Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies

Christie Y. Jeon*, **Megan B. Murray**

Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America

Funding: CYJ is supported by a departmental grant from the Department of Epidemiology at Harvard School of Public Health. The department had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Academic Editor: Brian Williams, World Health Organization, Switzerland

Citation: Jeon CY, Murray MB (2008) Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies. PLoS Med 5(7): e152. doi:10.1371/journal.pmed.0050152

Received: March 18, 2008
Accepted: June 3, 2008
Published: July 15, 2008

Abbreviations: CI, confidence interval; DM, diabetes mellitus; RR, relative risk; TB, tuberculosis

* To whom correspondence should be addressed. E-mail: chjeon@hsph.harvard.edu

ABSTRACT

Background

Several studies have suggested that diabetes mellitus (DM) increases the risk of active tuberculosis (TB). The rising prevalence of DM in TB-endemic areas may adversely affect TB control. We conducted a systematic review and a meta-analysis of observational studies assessing the association of DM and TB in order to summarize the existing evidence and to assess methodological quality of the studies.

Methods and Findings

We searched the PubMed and EMBASE databases to identify observational studies that had reported an age-adjusted quantitative estimate of the association between DM and active TB disease. The search yielded 13 observational studies ($n = 1{,}786{,}212$ participants) with 17,698 TB cases. Random effects meta-analysis of cohort studies showed that DM was associated with an increased risk of TB (relative risk = 3.11, 95% CI 2.27–4.26). Case-control studies were heterogeneous and odds ratios ranged from 1.16 to 7.83. Subgroup analyses showed that effect estimates were higher in non-North American studies.

Conclusion

DM was associated with an increased risk of TB regardless of study design and population. People with DM may be important targets for interventions such as active case finding and treatment of latent TB and efforts to diagnose, detect, and treat DM may have a beneficial impact on TB control.

The Editors' Summary of this article follows the references.

Introduction

Despite the availability of effective therapy, tuberculosis (TB) continues to infect an estimated one-third of the world's population, to cause disease in 8.8 million people per year, and to kill 1.6 million of those afflicted [1]. Current TB control measures focus on the prompt detection and treatment of those with infectious forms of the disease to prevent further transmission of the organism. Despite the enormous success of this strategy in TB control, the persistence of TB in many parts of the world suggests the need to expand control efforts to identify and address the individual and social determinants of the disease. Since the early part of the 20th century, clinicians have observed an association between diabetes mellitus (DM) and TB, although they were often unable to determine whether DM caused TB or whether TB led to the clinical manifestations of DM [2–6]. Furthermore, these reports did not address the issues of confounding and selection bias. More recently, multiple rigorous epidemiological studies investigating the relationship have demonstrated that DM is indeed positively associated with TB [7–11]. While the investigators suggested that the association reflects the effect of DM on TB, some controversy over the directionality of the association remains due to observations that TB disease induces temporary hyperglycemia, which resolves with treatment [12,13]. A causal link between DM and TB does not bode well for the future, as the global burden of DM is expected to rise from an estimated 180 million prevalent cases currently to a predicted 366 million by 2030 [14]. Experts have raised concerns about the merging epidemics of DM and TB [15–17], especially in low- to middle-income countries, such as India and China, that are experiencing the fastest increase in DM prevalence [18] and the highest burden of TB in the world [19]. Given the public health implications of a causal link between DM and TB, there is a clear need for a systematic assessment of the association in the medical literature. We undertook a systematic review to qualitatively and quantitatively summarize the existing evidence for the association between DM and TB, to examine the heterogeneity underlying the different studies, and to evaluate the methodological quality of the studies. As our aim was to summarize the effect of DM on TB, we did not include studies that investigated the reverse association.

Methods

We conducted our systematic review according to the guidelines set forth by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group for reporting of systematic reviews of observational studies (see Text S2 for the MOOSE Checklist) [20].

Search Strategy and Selection Criteria

We searched the PubMed database from 1965 to March 2007 and the EMBASE database from 1974 to March 2007 for studies of the association between DM and TB disease; our search strategy is detailed in Box 1. We also hand-searched bibliographies of retrieved papers for additional references and contacted experts in the field for any unpublished studies. Since we speculated that studies that examined the association between DM and TB may not have referred to the term "diabetes" in the title or abstract, we also searched for studies that examined any risk factors for active TB. We restricted our analysis to human studies, and placed no restrictions on language. We included studies if they were peer-reviewed reports of cohort, case-control, or cross-sectional studies that either presented or allowed computation of a quantitative effect estimate of the relationship between DM and active TB and that controlled for possible confounding by age or age groups. We also included studies that compared prevalence or incidence of DM or TB of an observed population to a general population as long as they had performed stratification or standardization by age groups. We excluded studies if they were any of the following: case studies and reviews; studies among children; studies that did not provide effect estimates in odds ratios, rate ratios, or risk ratios, or did not allow the computation of such; studies that did not adjust for age; studies that employed different methods for assessing TB among individuals with and without DM or for assessing DM among TB patients and controls; studies that investigated the reverse association of the impact of TB disease or TB treatment on DM; anonymous reports; and duplicate reports on previously published studies.

Box 1. Search Strategy to Identify Observational Studies on the Association of Diabetes and Active Tuberculosis

PubMed

MeSH terms

1. "tuberculosis"
2. "diabetes mellitus"
3. "cohort studies" OR "case-control studies" OR "cross-sectional studies" OR "epidemiologic studies" OR "follow-up studies" OR "longitudinal studies" OR "prospective studies" OR "retrospective studies"

Text terms

1. "tuberculosis"
2. "diabetes" OR "glucose intolerance" OR "glucose tolerance" OR "insulin resistance"
3. "chronic disease(s)" OR "non-communicable disease(s)"
4. "risk factor(s)"

Search strings (all inclusive):

1. 1 AND 2
2. 1 AND 3 AND 5
3. 1 AND 3 AND 6
4. 1 AND 3 AND 7
5. 4 AND 5 (for the year preceding 3/2/07 for articles that may not have been assigned MeSH terms)

EMBASE

Text terms

1. "tuberculosis", major subject
2. "diabetes mellitus"
3. "risk factor(s)"
4. "observational study" OR "longitudinal study" OR "prospective study" OR "case-control study" OR "cross-sectional study"

Search strings (all inclusive):

1. 1 AND 2
2. 1 AND 3
3. 1 AND 4

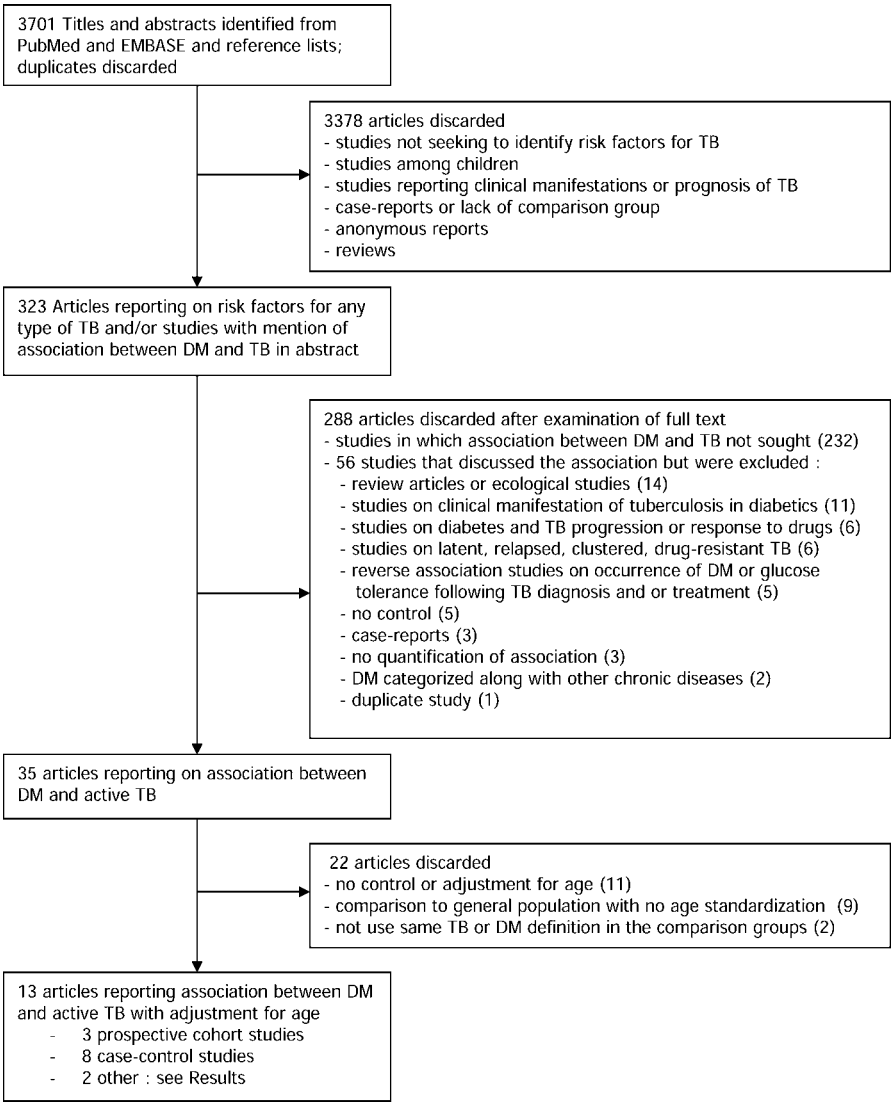

Figure 1. Flow Chart of Literature Search for Studies on the Association between Diabetes Mellitus and Active Tuberculosis
doi:10.1371/journal.pmed.0050152.g001

Data Extraction

The two investigators (CJ, MM) independently read the papers and extracted information on the year and country of the study, background TB incidence, study population, study design, number of exposed/unexposed people or cases/controls, definitions and assessment of DM and TB, statistical methods, effect estimates and their standard errors, adjustment and stratification factors, response rates, the timing of diagnosis of DM relative to that of TB, and the potential duplication of data on the same individuals. Differences were resolved by consensus. For the studies that did not directly report the background TB incidence, we obtained data for the closest matching year and state (or country) made available by public databases (WHO global tuberculosis database, http://www.who.int/globalatlas/dataQuery/; CDC Wonder, http://wonder.cdc.gov/TB-v2005.html).

Data Analysis

We separated the studies by study design and assessed heterogeneity of effect estimates within each group of studies using the Cochrane Q test for heterogeneity [21] and the I^2 statistic described by Higgins et al. [22]. We determined the 95% confidence intervals (CIs) for the I^2 values using the test-based methods [22]. We performed meta-analysis for computation of a summary estimate only for the study design (i.e., cohort) that did not show significant heterogeneity. Effect estimates of other study designs were not summarized due to significant heterogeneity. For those studies that reported age, sex, race, or region stratum-specific effects, we calculated an overall adjusted effect estimate for the study using the inverse-variance weighting method, then included this summary estimate in the meta-analyses and sensitivity analyses. We decided a priori to use the Dersimonian and Laird random effects method to pool the effect estimates across studies for the meta-analyses, because the underlying true effect of DM would be expected to vary with regard to underlying TB susceptibility and the severity of DM, and because it would yield conservative 95% confidence intervals [23].

In order to identify possible sources of heterogeneity and

Table 1. Summary of the 13 Observational Studies of Association between Diabetes and Active Tuberculosis Included in the Meta-analysis

Type of Study	Study	Country, Population	Study Period	Background TB Incidence[a]
Prospective cohort	Kim et al., 1995 [7]	South Korea, civil servants	1988–1990	306
	John et al., 2001 [32]	India, renal transplant patients in Vellore	1986–1999	168[c]
	Chen et al., 2006 [30]	Taiwan, renal transplant recipients in Taichung	1983–2003	66.7
Case-control	Mori et al., 1992 [34]	US, Oglala Sioux Indians in South Dakota	1986	90.9
	Buskin et al., 1994 [35]	US, residents seen at TB clinic in Washington	1988–1990	9
	Rosenman and Hall 1996 [36]	US, male residents registered at New Jersey Department of Health	Jan 1985, May 1987	9.5
	Pablos-Mendez et al., 1997 [8]	US, civilians in California (based on discharge records)	1991	17.3[c]
	Brassard et al., 2006 [31]	US, PharMetrics Database with $\geq$1 prescription for antirheumatic medication	September 1998–December 2003	5.6
	Coker et al., 2006 [37]	Russia, residents in the city of Samara	January 2003–December 2003	118[c]
	Jick et al., 2006 [33]	UK, General Practice Research Database	1990–2001	3
	Perez et al., 2006 [11]	US Residents of 15 Texas/Mexico border counties (based on discharge records)	1999–2001	13.1
Other[d]	Ponce-de-Leon et al., 2004 [9]	Mexico, civilians in Veracruz	March 1995–April 2003 for TB case accrual; 2005 for diabetes survey	28
	Dyck et al., 2007 [25]	Canada, registered Indians and other Saskatchewans	January 1986–December 2001 for TB case accrual; January 1991–December 1995 for diabetes survey	44

[a]Background incidence of TB per 100,000 person-years.
[b]Stratum-specific RRs were pooled by inverse-variance weighting method.
[c]Data obtained from external source.
[d]Other: Neither the study by Ponce-de-Leon et al. [9] or by Dyck et al. [25] were specified as prospective cohort, or case-control study. TB case accrual was conducted prospectively, while the underlying distribution of diabetes was determined from a separate registry during a period of time after the start of case accrual.
AFB, acid-fast bacilli stain; BMI, body mass index; CDC 1990, 1990 Case Definition for Tuberculosis by Center for Disease Control (US): http://www.cdc.gov/ncphi/disss/nndss/casedef/tuberculosis_1990.htm; CMV, cytomegalovirus; FBG, fasting blood glucose; ICD-9, International Statistical Classification of Diseases and Related Health Problems 9th edition; PCP, pneumocystis pneumonia; PPBG, postprandial blood glucose; NSAID, non-steroidal anti-inflammatory drug.
doi:10.1371/journal.pmed.0050152.t001

to assess the effect of study quality on the reported effect estimates, we performed sensitivity analyses in which we compared pooled effect estimates for subgroups categorized by background TB incidence, geographical region, underlying medical conditions of the population under study, and the following quality-associated variables: time of assessment of DM in relation to TB diagnosis, method of DM assessment (self-report or medical records versus laboratory tests), method of TB assessment (microbiologically confirmed versus other), adjustment for important potential confounders, and the potential duplication of data on the same individuals. To determine whether the effect estimates varied significantly by the above-mentioned factors, we performed univariate meta-regressions, in which we regressed the study-specific log-transformed relative risks (RRs) by the variables representing the study characteristics, weighting the studies by the inverse of the sum of within-study and between-study variance for all studies within the comparison. For background TB incidence, we created an ordinal variable, 1 representing $<$ 10/100,000 person-years to 3 representing $\geq$ 100/100,000 person-years. Coefficients of meta-regression represent differences in log-transformed RRs between the subgroups; we tested the significance of these coefficients by Student *t*-test, and significance was set at $p < 0.10$. We considered studies to be of higher quality if they specified that DM be diagnosed prior to the time of TB diagnosis; used blood glucose tests for diagnosis of DM; used a microbiological definition of TB; adjusted for at least age and sex; were cohort, nested case-control, or population-based case-control studies; or did not have the potential for duplication of data. As the average

Table 1. Extended.

Exposure	Outcome	Adjusted Variables
DM diagnosed as ≥119 mg/dl at screening, followed by FBG ≥150 mg/dl and PPBG ≥ 180 mg/dl	Pulmonary TB determined by X-ray	Age[b]
DM diagnosed as FBG >120 mg/dl or PPBG >200 mg/dl; or two elevated levels of either measurement	All TB diagnosed by X-ray, AFB, gastric juice, bronchoalveolar specimen, or culture of affected tissue	Age, chronic liver disease, other coexisting infections (CMV, PCP, nocardia, deep mycoses), immunosuppressive medications
DM diagnosis from medical chart	All TB diagnosed by (1) positive culture, (2) presence of granuloma in biopsy, (3) typical chest X-ray finding, or (4) clinical presentation consistent with TB and favorable response to treatment	Age, sex, dialysis duration, HBV and HCV infection, graft rejection >3, immunosuppressive medications
DM determined by antidiabetic treatment; or ≥11.1 mmol/l at screening or ≥7.8 mmol/l FBG	Clinically diagnosed TB, not otherwise specified	Age, sex, alcohol abuse, isoniazid therapy, residence
DM by self-report	All TB defined by CDC 1990	Age
DM by self-report	All TB diagnosed by positive culture, or physician's diagnosis with anti-TB medication	Age, sex, race
DM from medical chart coded as ICD-9 250.0–250.9	All TB coded as ICD-9 010–018	Age, sex, race[b], poor education, median income, health insurance, HIV-related conditions, chronic renal insufficiency, alcohol-related conditions, drug use
DM from medical chart coded as ICD-9 250.0–250.9	All TB coded as ICD-9 010–018	Age, sex, silicosis, chronic renal failure, hemodialysis, solid organ transplant, head and neck cancer, NSAIDs, steroids, Cox-2 inhibitors
DM by self-report	Pulmonary TB diagnosed by positive culture	Age, sex, relative with TB, drinking raw milk, assets, number of cohabiting persons, employment, smoking, alcohol, financial security, illicit drugs, history of imprisonment
DM determined by antidiabetic treatment	All TB treated with anti-TB medication	Age, sex, index date, amount of computerized medical history, glucocorticoid use, smoking, BMI, pulmonary disease, use of anti-rheumatic or immunosuppressive agents
DM from medical chart coded as ICD-9: 250.0 - 250.9	All TB coded as ICD-9 010–018	Age, sex, race, insurance, chronic renal failure, nutrition deficiency, income, education, residence at border[b]
DM previously diagnosed by a physician; or FBG ≥ 126 mg/dl or ≥200 mg/dl for random samples	All TB diagnosed by positive AFB or positive culture	Age[b], and standardized by sex
DM from medical chart coded as ICD-9: 250	All TB cases reported to Saskatchewan Health	Age[b], sex[b], race[b]

background incidence rate of TB did not exceed 2 per 100 person-years in any of the of the case-control studies that had not employed incidence density sampling, we assumed TB to be sufficiently rare that the odds ratios would estimate the risk ratios [24], and that it would therefore be valid to compute summary RR in the sensitivity analyses regardless of the measure of association and design of the study.

We explored possible effect modification by age by examining the three studies that reported results by age groups [7,9,25]. For this analysis, we graphed the stratum-specific estimates in a forest plot, and tested for heterogeneity of the effects within each study by the Q-test and I^2 value. We also performed meta-regression within each study in which we regressed the log-transformed RRs by the mid-points of the age-bands. For the unbound age group, ≥ 60 y, we added half the range of the neighboring age-band, or 5 y, to the cutoff. We computed the factor reduction in RR with 10 y increases in age, and reported the *p*-value for significance of trend.

We assessed publication bias using the Begg test and Egger test [26,27]. Statistical procedures were carried out using R version 2.5.1 [28]. 95% CI of the I^2 value was computed using the "heterogi" module in STATA version 10 [29].

Results

We identified and screened 3,701 papers by titles and abstracts; of these, 3,378 were excluded because they did not study risk factors for TB, were studies among children, were case reports, reviews, or studies of TB treatment outcome (Figure 1). Of the remaining 323 articles, 232 studies were excluded because they did not report on the association between DM and TB, and 56 studies were excluded because they were review articles (12) or ecological studies (2); studied the clinical manifestations of TB in people with diabetes (11); studied the association of DM and TB treatment outcome (6); assessed latent, relapsed, clustered, or drug-resistant TB as the outcome (6); studied the reverse association of the effect of TB on DM (5); had no comparison group (5); were case reports (3); did not give a quantitative effect estimate (3); had collapsed DM and other chronic diseases into a single covariate (2); or was a study that had been reported elsewhere (1). We contacted the authors of four papers that reported including DM in a multivariate analysis but that did not provide the adjusted effect estimate for DM; we included the papers of the two authors who responded and provided these adjusted estimates [30,31]. Further exclusion of studies that

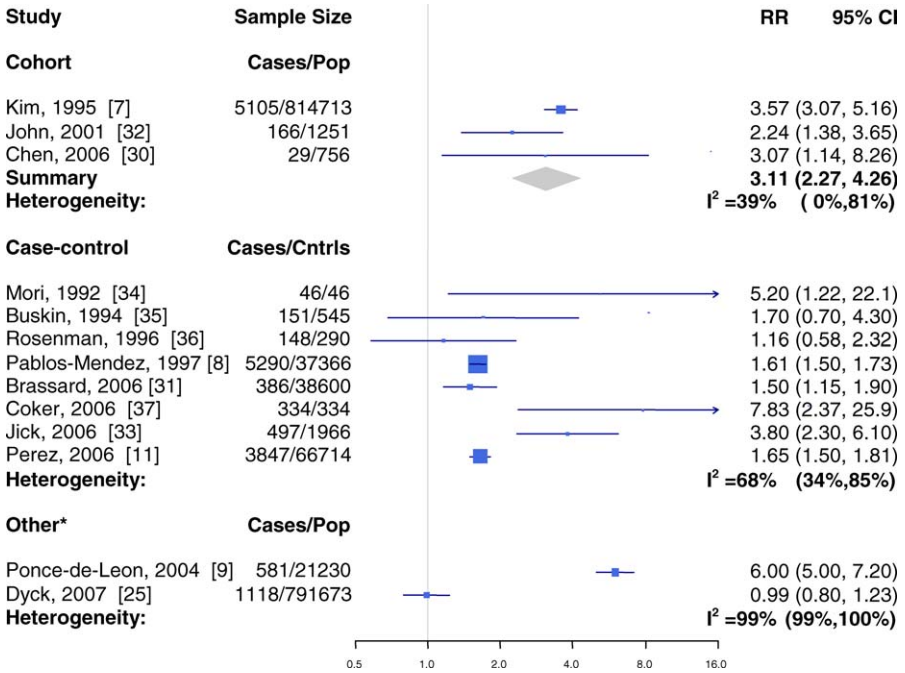

Figure 2. Forest Plot of the 13 Studies That Quantitatively Assessed the Association between Diabetes and Active Tuberculosis by Study Designs

Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% CIs. Arrows indicate that the bars are truncated to fit the plot. The diamond is centered on the summary RR of the cohorts studies, and the width indicates the corresponding 95% CI. *Other: The studies by Ponce-de-Leon et al. [7] and Dyck et al. [25] were not specified as prospective cohort or case-control. TB case accrual occurred prospectively, while the underlying distribution of diabetes was determined during a different time period after baseline.

doi:10.1371/journal.pmed.0050152.g002

did not adjust for age (11), studies that used a general population as the comparison group for TB incidence or DM prevalence without standardization by age (9), and studies that used different methods for ascertaining TB in the people with diabetes and control group (2), left 13 eligible studies. These included three prospective cohort studies [7,30,32], eight case-control studies [8,11,31–37], and two studies for which study design could not be classified as either cohort or case control, as TB case accrual occurred prospectively while the distribution of diabetes in the population was assessed during a different time period after baseline [9,25]. The studies were set in Canada (1), India (1), Mexico (1), Russia (1), South Korea (1), Taiwan (1), the UK (1), and the US (6), and were all reported in English and conducted in the last 15 y. Two of the cohort studies were among renal transplant patients [30,32], and three of the case-control studies were hospital-based or based on discharge records [8,11,35]. The studies are summarized in Table 1.

Figure 2 summarizes the adjusted effect estimates of the 13 studies categorized by the study design. We found substantial heterogeneity of effect estimates from studies within each study design; between-study variance accounted for 39% of the total variance among cohort studies, 68% of the total variance among case-control studies, and 99% of the total variance in the remaining two studies. Despite this heterogeneity, the forest plot shows that DM is positively associated with TB regardless of study design, with the exception of the study by Dyck et al. [25]. DM was associated with a 3.11-fold (95% CI 2.27–4.26) increased risk of TB in the cohort studies. Of note, the study conducted within a nontransplant population provided greater weight (63%) to the summary estimate than the other two cohort studies combined. The effect estimates in the remaining studies were heterogeneous and varied from a RR of 0.99 to 7.83.

Table 2 shows that there is an increased risk of active TB among people with diabetes regardless of background incidence, study region, or underlying medical conditions in the cohort. In the sensitivity analyses, we noticed that the strength of association increased from a RR of 1.87 to a RR of 3.32 as background TB incidence of the study population increased from $<$ 10/100,000 person-years to $\geq$ 100/100,000 person-years, but the trend was not significant (trend p = 0.229). Effect estimates were heterogeneous within each category of background TB incidence (I^2 = 60%, 98%, and 76% from highest to lowest background TB incidence category).

We also found that the associations of DM and TB in the study populations from Central America [9], Europe [33,37], and Asia [7,30,32] ($RR_{CentralAm}$ = 6.00, RR_{Europe}=4.40, RR_{Asia} = 3.11) were higher than those of North American studies [8,11,33,34–36] (RR_{NA} = 1.46) (meta-regression $p_{CentralAm}$ = 0.006, p_{Europe} = 0.004, p_{Asia} = 0.03). Among North American studies, the pooled estimate of the relative risks for Hispanics from two studies [8,11] was higher (RR = 2.69) than that of non-Hispanics from the same study [8] and other North American studies (RR = 1.23) (meta-regression p = 0.060) (Table 2).

In general, stratification of the studies by quality-associated variables did not reduce the heterogeneity of effect estimates. Nonetheless, DM remained positively associated with TB in all strata. Studies that explicitly reported that DM was diagnosed prior to TB showed stronger associations (RR = 2.73) [7,31–34] than those that did not establish the temporal order of DM and TB diagnosis (RR = 2.10) [8,9,11,25,30,35–

Table 2. Results of Sensitivity Analyses to Identify Sources of Heterogeneity in the Magnitudes of the Association between Diabetes and Active Tuberculosis

Category of Variables	Variables of Study Characteristics	Study Characteristics (No. of Studies)	Summary RR	95% CI	I^{2a}	95% CI for I^2	*p*-Value Heterogeneity[b]	*p*-Value Meta-regression[c]
Population	Background TB incidence[d]	≥100 (3)	3.32	2.13–5.17	60%	0%–89%	0.081	0.229
		≥10 and <100 (6)	2.22	1.42–3.48	98%	96%–98%	<0.001	—
		<10 (4)	1.87	1.09–3.20	76%	34%–91%	0.006	—
	Region	Central America (1)	6.00	5.00–7.20	N/A	N/A	N/A	0.006
		Europe (2)	4.40	2.49–7.79	17%	0%–57%	0.272	0.004
		Asia (3)	3.11	2.27–4.26	39%	0%–81%	0.196	0.030
		All North America (7)	1.46	1.25–1.71	74%	43%–88%	0.001	Ref
		North America: Hispanics (2)[e]	2.69	2.27–3.19	80%	13%–95%	0.026	0.060[f]
		North America: American Indians (2)[g]	1.85	0.34–10.19	82%	23%–96%	0.019	0.913[f]
		North America: non-Hispanics, non-American Indians (5)	1.23	1.13–1.32	0%	0%–79%	0.488	Ref [f]
	Underlying conditions	Transplant or arthritis patients (3)	1.86	1.28–2.70	44%	0%–83%	0.169	0.688
Quality assessment	DM pre-dated TB	Explicitly stated (5)	2.73	1.68–4.44	89%	77%–95%	<0.001	0.483
		Unclear (8)	2.10	1.41–3.12	97%	95%–98%	<0.001	—
	DM diagnosis	Laboratory test (4)	3.89	2.52–6.03	88%	72%–95%	<0.001	0.051
		Self-report (3)	2.26	0.82–6.23	73%	9%–92%	0.025	0.692
		Medical records (6)	1.61	1.33–1.95	85%	69%–93%	<0.001	Ref
	TB diagnosis	Microbiological (4)[h]	4.91	3.41–7.06	63%	0%–87%	0.045	0.015
		Other (9)	1.66	1.39–1.98	79%	61%–89%	<0.001	—
	Control selection (case-control studies)	Nested or population-based (4)	3.36	1.52–7.42	84%	59%–94%	<0.001	0.321
		Hospital or discharge data based (3)	1.62	1.54–1.72	0%	0%–90%	0.920	—
	Adjustment factors	Age+sex (10)	2.25	1.59–3.19	96%	94%–97%	<0.001	N/A
		Age+sex+race (7)[i]	2.05	1.35–3.12	97%	96%–98%	<0.001	N/A
		Age+sex+immunosuppressive drugs (4)	2.37	1.45–3.87	76%	34%–91%	0.006	N/A
		Age+sex+alcohol (3)	3.51	1.10–11.23	78%	30%–93%	0.010	N/A
		Age+sex+socioeconomic status (3)	1.66	1.45–1.91	71%	0%–91%	0.033	N/A
		Age+sex+smoking (2)	4.40	2.49–7.29	17%	0%–57%	0.272	N/A
	Potential for duplicate data on same patient	No (11)	2.60	1.62–4.18	95%	93%–97%	<0.001	0.324
		Yes (2)	1.62	1.53–1.72	0%	N/A[j]	0.683	—

RR indicates risk ratio, hazard ratio, or odds ratio.
[a]Percentage of total variance due to between-study heterogeneity.
[b]*p*-Value for Cochrane Q test of heterogeneity within subgroup.
[c]*p*-Value for the difference in ln(RR) from meta-regression weighting the studies by the inverse of the sum of within and between-study variance.
[d]Background TB incidence per 100,000 person-years.
[e]Results for analysis restricted to Hispanics in the two US studies by Pablos-Mendez et al. [8] and Perez et al. [11].
[f]Meta-regression *p*-values for these three rows are for comparison within the North American studies.
[g]Results for analysis restricted to American Indians in studies by Mori et al. [34] and Dyck et al. [25].
[h]Positive for acid-fast bacilli in sputum, or for *M. tuberculosis* in culture; includes results for culture positive or smear-positive TB from Kim et al. [7].
[i]Includes studies that had adjusted for race, as well as studies with ethnically homogeneous populations.
[j]Test-based confidence interval for $I^2 = 0\%$ with one degree of freedom could not be computed with STATA or manually.
N/A, not applicable.
doi:10.1371/journal.pmed.0050152.t002

37], although the difference was not significant (meta-regression $p = 0.483$). Associations were stronger in studies that classified DM exposure through empirical testing (RR = 3.89) [7,9,32,34] rather than medical records (RR = 1.61) (meta-regression $p = 0.051$) [8,11,25,30,31,33]; and in those that confirmed TB status using microbiological diagnosis (RR = 4.91) [7,9,35,37] than in the studies that did not confirm by microbiological tests (RR = 1.66) (meta-regression $p = 0.015$) [8,11,25,30–34,36]. Among case-control studies, those that were nested in a clearly identifiable population or were population-based also reported stronger associations (RR = 3.36) [31,33,34,37] than those that used hospital based controls (RR = 1.62) [8,11,37], but the difference was not significant (meta-regression $p = 0.321$). Studies that had adjusted for smoking showed stronger associations (RR = 4.40) [33,37], while studies in which an individual may have contributed more than one observation to the data revealed weaker associations (RR = 1.62) [8,11]. Although these results suggest that higher-quality studies gave stronger estimates of association, we also found that the association was weaker in studies that adjusted for socioeconomic status (RR = 1.66) (Table 2) [8,11,37].

Figure 3 presents the summary measures of the association between DM and TB by age group based on the data from the three studies that presented age-stratified RRs. The plots from Kim et al. [7] and Ponce-de-Leon et al. [9] demonstrate stronger associations of DM and TB under the age of 40 y and declining RR with increasing age in age groups over 40 y

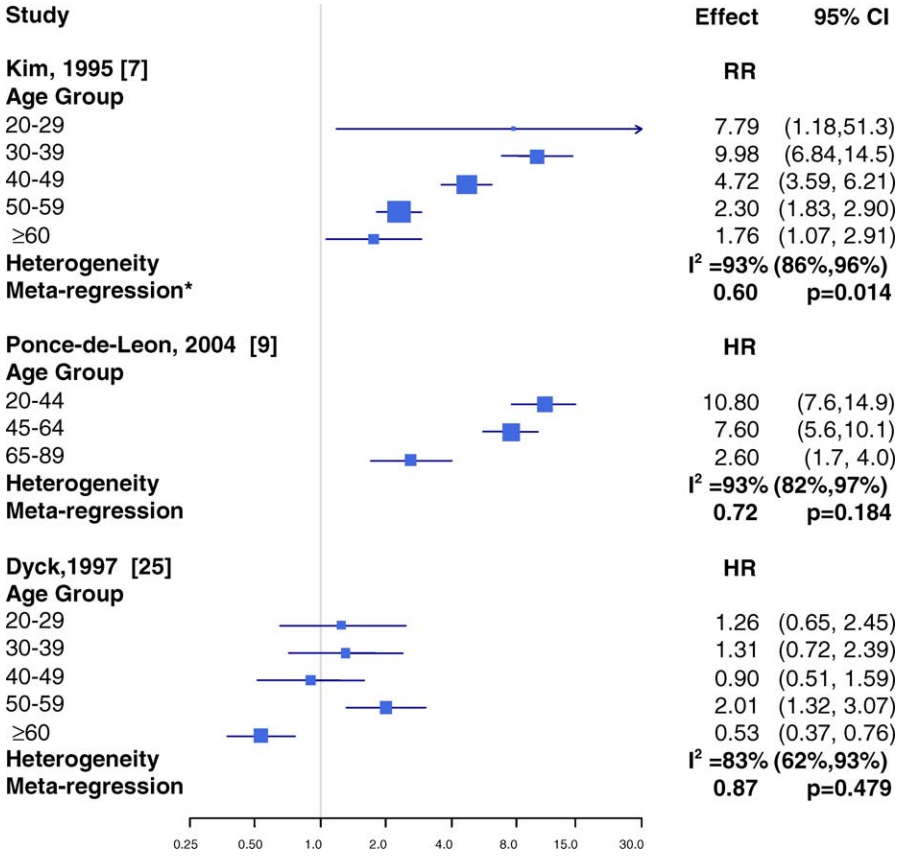

Figure 3. Forest Plot of Age-Specific Association between Diabetes and Active Tuberculosis from Kim et al. [7], Ponce-de-Leon et al. [9], and Dyck et al. [25]

Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate 95% CI of the effect estimates. Arrows indicate that the bars are truncated to fit the plot. *Meta-regression: Factor reduction in RR with 10 y increase in age; p-values are given for test of linear trend. HR, hazard ratio.

doi:10.1371/journal.pmed.0050152.g003

(trend $p_{\text{Kim}} = 0.014$, $p_{\text{Ponce-de-Leon}} = 0.184$). Each 10 y increase in age was associated with a 0.6-fold reduction in magnitude of association in the study by Kim et al. [7]. This trend was not apparent in the study by Dyck et al. (Figure 3) [25].

Both the Egger test and Begg test for publication bias were insignificant ($p = 0.37$, $p = 0.14$).

Discussion

Summary of Findings

Our meta-analysis shows that DM increases the risk of TB, regardless of different study designs, background TB incidence, or geographic region of the study. The cohort studies reveal that compared with people who do not have diabetes, people with diabetes have an approximately 3-fold risk of developing active TB. Higher increases in risk were seen among younger people, in populations with high background TB incidence, and in non-North American populations. Heterogeneity of strengths of association may reflect true geographic/ethnic differences in severity of DM, transmission dynamics of TB, and the distribution of effect modifiers such as age, or it may be due to differences in study methodology or rigor. Given this heterogeneity of the RR estimates and the fact that all the cohort studies were conducted in Asia, we note that the summary estimate may not be applicable to other populations and study types. While the included studies covered a relatively broad range of geographic areas, there were none from Africa, where TB incidence is high. Nonetheless, a positive association of DM and TB was noted in two African studies [38,39] and several other studies that we excluded from the meta-analysis [10,40–42], as well as in a previous narrative review [43] of the association of DM and TB. Unlike the previous review, our systematic review identified five additional studies that had examined the association of DM and TB, computed a pooled summary estimate among the cohort studies, and determined important sources of heterogeneity through rigorous sensitivity analyses.

Public Health Implication

With an estimated 180 million people who have diabetes, a figure expected to double by year 2030, it is clear that DM constitutes a substantial contributor to the current and future global burdens of TB. For example, if we assume a RR of 3 and a prevalence of DM in Mexico of 6%, we can conclude that DM accounts for 67% of active TB cases among people with diabetes, and 11% of cases among the entire Mexican population (see Text S1 for the calculation) [44]. The contribution of DM to the burden of TB may be even higher in countries such as India and China where the incidence TB is greater and mean age is lower. In fact, a recent study by Stevenson et al. determined that DM accounts for 80.5% of

incident pulmonary TB among people with diabetes, and 14.8% of incident TB in the total population in India [16]. The population-attributable risk for diabetes is comparable to that of HIV/AIDS; while HIV/AIDS is strong risk factor for TB (RR_{HIV} = 6.5–26 [45], approximately 2–9 times greater than the RR_{DM} estimated in this study), it is a less prevalent medical condition (33 million people infected in 2007 [46], approximately 5–6 times less prevalent than DM). Given these figures it may be puzzling to observe a decrease in TB in those areas that have experienced a growing burden of DM. We attribute this observation to negative confounding by factors such as improved nutrition and TB control measures in the areas of increasing DM such as India and China. Were these other factors to remain the same, we would expect to see a TB incidence trend reflecting that of DM in accordance with the positive association.

Biological Plausibility

Numerous studies have presented convincing biological evidence in support of the causal relationship between DM and impaired host immunity to TB. Studies in animal models have demonstrated that diabetic mice experimentally infected with *M. tuberculosis* have higher bacterial loads compared to euglycemic mice, regardless of the route of inoculation of *M. tuberculosis* [47,48]. Compared to euglycemic mice, chronically diabetic mice also had significantly lower production of interferon-γ (IFN-γ) and interleukin-12 (IL-12) and fewer *M. tuberculosis* antigen (ESAT-6)-responsive T cells early in the course of *M. tuberculosis* infection, marking a diminished T helper 1 (Th1) adaptive immunity, which plays a crucial role in controlling TB infection [48]. In experimental studies of human plasma cells, high levels of insulin have been shown to promote a decrease in Th1 immunity through a reduction in the Th1 cell to Th2 cell ratio and IFN-γ to IL-4 ratio [49]. Additionally, an ex vivo comparison study of production of Th1 cytokines showed that nonspecific IFN-γ levels were significantly reduced in people with diabetes compared to controls without diabetes [50]. Another study indicated a dose–response relationship; levels of IFN-γ were negatively correlated with levels of HbA1c (a measure of serum glucose levels over time in humans) [51]. Furthermore, neutrophils from people with diabetes had reduced chemotaxis and oxidative killing potential than those of nondiabetic controls [52], and leukocyte bactericidal activity was reduced in people with diabetes, especially those with poor glucose control [53]. Taken together, these studies strongly support the hypothesis that DM directly impairs the innate and adaptive immune responses necessary to counter the proliferation of TB.

Limitations

There are several potential limitations to this study. Our analysis was based on estimates derived from observational studies that are vulnerable to confounding by variables associated with both DM and TB. To address the issue of potential confounding, we performed a sensitivity analysis in which we reported separate summary estimates for the studies that adjusted for important potential confounders and those that did not. Studies that controlled for socioeconomic status in a multivariable model found that the adjusted effect of DM was reduced, but not eliminated. Crude effect estimates were not provided in two of the larger studies that adjusted for socioeconomic status, thus the direction of bias cannot be determined. The three studies that did report both crude and the adjusted estimates [33,34,37] found that the adjusted RRs for DM were higher. Although we could not exclude the possibility of residual confounding by unmeasured confounders in these observational studies, such as other chronic diseases that often coexist with diabetes, we found that the effect of DM on TB risk persisted even after adjustment for multiple potential confounders that are likely to be correlated with unmeasured factors.

Eight of the studies included in this meta-analysis were case-control studies. Control selection strategies included sampling from hospitals, discharge records, department of health records, the general population, and the cohort in which the study was nested. Sampling controls from hospital or discharge records may have introduced a Berkson bias—a selection bias that can occur when both the exposure and the outcome are associated with attendance at a health-care facility from which cases and controls are recruited [54]. Since DM can lead to multiple health problems, the prevalence of DM is likely to be higher among persons attending clinics or being admitted to hospitals than it is in the general population. This bias would be expected to result in an underestimation of the effect of DM on TB, an expectation that was consistent with our finding that studies using hospital-based controls reported lower effect estimates [54]. Other sources of potential bias include misclassification of either exposure or outcome, such as may have occurred in studies that did not employ laboratory tests to diagnose DM or TB. When we restricted our analysis to studies that used glucose tests to determine DM status, we found that effect estimates were higher than in the studies that relied on less-rigorous methods, consistent with our expectation of a bias toward the null among studies that nondifferentially misclassify the exposure. Studies that utilized glucose tests to classify the exposure may also have reported higher RRs of TB among people with diabetes, since they may have identified undiagnosed people with diabetes who remained untreated and therefore may have had higher glycemic levels that those who self-reported their status. Those studies that confirmed TB through microbiological diagnosis also reported stronger associations, suggesting that diabetes may have a stronger impact on smear-positive and thus transmissible forms of TB. Our result underscores the conclusion by Stevenson et al. that DM accounts for a greater proportion of smear-positive TB than of other forms [17]. In short, we found that magnitudes of association varied by the quality of the studies; at the same time, variations may have been influenced by differences in population characteristics that are correlated with quality-associated variables.

Another important limitation of our systematic review is that most of the studies we included failed to examine age as an effect modifier of the relationship between DM and TB. The studies by Kim et al. [7] and Ponce-de-Leon et al. [9] found that estimates varied markedly by age, with substantially higher estimates among younger people. This finding may be explained by heterogeneity of the individuals without diabetes between the age groups. Because baseline glucose tolerance is lower in older persons without diabetes, elderly controls may have had an elevated risk of TB compared to younger ones [55], thus reducing the apparent effect of DM. It is possible that younger people with diabetes might have had type I diabetes, a more severe form of diabetes with a juvenile

onset; however, because most studies did not distinguish between type I and type II diabetes we cannot conclude whether the effect modification by age would have been due to differences in types of diabetes. Notably, the study by Dyck et al. [25] did not demonstrate this trend in the age-specificity of the effect of DM on TB and in fact showed a negative association among the elderly. The authors of the study note that results may have been biased by differential mortality in the elderly since individuals with diabetes who would have been most at risk for TB would have already died. Moreover, this study also differed from the others in that it relied on medical records rather than laboratory tests to determine DM status, and it had not included DM occurring in the last six of the 16 y during which TB case accrual occurred.

Conclusions

In summary, we found consistent evidence for an increased risk of TB among people with diabetes despite heterogeneity in study design, geographic area, underlying burden of TB, assessment of exposure and outcome, and control of potential confounders. Data from these human studies are consistent with emerging information on the biological mechanisms by which hyperglycemia may affect the host immune response to TB. Our findings suggest that TB controls programs should consider targeting patients with diabetes for interventions such as active case finding and the treatment of latent TB and, conversely, that efforts to diagnose, detect, and treat DM may have a beneficial impact on TB control. We also recommend further studies investigating how TB risk varies by type, duration, and severity of DM, for a more thorough understanding of the association that could be translated to a clear public health message.

Supporting Information

Text S1. Calculation of Attributable Risk Fraction of TB among Patients with Diabetes and Population-Attributable Risk Fraction of TB Due to Diabetes

Found at doi:10.1371/journal.pmed.0050152.sd001 (17 KB DOC).

Text S2. MOOSE Checklist

Found at doi:10.1371/journal.pmed.0050152.sd002 (61 KB DOC).

Acknowledgments

We thank Sasha Appleton, Alexandra Belcher, Kosuke Kawai, Hsien-Ho Lin, Milena Petranovic, Sasha Pichugin, Eva Schernhammer, and Krzysztof Trzcinski for their help in translating non-English articles. We also thank Taliser Avery and Alexandra Belcher for their assistance in the computerized and manual literature search.

Author contributions. CYJ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. CYJ and MBM were responsible for study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. CYJ performed the statistical analysis. MBM supervised the study.

References

1. World Health Organization (2007) Tuberculosis Fact Sheet. Fact Sheet No. 104. Available: http://www.who.int/mediacentre/factsheets/fs104/en/print.html. Accessed 25 September 2007.
2. Banyai A (1931) Diabetes and pulmonary tuberculosis. Am Rev Tuberc 24: 650–667.
3. Root H (1934) The association of diabetes and tuberculosis. New Engl J Med 210: 1–13.
4. Boucot KR, Dillon ES, Cooper DA, Meier P, Richardson R (1952) Tuberculosis among diabetics: the Philadelphia survey. Am Rev Tuberc 65: 1–50.
5. Nichols GP (1957) Diabetes among young tuberculous patients; a review of the association of the two diseases. Am Rev Tuberc 76: 1016–1030.
6. Silwer H, Oscarsson PN (1958) Incidence and coincidence of diabetes mellitus and pulmonary tuberculosis in a Swedish county. Acta Med Scand Suppl 335: 1–48.
7. Kim SJ, Hong YP, Lew WJ, Yang SC, Lee EG (1995) Incidence of pulmonary tuberculosis among diabetics. Tuber Lung Dis 76: 529–533.
8. Pablos-Mendez A, Blustein J, Knirsch CA (1997) The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. Am J Public Health 87: 574–579.
9. Ponce-De-Leon A, Garcia-Garcia Md Mde L, Garcia-Sancho MC, Gomez-Perez FJ, Valdespino-Gomez JL, et al. (2004) Tuberculosis and diabetes in southern Mexico. *Diabetes Care* 27: 1584–1590.
10. Alisjahbana B, van Crevel R, Sahiratmadja E, den Heijer M, Maya A, et al. (2006) Diabetes mellitus is strongly associated with tuberculosis in Indonesia. Int J Tuberc Lung Dis 10: 696–700.
11. Perez A, Brown HS 3rd, Restrepo BI (2006) Association between tuberculosis and diabetes in the Mexican border and non-border regions of Texas. Am J Trop Med Hyg 74: 604–611.
12. Oluboyo PO, Erasmus RT (1990) The significance of glucose intolerance in pulmonary tuberculosis. Tubercle 71: 135–138.
13. Basoglu OK, Bacakoglu F, Cok G, Sayiner A, Ates M (1999) The oral glucose tolerance test in patients with respiratory infections. Monaldi Arch Chest Dis 54: 307–310.
14. World Health Organization (2006) Diabetes fact sheet No. 312. Available: http://www.who.int/mediacentre/factsheets/fs312/en/index.html. Accessed 12 March 2008.
15. Restrepo BI (2007) Convergence of the tuberculosis and diabetes epidemics: Renewal of old acquaintances. Clin Inf Dis 45: 436–438.
16. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, et al. (2007) DM and tuberculosis: the impact of the DM epidemic on tuberculosis incidence. BMC Public Health 7: 234.
17. Dixon B (2007) Diabetes and tuberculosis: an unhealthy partnership. Lancet Infect Dis 7: 444.
18. Wild S, Sicree R, Roglic G, King H, Green A (2004) Global prevalence of diabetes: Estimates for the year 200 and projections for 2030. Diabetes Care 27: 1047–1053.
19. WHO (2007) Global tuberculosis control: surveillance, planning, financing. WHO report 2007. WHO/HTM/TB/2007.376. Geneva: WHO. Available: http://www.who.int/tb/publications/global_report/2007/en/index.html. Accessed 10 June 2008.
20. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, et al. (2000) Meta-analysis of observational studies in epidemiology: A proposal for reporting. JAMA 283: 2008–2012.
21. Cochran WG (1954) The combination of estimates from different experiments. Biometrics 10: 101–129.
22. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in meta-analyses. Stat Med 21: 1539–1558.
23. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177–188.
24. Greenland S, Thomas DC (1982) On the need for the rare disease assumption in case-control studies. Am J Epidemiol 116: 547–553.
25. Dyck RF, Klomp H, Marciniuk DD, Tan L, Stang MR, et al. (2007) The relationship between diabetes and tuberculosis in Saskatchewan. Can J Public Health 98: 55–59.
26. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088–1101.
27. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629–634.
28. R Development Core Team (2007) R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing. Available: http://www.R-project.org.
29. StataCorp (2007) Stata Statistical Software: Release 10. College Station (Texas): StataCorp LP.
30. Chen CH, Lian JD, Cheng CH, Wu MJ, Lee WC, et al. (2006) *Mycobacterium tuberculosis* infection following renal transplantation in Taiwan. Transpl Infect Dis 8: 148–156.
31. Brassard P, Kezouh A, Suissa S (2006) Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis 43: 717–722.
32. John GT, Shankar V, Abraham AM, Mukundan U, Thomas PP, et al. (2001) Risk factors for post-transplant tuberculosis. Kidney Int 60: 1148–1153.
33. Jick SS, Lieberman ES, Rahman MU, Choi HK (2006) Glucocorticoid use, other associated factors, and the risk of tuberculosis. Arthritis Rheum 55: 19–26.
34. Mori MA, Leonardson G, Welty TK (1992) The benefits of isoniazid chemoprophylaxis and risk factors for tuberculosis among Oglala Sioux Indians. Arch Intern Med 152: 547–550.
35. Buskin SE, Gale JL, Weiss NS, Nolan CM (1994) Tuberculosis risk factors in adults in King County, Washington, 1988 through 1990. Am J Public Health 84: 1750–1756.
36. Rosenman KD, Hall N (1996) Occupational risk factors for developing tuberculosis. Am J Ind Med 30: 148–154.
37. Coker R, McKee M, Atun R, Dimitrova B, Dodonova E, et al. (2006) Risk factors for pulmonary tuberculosis in Russia: case-control study. BMJ 332: 85–87.

38. Lienhardt C, Fielding K, Sillah JS, Bah B, Gustafson P, et al. (2005) Investigation of the risk factors for tuberculosis: A case-control study in three countries in West Africa. Int J Epidemiol 34: 914–923.
39. Mugusi F, Swai AB, Alberti KG, McLarty DG (1990) Increased prevalence of diabetes mellitus in patients with pulmonary tuberculosis in Tanzania. Tubercle 71: 271–276.
40. Abe T, Iinuma Y, Ando M, Yokoyama T, Yamamoto T, et al. (2003) NRAMP1 polymorphisms, susceptibility and clinical features of tuberculosis. J Infect 46: 215–220.
41. Al Kubaisy W, Al Dulayme A, Hashim DS (2003) Active tuberculosis among Iraqi schoolchildren with positive skin tests and their household contacts. East Mediterr Health J 9: 675–688.
42. Tocque K, Bellis MA, Beeching NJ, Syed Q, Remmington T, et al. (2001) A case-control study of lifestyle risk factors associated with tuberculosis in Liverpool, North-West England. Eur Respir J 18: 959–964.
43. Stevenson CR, Critchley JA, Forouhi NG, Roglic G, Williams BG, et al. (2007) Diabetes and the risk of tuberculosis: a neglected threat to public health. Chronic Illn 3: 228–245.
44. World Health Organization (2000) WHO Global InfoBase. Mexico Encuesta Nacional de Salud 2000: tomo 2 la salud de los adultos. Available: http://www.who.int/infobase/reportviewer.aspx?rptcode=ALL&uncode=484&dm=2&surveycode=101056a1. Accessed 12 March 2008.
45. Lienhardt C, Rodrigues LC (1997) Estimation of the impact of the human immunodeficiency virus infection on tuberculosis: tuberculosis risks revisited? Int J Tuberc Lung Dis 1: 196–204.
46. UNAIDS (2007) AIDS epidemic update 2007. UNAIDS/07.27E / JC1322E. Available: http://data.unaids.org/pub/EPISlides/2007/2007__epiupdate__en.pdf. Accessed 12 March 2008.
47. Yamashiro S, Kwakami K, Uezu K, Kinjo T, Miyagi K, et al. (2005) Lower expression of Th1-related cytokines and inducible nitric oxide synthase in mice with streptozotocin-induced diabetes mellitus infected with *Mycobacterium tuberculosis*. Clin Exp Immunol 139: 57–64.
48. Martens GW, Arikan MC, Lee J, Ren F, Greiner D, et al. (2007) Tuberculosis susceptibility of diabetic mice. Am J Respir Cell Mol Biol 37: 518–524.
49. Viardot A, Grey ST, Mackay F, Chisholm D (2007) Potential antiinflammatory role of insulin via the preferential polarization of effector T cells toward a T helper 2 phenotype. Endocrinology 148: 346–353.
50. Stalenhoef JE, Alisjahbana B, Nelwan EJ, van der Ven-Jongekrijg J, Ottenhoff THM, et al. (2008) The role of interferon-gamma in the increased tuberculosis risk in type 2 diabetes mellitus. Eur J Clin Microbiol Infect Dis 27: 97–103.
51. Tsukaguchi K, Okamura H, Ikuno M, Kobayashi A, Fukuoka A, et al. (1997) [The relation between diabetes mellitus and IFN-gamma, IL-12 and IL-10 productions by CD4+ alpha beta T cells and monocytes in patients with pulmonary tuberculosis]. Kekkaku 72: 617–622.
52. Delamaire M., Maugendre D, Moreno M, Le Goff MC, Allannic H, et al. (1997) Impaired Leucocyte functions in diabetic patients. Diabet Med 14: 29–34
53. Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Nechemias C, et al. (1982) Infection and diabetes: The case for glucose control. Am J Med 72: 439–450.
54. Feinstein AR, Walter SD, Horwitz RI (1986) An analysis of Berkson's bias in case-control studies. J Chron Dis 39: 495–504.
55. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, et al. (1998) Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. Adults: The Third National Health and Nutrition Examination Survey, 1988–1994. Diabetes Care 21: 518–524.

Editors' Summary

Background. Every year, 8.8 million people develop active tuberculosis and 1.6 million people die from this highly contagious infection that usually affects the lungs. Tuberculosis is caused by *Mycobacterium tuberculosis*, bacteria that are spread through the air when people with active tuberculosis cough or sneeze. Most infected people never become ill—a third of the world's population is actually infected with *M. tuberculosis*—because the human immune system usually contains the infection. However, the bacteria remain dormant within the body and can cause disease many years later if host immunity declines because of increasing age or because of other medical conditions such as HIV infection. Active tuberculosis can be cured by taking a combination of several antibiotics every day for at least six months, and current control efforts concentrate on prompt detection and carefully monitored treatment of people with active tuberculosis to prevent further transmission of the bacteria.

Why Was This Study Done? Despite this control strategy, tuberculosis remains a major health problem in many countries. To reduce the annual number of new tuberculosis cases (incidence) and the number of people with tuberculosis (prevalence) in such countries, it may be necessary to identify and target factors that increase an individual's risk of developing active tuberculosis. One possible risk factor for tuberculosis is diabetes, a condition characterized by high blood sugar levels and long-term complications involving the circulation, eyes and kidneys, and the body's ability to fight infection. 180 million people currently have diabetes, but this number is expected to double by 2030. Low- to middle-income countries (for example, India and China) have the highest burden of tuberculosis and are experiencing the fastest increase in diabetes prevalence. If diabetes does increase the risk of developing active tuberculosis, this overlap between the diabetes and tuberculosis epidemics could adversely affect global tuberculosis control efforts. In this study, the researchers undertake a systematic review (a search using specific criteria to identify relevant research studies, which are then appraised) and a random effects meta-analysis (a type of statistical analysis that pools the results of several studies) to learn more about the association between diabetes and tuberculosis.

What Did the Researchers Do and Find? From their search of electronic databases, the researchers found 13 observational studies (nonexperimental investigations that record individual characteristics and health outcomes without trying to influence them in any way) that had examined whether diabetes mellitus increases the risk of active tuberculosis. Diabetes was positively associated with tuberculosis in all but one study, but the estimates of how much diabetes increases the risk of developing active tuberculosis were highly variable, ranging from no effect to an increased risk of nearly 8-fold in one study. The variability may represent true differences between the study populations, as higher increases in risk due to diabetes was found in studies conducted outside of North America, including Central America, Europe, and Asia; or it may reflect differences in how well each study was done. This variability meant that the researchers could not include all of the studies in their meta-analysis. However, the three prospective cohort studies (studies that follow a group of individuals with potential risk factors for a disease over time to see if they develop that disease) that they had identified in their systematic review had more consistent effects estimates, and were included in the meta-analysis. This meta-analysis showed that, compared to people without diabetes, people with diabetes had a 3-fold increased risk of developing active tuberculosis.

What Do These Findings Mean? These findings support the idea that diabetes increases the risk of tuberculosis, a biologically plausible idea because, in experimental and clinical studies, diabetes was found to impair the immune responses needed to control bacterial infections. The 3-fold increased risk of tuberculosis associated with diabetes that the meta-analysis reveals suggests that diabetes may already be responsible for more than 10% of tuberculosis cases in countries such as India and China, a figure that will likely increase as diabetes becomes more common.

However, the estimate of this impact is based on three cohort studies from Asia; other studies suggest that the extent of the impact due to diabetes may vary by region and ethnicity. In populations where diabetes affects the risk of tuberculosis to a similar or greater extent, global tuberculosis control might benefit from active case finding and treatment of dormant tuberculosis in people with diabetes and from increased efforts to diagnose and treat diabetes.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0050152.

- The US National Institute of Allergy and Infectious Diseases provides information on all aspects of tuberculosis
- The US Centers for Disease Control and Prevention provide several fact sheets and other information resources about tuberculosis
- The World Health Organization provides information (in several languages) on efforts to reduce the global burden of tuberculosis, including information on the Stop TB Strategy and the 2008 report Global Tuberculosis Control—Surveillance, Planning, Financing
- The US Centers for Disease Control and Prevention provides information for the public and professionals on all aspects of diabetes
- The US National Institute of Diabetes and Digestive and Kidney Diseases also provides information about diabetes (in English and Spanish)