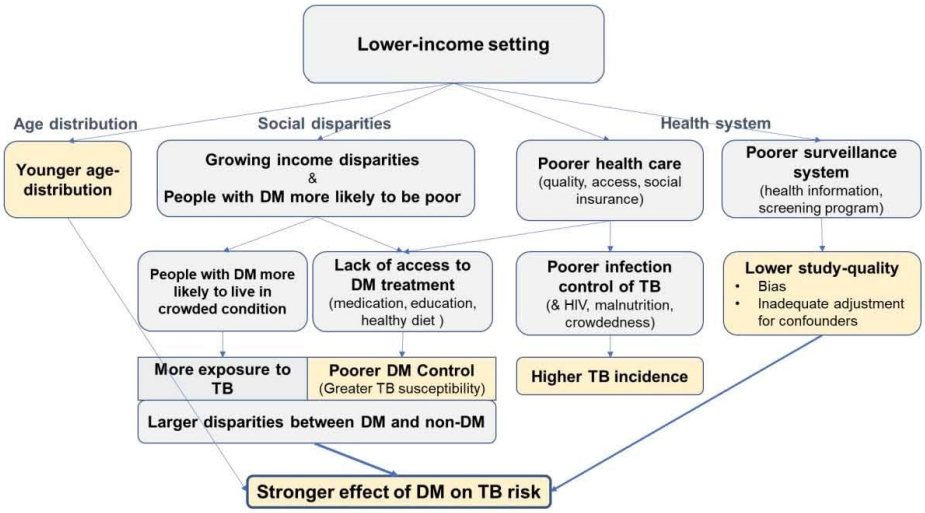
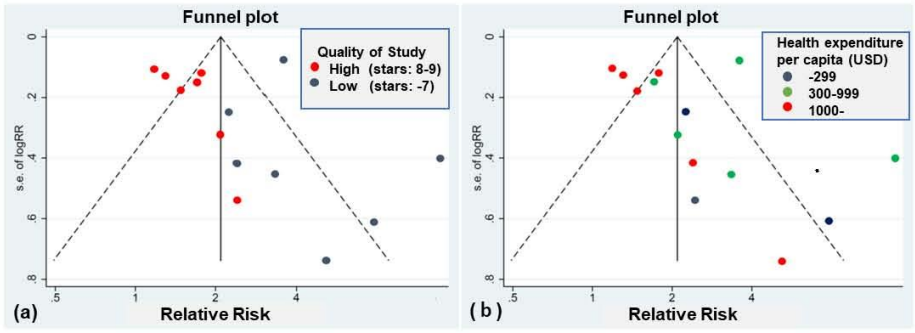


Figure 6 Relationships between factors and the strength of the effect of DM on TB



s.e of logRR: standard error of log (Relative Risk)

Figure 7 Funnel plots with pseudo 95% confidence limits of the studies, grouped by quality of study (a), and health expenditure per capita (b)

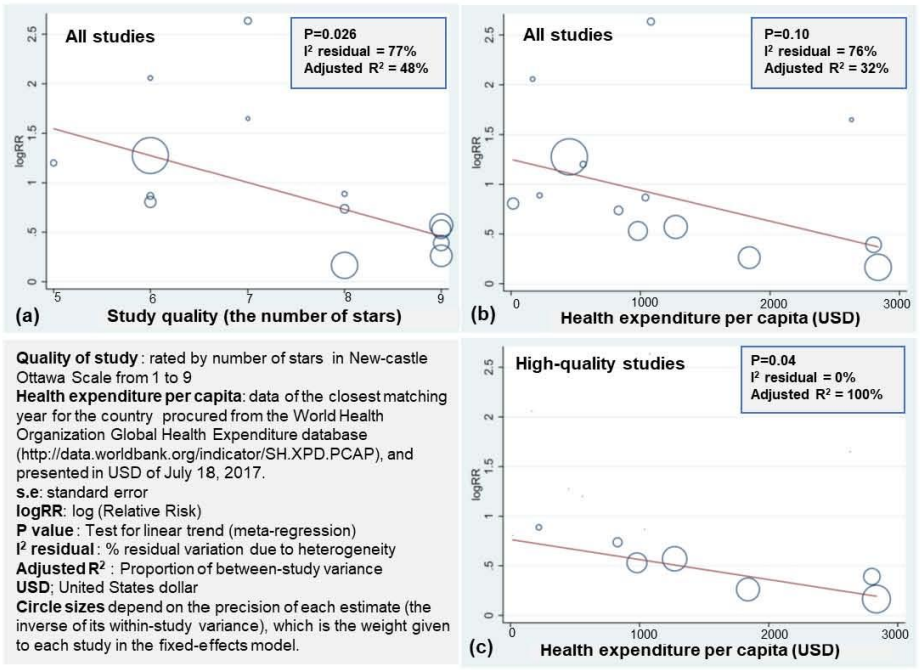


Figure 8 Association between study quality and estimated effect of DM on TB (a), and association between health expenditure per capita and estimated effect of DM on TB in all studies (b) and in high-quality studies (c)