Forecasting the impact of diabetes mellitus on tuberculosis disease incidence and mortality in India

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Background In context of the rapidly expanding diabetes mellitus (DM) epidemic in India and slowly declining tuberculosis (TB) incidence, we aimed to estimate the past, current, and future impact of DM on TB epidemiology.

Methods An age-structured TB-DM dynamical mathematical model was developed and analyzed to assess the DM-on-TB impact. The model was calibrated using a literature review and meta-analyses. The DM-on-TB impact was analyzed using population attributable fraction metrics. Sensitivity analyses were conducted by accommodating less conservative effect sizes for the TB-DM interactions, by factoring the age-dependence of the TB-DM association, and by assuming different TB disease incidence rate trajectories.

Results In 1990, 11.4% (95% uncertainty interval (UI) = 6.3%-14.4%) of new TB disease incident cases were attributed to DM. This proportion increased to 21.9% (95% UI = 12.1%-26.4%) in 2017, and 33.3% (95% UI = 19.0%-44.1%) in 2050. Similarly, in 1990, 14.5% (95% UI = 9.5%-18.2%) of TB-related deaths were attributed to DM. This proportion increased to 28.9% (95% UI = 18.9%-34.1%) in 2017, and 42.8% (95% UI = 28.7%-53.1%) in 2050. The largest impacts originated from the effects of DM on TB disease progression and infectiousness. Sensitivity analyses suggested that the impact could be even greater.

Conclusions The burgeoning DM epidemic is predicted to become a leading driver of TB disease incidence and mortality over the coming decades. By 2050, at least one-third of TB incidence and almost half of TB mortality in India will be attributed to DM. This is likely generalizable to other Asian Pacific countries with similar TB-DM burdens. Targeting the impact of the increasing DM burden on TB control is critical to achieving the goal of TB elimination by 2050.

Although tuberculosis (TB) remains a public health concern globally, several countries are disproportionately affected by TB [1]. India harbors the largest number of individuals with TB worldwide, with at least twice as many cases as any other country [1]. In 2016, 2.8 million incident TB disease cases (27% of global TB incidence) and 435,000 TB deaths (26% of global TB deaths) were estimated in India [1].

TB disease incidence is affected by key risk factors such as diabetes mellitus (DM), HIV, under-nutrition, and smoking [2]. In 2017, 73 million Indians were
living with DM at a prevalence of 8.8% (95% confidence interval (CI) = 6.7%-10.9%) [3]. India was projected to account for the highest number of DM cases globally by 2045 at 134 million cases [3]. With India burdened by both TB and DM, their synergetic relationship is a major public health concern. A number of TB-DM epidemiological studies have been conducted in this country [4-9], with recent data reporting high DM prevalence among TB patients [10].

DM increases the risk of TB infection [11] and disease [12-14], and has adverse impacts on TB treatment outcomes (eg, DM increases the risk of mortality during TB treatment, TB relapse, and possibly multidrug resistant TB) [15-20]. Several biological mechanisms appear to explain the synergetic TB-DM association [21-33]. For example, the hypothesis that DM impairs the innate and adaptive immune responses, such as interferon-C (IFN-c), necessary to prevent the proliferation of TB, is supported by existing studies [13,28,30]. Studies showed that, compared to people with no DM, IFN-c levels were significantly reduced in people with DM [30], and that IFN-c levels were negatively associated with glycated hemoglobin levels [31].

A recent study of TB-DM interactions indicated large potential impact for DM on TB incidence including both direct (eg, DM increasing the risk of onset of TB disease) and indirect effects (eg, onward transmission of TB from people with and without DM) [34]. The study concluded that the impact of DM on TB epidemiology could be underestimated, if assessed using more conventional population attributable fraction (PAF) approaches such as Levin's formula [35], that capture only the direct impact of DM on TB [34].

Against this background, we aimed to estimate the past, current, and future impact of DM on TB epidemiology in India using a dynamical mathematical model. A strength of this study is that it accounts for the different pathways in which DM affects TB natural history and treatment outcomes, and incorporates a detailed quantitative assessment of the effect sizes of each of the DM-on-TB effects. The study also factors the projected rise of the DM epidemic in India over the coming decades, and assesses both the direct and indirect population impacts of DM on TB. The TB-DM model was applied to India to demonstrate the utility of our approach in a country highly burdened with both diseases, however, can be implemented in additional countries.

METHODS

We constructed an age-structured deterministic compartmental model to characterize the impact of DM on TB epidemiology in India by extending a recently developed analytical approach [34]. The model was also designed based on a recently developed conceptual framework for TB-DM interactions [34]. The model was coded and analyzed in MATLAB R2015a [36].

Mathematical model

The model is described by a system of coupled nonlinear differential equations stratifying the Indian population by age group, TB infection status, TB infection stage, TB disease form, TB treatment status, TB recovery status, and DM status. Details of the model can be found in the Online Supplementary Documents (Appendix S1 and S2 in the Online Supplementary Document).

The population was stratified into 20 5-year age bands representing the age cohort 0-99 years. Upon infection, TB progression was stratified into the two stages: latent-slow TB infection (LSI) and latent-fast TB infection (LFI). TB disease was stratified into the three clinically-relevant forms: smear-positive pulmonary (SP-PTB), smear-negative pulmonary (SN-PTB), and extra-pulmonary (EP-TB) [37,38]. The proportion of individuals developing each infection and disease form was age-dependent, and only the pulmonary forms were considered infectious. Treatment was assumed to last for six-months reflecting the directly-observed treatment short-course (DOTS) therapy [39].

Individuals with DM followed a distinct TB natural history from that of non-DM individuals—TB natural history was modulated by specific effects of having concurrent DM (Figure S1 in the Online Supplementary Document). Based on empirical evidence, DM was assumed to affect TB natural history and treatment outcomes through 10 different pathways [34]. The effects, their definitions, their effect sizes, and the evidence supporting them are summarized in Table 1 and discussed in Appendix S2.2 in Online Supplementary Document.

Briefly, compared to non-DM individuals, DM increased susceptibility to TB infection (Effect 1—Susceptibility), proportion of TB infections entering LFI vs LSI states (Effect 2—Fast progression), proportion of those
Table 1. Key assumptions for the effects of diabetes mellitus (DM) on tuberculosis (TB) natural history and treatment outcomes

| Effect                          | Description                                                                 | Effect Size | Range for Uncertainty Analysis | Sources                                                                 |
|---------------------------------|-----------------------------------------------------------------------------|-------------|--------------------------------|-------------------------------------------------------------------------|
| Effect 1—Susceptibility         | DM increases susceptibility to TB infection                                  | 1.50        | 1.0-2.2                        | Lognormal [40], [11]                                                    |
| Effect 2—Fast progression       | DM increases the proportion of TB infections entering latent-fast state as opposed to latent-slow state | 1.25        | 1.0-1.32                       | Lognormal (95% CI: 1.18-1.32)                                          |
| Effect 3—Reactivation           | DM increases the rate of developing TB disease among those with latent TB infection | 1.96        | 1.00-3.25                      | Normal                                                                  |
| Effect 4—Latent reinfection     | DM increases the susceptibility to TB reinfection among those with latent TB infection | 2.11        | 1.76-2.51                      | Lognormal [40], [4]                                                    |
| Effect 5—Smear positivity       | DM increases the proportion of new PTB disease cases progressing to SP-PTB as opposed to SN-PTB | 0.82 ±25%  | Uniform                        | Estimate based on weighted average of existing data [19]                |
| Effect 6—Disease infectiousness | DM increases the infectiousness of PTB (SP-PTB and SN-PTB) for untreated and treated TB disease cases | 1.46        | 1.00-2.00                      | Uniform                                                                  |
| Effect 7—TB mortality           | DM reduces the proportion of successful treatment among those with DM undergoing TB treatment | 2.11        | 1.76-2.51                      | Evaluation of existing literature [12]                                   |
| Effect 8—Treatment failure      | DM reduces the proportion of successful treatment among those with DM undergoing TB treatment | 1.80        | 1.40-2.30                      | Lognormal [40]                                                          |
| Effect 9—Recovery               | DM reduces the rate of TB recovery for those who recover naturally or due to treatment | 1.00        | 1.00-1.00                      | Uniform                                                                  |
| Effect 10—Cured reinfection     | DM reduces the rate of TB recovery for those who recover naturally or due to treatment | 1.80        | 1.40-2.30                      | Lognormal [40]                                                          |

Developing SP-PTB (vs SN-PTB) for those with pulmonary TB disease (Effect 5—Smear positivity), and TB infectiousness among those with pulmonary TB disease (Effect 6—Disease infectiousness). Furthermore, compared to non-DM individuals, DM increased the risk of TB-related mortality (Effect 7—TB mortality), reduced the proportion of successful treatment among those undergoing TB treatment (Effect 8—Treatment failure), delayed the resolution of TB disease (Effect 9—Recovery), and increased susceptibility to TB reinfection after recovery (Effect 10—Cured reinfection).

Amongst those with DM comparative to without, susceptibility to develop TB disease among those with LSI (Effect 3—Reactivation), and susceptibility to TB reinfection among those with LSI (Effect 4—Primary reinfection), were set as having no effect, as the impacts of these pathways were captured by Effect 2—Fast progression (Appendix S2.2 in the Online Supplementary Document). Also, given heterogeneity of evidence [20], the proportion of successful treatment among those with DM undergoing TB treatment (Effect 8—Treatment failure) was set as equal to those without DM undergoing TB treatment (Appendix S2.2 in Online Supplementary Document).

**Data sources and model fitting**

TB natural history model parameters (in absence of DM) were based on available empirical evidence [37], or through model fitting to empirical data. Table S1 in Online Supplementary Document lists the parameter values and their sources.

The key assumptions for the effect sizes of the 10 DM-on-TB effects were based mostly on pooled evidence from systematic reviews and/or meta-analyses, or derived from specific observational studies (Table 1 and Appendix S2.2 in Online Supplementary Document). Given heterogeneities and uncertainties around the exact effect sizes, we opted for a conservative approach whereby each effect size was modest, or set at the null value if the evidence is conflicting or not firmly established (ie, DM has no effect on TB). For example, the effect size for Effect 2—Fast progression was set as derived using an effect size of only 2.00 for the TB-DM association – based on a conservative meta-analysis that pooled studies of different study designs (Appendix S2.2 in Online Supplementary Document) [12]. The effect size for Effect 7—TB mortality was based on a recent meta-analysis estimating a pooled mean crude odds ratio (OR) of 2.11 across 48 studies [20]. Despite evidence suggesting that previous TB disease could increase the risk of developing DM [49], we opted not to account for this bi-directionality given that cur-

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rent evidence is not yet conclusive for this effect. Therefore, our estimates for the impact of the TB-DM interactions on TB epidemiology are more likely to underestimate the impact, rather than overestimate it.

The model was fitted using the following India-specific data: TB-incidence and mortality rates as reported in the World Health Organization (WHO) Global Health Observatory data repository [50], national and age-specific DM prevalence as reported by the International Diabetes Federation [3,51-55], age-specific DM prevalence distribution as reported by the nationally-representative Indian Council of Medical Research-India Diabetes study [56], and demographics as reported in the database of the Population Division of the United Nations Department of Economic and Social Affairs [57]. TB contact and case-detection rates were derived by model fitting to the above data.

**TB-DM synergy metric**

We estimated the impact of DM on each of TB disease incidence and mortality between 1990 and 2050 by calculating the “true” PAF [34], ie, the proportion of each of TB incidence and mortality that is directly (etiologically) and indirectly (such as onward transmission) attributed to DM (Appendix S3 in Online Supplementary Document). In contrast with Levin’s PAF [35] which only estimates the direct population impact of DM on TB disease, “true” PAF (below noted only as PAF) was estimated for each of TB incidence and mortality as the proportional reduction between the measures in a scenario where the synergy in the TB-DM relationship is active, compared to a scenario where the synergy is inactive. We assessed the impact of DM on TB epidemiology for each of the DM effects in combinations and individually.

**Uncertainty analysis**

A multivariate uncertainty analysis was conducted factoring the uncertainty in our knowledge of the DM-on-TB effect sizes (Table 1). We used Monte Carlo sampling from either the CI for the TB-DM effect sizes, or assuming (if uncertainty is not captured by CI) ±25% uncertainty around the point estimates for the effect sizes. We implemented 500 uncertainty runs of the model. In each run, the values of the effect sizes were randomly selected from their specified ranges, and the model was refitted to India’s country-specific data. The mean and 95% uncertainty intervals (UI) for the PAFs were derived from the likelihood distribution generated by the uncertainty runs.

**Sensitivity analyses**

Given that our main estimates were generated using a conservative approach, we conducted two sensitivity analyses with less conservative effect sizes for the TB-DM interactions. In the first sensitivity analysis, we used, for Effect 2-Fast progression, the TB-DM association effect size of 3.59 based on the prospective cohort studies (Appendix S2.2 in Online Supplementary Document) [12]. In the second sensitivity analysis, we used, for Effect 7-TB mortality, the effect size of 4.95 based on the pooled analysis that included studies that appropriately adjusted for confounders Appendix S2.2 in Online Supplementary Document) [20].

In a third sensitivity analysis, we explored the TB-DM synergy implications by factoring the age-dependence of the TB-DM association, based on a cohort study that estimated the age-specific relative risks (RRs) of the effect of DM on TB disease [58]. In doing so, we scaled down (conservatively) the age effects reported by Kim et al [58], to reach the assumed 2-fold overall RR (Appendix S2.2 in Online Supplementary Document).

In a fourth sensitivity analysis, in context of uncertainty about the future trajectory of the TB epidemic over the coming decades, we assessed the TB-DM synergy implications assuming 10 different TB disease incidence rate trajectories over the coming decades. The change in TB incidence rate at 2050, relative to the baseline model scenario, was assumed to range between ±50%.

In a fifth sensitivity analysis, we accounted for the age-dependency in the proportion of individuals developing each infection form (LSI vs LFI) for those aged 15 years and above, compared with the baseline analysis in which this proportion did not differ by age for adults. Specifically, as informed by evidence [59], we assessed the TB-DM synergy implications assuming that 25% of individuals who progress to TB infection aged 15-35 years develop LFI, while only 5% of individuals aged 35+ years develop LFI.

In a sixth sensitivity analysis, we assessed the implications of assuming different TB reinfection risks [60,61]. We compared a 65% fractional reduction in the susceptibility to TB reinfection (compared to initial TB infection risk; our baseline assumption, Table S1 in Online Supplementary Document) [62,63], to no reduction, and to a 35% fractional increase. The different risks of reinfection were assumed for 1)
individuals with LSI (that is those in latent infection), 2) individuals who successfully completed TB treatment, or 3) both individuals with LSI and those who successfully completed TB treatment.

Finally, additional sensitivity analyses were conducted to assess the sensitivity of model predictions to variations in the effect sizes of the DM-on-TB effects (Table 1). For each individual effect, we used the lower and upper values from either the CI for the TB-DM effect sizes, or assuming (if uncertainty is not captured by CI) ±25% uncertainty around the point estimates.

RESULTS

The model fitted well the demographic (Figure S4 in Online Supplementary Document), TB incidence rate (Figure 1, Panel A), TB mortality rate (Figure 1, Panel C), and DM prevalence data for India (Figure 2, Panel A). From 2017 to 2050, TB disease incidence rate (defined as the ratio of total annual number of TB disease cases over total Indian population) was projected to decrease from 215 to 116 per 100 000 persons per year (Figure 1, Panel A). Meanwhile, the number of annual new (incident) cases was projected to decrease from 2.8 to 2.0 million (Figure 1, Panel B). Likewise, TB mortality rate (defined as the ratio of total annual number of TB-related deaths over total Indian population) was projected to decrease from 40.7 to 15.7 per 100 000 persons per year (Figure 1, Panel C). Meanwhile, the number of annual TB deaths was projected to decrease from 534 000 to 287 000 (Figure 1, Panel D). DM prevalence in India was projected to increase from 8.5% in 2017 to 12.1% in 2050 (Figure 2, Panel A).

While DM prevalence increased (Figure 2, Panel A) and TB incidence rate decreased (Figure 1, Panel A), the proportion of new TB incidence cases and proportion of TB-related deaths attributed to DM increased steadily (Figure 2, Panel B). In 1990, 11.4% (95% UI = 6.3%-14.4%) of new TB disease incident cases were attributed to DM. This proportion increased to 21.9% (95% UI = 12.1%-26.4%) in 2017, and was predicted to continue increasing to 33.3% (95% UI = 19.0%-44.1%) by 2050. Similarly, in 1990, 14.5% (95% UI = 9.5%-18.2%) of TB-related deaths were attributed to DM. This proportion increased to 28.9% (95% UI = 18.9%-34.1%) in 2017, and was predicted to continue increasing to 42.8% (95% UI = 28.7%-53.1%) by 2050.

Relaxing the conservative approach by using, for Effect 2-Fast progression, the TB-DM association effect size of 3.59 [12], resulted in a larger impact for the TB-DM synergy on TB disease incidence and mortality (Figure 3, Panel A). In 1990, 17.2% of TB disease incident cases were attributed to DM, and this pro-

Figure 1. Model projections. Panel A. Tuberculosis (TB) disease incidence rate. Panel B. Number of annual new (incident) TB disease cases. Panel C. TB mortality rate. Panel D. Number of annual TB deaths, in India between 1990 and 2050. The red asterisks in panels A and C are the data provided by the World Health Organization’s Global Health Observatory data repository [50].
portion increased to 37.0% by 2017 and 55.4% by 2050. Meanwhile, in 1990, 19.2% of TB-related deaths were attributed to DM, and this proportion increased to 42.1% by 2017 and 60.8% by 2050.

Relaxing the conservative approach by using, for Effect 7-TB mortality, the effect size of 4.95 [20], resulted in a larger impact for the TB-DM synergy on TB mortality but slightly smaller impact on TB disease incidence (Figure 3, Panel B). In 1990, 7.4% of new TB incident cases were attributed to DM, and this proportion increased to 16.2% by 2017 and 28.2% by 2050. Meanwhile, in 1990, 14.9% of TB-related deaths were attributed to DM, and this proportion increased to 31.2% by 2017 and 47.5% by 2050.

Exploring the TB-DM synergy implications by factoring the age-dependence of the TB-DM association, resulted in a larger impact on TB disease incidence and mortality (Figure 3, Panel C). In 1990, 13.2% of new TB incident cases were attributed to DM, and this proportion increased to 27.9% by 2017 and 39.2% by 2050. Meanwhile, in 1990, 15.3% of TB-related deaths were attributed to DM, and this proportion increased to 33.3% by 2017 and 45.41% by 2050.

Assessing the TB-DM synergy implications at different TB disease incidence trajectories over the coming decades resulted in minimal changes in the assessed impact of DM on TB incidence and mortality (Figure S5 in Online Supplementary Document). In 2050, new TB incident cases attributed to DM ranged between 26.5% and 34.5%, and TB-related deaths attributed to DM ranged between 37.2% and 43.7%.

Factoring the age-dependency in the proportion of individuals developing each infection form (LSI vs LFI) for those aged 15 years and above, the impact of DM on TB disease incidence and mortality was reduced (Figure S6 in Online Supplementary Document). In 1990, only 6.2% of new TB incident cases were attributed to DM, and this proportion increased to 12.6% by 2017 and 20.4% by 2050. Meanwhile, in 1990, 8.2% of TB-related deaths were attributed to DM, and this proportion increased to 17.7% by 2017 and 28.6% by 2050.

Exploring the TB-DM synergy implications assuming no change in the susceptibility to TB reinfection, resulted in slightly larger impact for DM on TB disease incidence and mortality (Figure S7 in Online Supplementary Document). By 2050, assuming no change in the susceptibility to TB reinfection among individuals who successfully completed TB treatment, with LSI, and both with LSI and those who successfully completed TB treatment, new TB incident cases attributed to DM were 33.8%, 38.6%, and 38.8%, respectively, and TB-related deaths attributed to DM were 42.1%, 44.9%, and 45.7%, respectively (Figure S7 in Online Supplementary Document). Exploring the TB-DM synergy implications assuming a 35% increase in the susceptibility to TB for reinfection, resulted in a relatively larger impact for DM on TB disease incidence and mortality (Figure S7 in Online Supplementary Document). By 2050, assuming 35% increase in the susceptibility to TB reinfection among individuals who successfully completed TB treatment, with LSI, and both with LSI and those who successfully completed TB treatment, new TB incident cases attributed to DM were 33.5%, 47.7%, and 48.9%, respectively, and TB-related deaths attributed to DM were 42.6%, 54.3%, and 57.1%, respectively (Figure S7 in Online Supplementary Document).

Table 2 and Table 3 show the individual impact of each of the DM-on-TB effects at six different time points. Most effects resulted in a larger TB disease incidence and mortality, as DM prevalence increased with time. The largest impact for TB incidence was for Effect 2-Fast progression followed by Effect 6-Infectiousness (Table 2). The proportion of TB incidence attributed to Effect 2-Fast progression increased from
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8.7% in 1990 to 25.1% by 2050. The proportion of TB incidence attributed to Effect 6-Disease infectiousness increased from 4.5% in 1990 to 14.8% by 2050. The largest impact for TB mortality was also for Effect 2-Fast progression followed by Effect 6-Infectiousness (Table 3). The proportion of TB-related deaths attributed to Effect 2-Fast progression increased from 9.9% in 1990 to 28.5% by 2050. The proportion of TB-related deaths attributed to Effect 6-Disease infectiousness increased from 4.3% in 1990 to 14.4% by 2050.

Effect 7-TB mortality increased TB-related deaths from 2.1% in 1990 to 10.3% by 2050, but it reduced TB disease incidence with less TB transmission (due to the premature death of persons with TB disease). The impact of Effect 5-Smear positivity and Effect 10-Cured reinfection on both TB incidence and mortality changed in direction with time—a consequence of a complex interplay between TB enhanced transmission, premature death of TB disease cases, and demographic factors relating to DM age-specific prevalence distribution and TB exposure risk variation in successive birth cohorts.

DISCUSSION

We provided a comprehensive quantitative assessment of the impact of DM on TB epidemiology in India, a country heavily burdened by both diseases. Anchored on a solid foundation of current empirical evidence, the assessment accounted for both direct and indirect impacts, and factored the different effects by which DM can affect TB natural history and treatment outcomes. As DM prevalence increased and TB disease incidence declined, DM was predicted to play a major and growing role in TB epidemiology. While in 1990 only one in 10 TB disease cases was attributed to DM, currently one in five is attributed to DM, and by 2050, nearly one in two will be attributed to DM. These findings highlight how DM could be emerging as the leading driver of TB incidence and mortality in India, and likely elsewhere.

The results support growing evidence highlighting the increasing role of DM on TB epidemiology [2,64,65], but also suggest that DM impact could be underestimated. We investigated DM role using a conservative approach whereby the effect size for each DM-on-TB effect was set at its lowest or null value. Setting effect sizes based on best quality evidence, resulted in even larger impact of DM on TB, particularly so for TB mortality – half of TB disease cases and TB-related deaths could be attributed to DM by 2050 (Figure 3).

Although the clinical effects of DM on TB treatment outcomes have been widely discussed and researched [20], the population impact has been less investigated but shown in this study to play an influential role (such as that of Effect 7-TB mortality). However, most of the impact of DM on TB was driven by the effects of DM on TB natural history – in particular Effect 2-Fast progression and Effect 6-Disease infectiousness (Table 2 and Table 3). These findings suggest that intervention strategies should target DM patients before onset of TB disease. The population-level impacts of different intervention strategies, such as screening,

Figure 3. Sensitivity analyses. Model predictions for the proportion of tuberculosis (TB) disease incident (solid black line) and mortality (dashed blue line) cases attributed to DM in India between 1990 and 2050 assuming: Panel A. TB-DM association effect size of 3.59 based on pooling the data only from the prospective cohort studies (Effect 2-Fast progression, Appendix S2.2 in Online Supplementary Document [12]. Panel B. Effect 7-TB mortality effect size of 4.95 based on the pooled analysis that included only studies that appropriately adjusted for confounders (Appendix S2.2 in Online Supplementary Document) [15]. Panel C. Age-dependence in the TB-DM association based on a cohort study that estimated the age-specific relative risks of the effect of DM on TB disease (Effect 2-Fast progression, Appendix S2.2 in Online Supplementary Document) [58].
Table 2. The epidemiologic impact of each of the individual diabetes mellitus (DM) effects on tuberculosis (TB) natural history and treatment outcomes on TB disease incidence as measured by the population attributable fraction

| Time (Year) | TB Disease Incident Cases | DM Prevalence (%) | Population Attributable Fraction (%) |
|-------------|--------------------------|-------------------|-------------------------------------|
|             | Effect 1-Susceptibility | Effect 2-Fast Progression | Effect 5-Smear Positivity | Effect 6-Disease Infectiousness | Effect 7-TB Mortality | Effect 9-Recovery | Effect 10-Cured Reinfection | All effects |
| 1990        | 3077706                  | 3.7               | 1.5                                  | 8.7                                  | 0.9                                  | 4.5                                  | 2.0                                  | 0.2                                  | 0.9                                  | 11.4                                  |
| 2010        | 2974690                  | 7.3               | 3.1                                  | 15.5                                 | 1.2                                  | 8.2                                  | 3.2                                  | 0.4                                  | 1.7                                  | 20.2                                  |
| 2020        | 2775774                  | 8.9               | 4.1                                  | 17.0                                 | 1.0                                  | 9.2                                  | 3.1                                  | 0.5                                  | 1.7                                  | 22.4                                  |
| 2030        | 2528050                  | 10.2              | 5.6                                  | 18.3                                 | 0.5                                  | 10.2                                 | 3.0                                  | 0.5                                  | 1.6                                  | 24.3                                  |
| 2040        | 2274153                  | 11.2              | 7.7                                  | 20.8                                 | 0.2                                  | 11.9                                 | 3.4                                  | 0.6                                  | 1.4                                  | 27.8                                  |
| 2050        | 2038877                  | 12.1              | 10.8                                 | 25.1                                 | 1.1                                  | 14.8                                 | 4.2                                  | 0.8                                  | 1.5                                  | 33.3                                  |

*The impact of Effect 7-TB mortality on TB incidence is negative due to the fact that Effect 7-TB mortality reduced TB disease incidence due to the premature death of persons with TB disease.
†The impact of Effect 5-Smear positivity and Effect 10-Cured reinfection on TB incidence changed in direction with time as a consequence of a complex interplay between TB enhanced transmission, premature death of persons with TB disease, and demographic factors relating to DM age-specific prevalence distribution and TB exposure risk variation in successive birth cohorts.

Table 3. The epidemiologic impact of each of the individual diabetes mellitus (DM) effects on tuberculosis (TB) natural history and treatment outcomes on TB-related deaths as measured by the population attributable fraction

| Time (Year) | TB-Related Deaths | DM Prevalence (%) | Population Attributable Fraction (%) |
|-------------|-------------------|-------------------|-------------------------------------|
|             | Effect 1-Susceptibility | Effect 2-Fast Progression | Effect 5-Smear Positivity | Effect 6-Disease Infectiousness | Effect 7-TB Mortality | Effect 9-Recovery | Effect 10-Cured Reinfection | All effects |
| 1990        | 802790            | 3.7               | 1.7                                  | 9.9                                  | 0.8                                  | 4.3                                  | 2.1                                  | 0.8                                  | 1.0                                  | 14.5                                  |
| 2010        | 586316            | 7.3               | 3.6                                  | 18.0                                 | 1.0                                  | 8.0                                  | 4.7                                  | 1.7                                  | 1.9                                  | 26.3                                  |
| 2020        | 491094            | 8.9               | 4.8                                  | 20.0                                 | 0.5                                  | 9.0                                  | 6.4                                  | 2.2                                  | 2.0                                  | 29.9                                  |
| 2030        | 412743            | 10.2              | 6.6                                  | 21.5                                 | 0.4                                  | 9.9                                  | 8.1                                  | 2.6                                  | 1.8                                  | 32.9                                  |
| 2040        | 350711            | 11.2              | 9.0                                  | 24.1                                 | 1.7                                  | 11.6                                 | 9.4                                  | 3.1                                  | 1.7                                  | 37.0                                  |
| 2050        | 302349            | 12.1              | 12.4                                 | 28.5                                 | 3.3                                  | 14.4                                 | 10.3                                 | 3.7                                  | 1.7                                  | 42.7                                  |

*The impact of Effect 5-Smear positivity and Effect 10-Cured reinfection on TB mortality changed in direction with time as a consequence of a complex interplay between TB enhanced transmission, premature death of persons with TB disease, and demographic factors relating to DM age-specific prevalence distribution and TB exposure risk variation in successive birth cohorts.
Evidence suggests heterogeneities and uncertainties around the exact effect sizes of several effects. For example, not all risk estimates were available by age strata, though age could be an important factor in determining the population impact of DM on TB. Moreover, even though evidence supports an increased risk of developing TB disease for those with DM [12], it does not differentiate the precise biological mechanism(s) of whether DM is acting through Effect 2–Fast progression, Effect 3–Reactivation, and/or Effect 4–Primary reinfection.

Our conclusion is predicated upon the assumption that the effect of DM on TB is causal. While strongly plausible, the scale of TB-DM biological/epidemiological synergy is not completely certain. The association could be affected by confounders (such as smoking and obesity), which are not controlled for given the very complex overlap and interactions between TB and DM. For example, the TB-DM interaction is paradoxical; while DM is known to be associated with obesity [69], TB is reportedly associated with low body mass index (ie, obesity is a protective factor against TB disease) [70]. However, when obesity and DM (a serious metabolic disorder) coexist, the protective effect of obesity on TB is attenuated [71].

We did not include all factors that may influence the impact of DM on TB, or the factors that may affect directly each of TB or DM burdens individually [12,17,72,73]. For example, the impact of HIV as a co-factor [17,72,73] was not incorporated. However, despite the potential public health implications, HIV prevalence is relatively low in India at less than 1.0% [74], hence, probably minimally affecting our results and conclusions.

We modeled TBs natural history and dynamics based on the canonical approach in the literature [37,75], but TBs complex natural history remains insufficiently-understood [59]. For instance, based on studies by Heimbeck [62,63], we assumed a proportional reduction in the susceptibility to TB reinfection with prior TB exposure (ie, acquired protective immunity), however, this immunity may be explained by selection bias as these studies were conducted among individuals who may not have been representative of the wider population [61]. Other evidence suggests a higher risk of reinfection rather than protective immunity [60]. Moreover, though we assumed that the proportion of individuals developing LSI vs LFI was age dependent, this was assumed for only children vs adults, but the variable age dependence could also affect the adult population [59].

We did not factor the effect of intermediate hyperglycemia (pre-DM) on TB, which may enhance the impact of DM on TB [12,76]. We only included the DM-on-TB effects, but the links between the two diseases could be bi-directional [49]. Last but not least, the impact of DM on TB depends on the trajectory of the TB epidemic over the coming decades, but this trajectory may change substantially with roll-out and scale-up of interventions in upcoming years [1].

Despite these limitations, our study has several strengths. Our model includes ten different effects in which DM affects TB natural history and treatment outcomes, incorporates a detailed quantitative assessment of the effect sizes for each effect, is age stratified to reflect the age-specific trends, and assesses both the direct and indirect population impacts of DM on TB. In addition, most of the potential limitations are likely to lead to underestimation rather than overestimation of the impact of DM on TB.

We also conducted sensitivity analyses to explore the potential impact of several mentioned limitations, and these analyses confirmed our results, or suggested that the impact could be underestimated (Figure 3 and Figures S5 and S7 in the Online Supplementary Document), or slightly overestimated (Figure S6 in Online Document). Furthermore, our sensitivity analyses demonstrated that our results are most sensitive to Effect 2–Fast progression, Effect 6–Disease infectiousness, and Effect 1–Susceptibility (Figure S9 in Online Supplementary Document), as expected given the impact of these effects on TB-epidemiology (Table 2 and Table 3). Otherwise, our results were largely insensitive to variations in the rest of explored effects (Figure S9 in Online Supplementary Document). We further conducted a multivariate uncertainty analysis by factoring the uncertainty in model parameters, and the uncertainty intervals of the model outcomes affirmed the validity of our predictions (Figure S8 in Online Supplementary Document). Finally, the aim of the present analysis was to assess the epidemiological implications of the TB-DM interactions focusing on the core interaction effects and at the national level. Thus, we resorted to a parsimonious model structure presenting “average” impact estimates of DM on TB, rather than stratified estimates for specific population strata.

In conclusion, the burgeoning DM epidemic in India is predicted to become a leading driver of TB disease incidence and mortality over the coming decades in India and possibly elsewhere. At present, one in five TB disease cases is attributed to DM, and by 2050, one in three will be attributed to DM. Nearly one
in three TB-related deaths is attributed to DM currently, and by 2050, nearly one in two will be attributed to DM. The slowly declining TB incidence, in context of rapidly expanding DM epidemic in multiple countries, could be driving a major turn in TB epidemiology. Targeting the impact of the increasing DM burden on TB control is critical to achieving the goal of TB elimination by 2050.

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Additional material
Online Supplementary Document

1 World Health Organization. Global tuberculosis report 2016. Available: http://apps.who.int/iris/bitstream/10665/250441/1/9789241563944-eng.pdf#page=1. Accessed: 21 May 2017.
2 Lönnroth K, Castro KG, Chakaya JM, Chauhan LS, Floyd K, Glaziou P, et al. Tuberculosis control and elimination 2010-50: cure, care, and social development. Lancet. 2010;375:1814-29. Medline:20488524 doi:10.1016/S0140-6736(10)60483-7
3 International Diabetes Federation. IDF Diabetes Atlas. Eighth edition. Brussels, Belgium. Available at: http://www.diabetesatlas.org. Accessed: 15 December 2017.
4 K V N, Duraisamy K, Balakrishnan S, M S, S JS, Sagili KD, et al. Outcome of tuberculosis treatment in patients with diabetes mellitus treated in the revised national tuberculosis control programme in Malappuram District, Kerala, India. PLoS One. 2013;8:e76275. Medline:24155897 doi:10.1371/journal.pone.0076275
5 Viswanathan V, Kumpatla S, Aravindalochanan V, Rajan R, Chinnasamy C, Srinivasan R, et al. Prevalence of diabetes and pre-diabetes and associated risk factors among tuberculosis patients in India. PLoS One. 2012;7:e1367. Medline:22848473 doi:10.1371/journal.pone.0041367
6 Viswanathan V, Vigneswari A, Selvan K, Satyavani K, Rajeswari R, Kapur A. Effect of diabetes on treatment outcome of smear-positive pulmonary tuberculosis—a report from South India. J Diabetes Complications. 2014;28:162-5. Medline:24461545 doi:10.1016/j.jdiacomp.2013.12.003
7 Balakrishnan S, Vijayan S, Nair S, Subramoniapillai J, Mrithyunjayan S, Wilson N, et al. High diabetes prevalence among tuberculosis cases in Kerala, India. PLoS One. 2012;7:e46502. Medline:23077512 doi:10.1371/journal.pone.0046502
8 Burki T. Why India should worry about a coepidemic of diabetes and tuberculosis. BMJ. 2015;350:h1111. Medline:25647583 doi:10.1136/bmj.h1111
9 Singh SP, Singh SP, Kishan J, Kaur S, Ramana S. Association of tuberculosis and diabetes Mellitus: an analysis of 1000 consecutively admitted cases in a tertiary care hospital of North India. Pan Afr Med J. 2016;24:4. Medline:27583068 doi:10.11604/pamj.2016.24.4.8153
10 Ministry of Health & Family Welfare (Supported by WHO Country Office for India). National framework for joint TB-Diabetes collaborative activities, Revised National Tuberculosis Control Programme (RNTCP). Available: https://tbchina.gov.in/WriteReadData/National%20framework%20for%20joint%20TB%20and%20Diabetes%202017.pdf. Accessed: 01 December 2018.
11 Martinez L, Zhu L, Castellanos ME, Liu Q, Chen C, Hallowell BD, et al. Glycemic control and the prevalence of tuberculosis infection: a population-based observational study. Clin Infect Dis. 2017;65:2060-2068. Medline:29059298 doi:10.1093/cid/cix632
12 Al-Rifai RH, Pearson F, Critchley JA, Abu-Raddad LJ. Association between diabetes mellitus and active tuberculosis: A systematic review and meta-analysis. PLoS One. 2017;12:e0187967. Medline:29161276 doi:10.1371/journal.pone.0187967
13 Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008;5:e152. Medline:18630984 doi:10.1371/journal.pmed.0050152
14 World Health Organization, International Union Against Tuberculosis and Lung Disease. Collaborative framework for care and control of tuberculosis and diabetes. Report No.: 9789241502252. Available: http://whqlibdoc.who.int/publications/2011/9789241502252_eng.pdf. Accessed: 16 November 2013.
15 Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: A systematic review. BMC Med. 2011;9:81. Medline:21722362 doi:10.1186/1741-7015-9-81
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REFERENCES

16 World Health Organization, International Union Against Tuberculosis and Lung Disease. Collaborative framework for care and control of tuberculosis and diabetes. Switzerland: World Health Organization, 2011 16/11/2013. Report No.

17 Faurel-Jepsen D, Range N, PrayGod G, Jeremiah K, Faurel-Jepsen M, Aaby MG, et al. Diabetes is a strong predictor of mortality during tuberculosis treatment: a prospective cohort study among tuberculosis patients from Mwanza, Tanzania. Trop Med Int Health. 2013;18:822-9. Medline:23648145 doi:10.1111/tmi.12120

18 Stevenson CR, Critchley JA, Forouhi NG, Roglic G, Williams BG, Dye C, et al. Diabetes and the risk of tuberculosis: a neglected threat to public health? Chronic Illn. 2007;3:228-45. Medline:17836379 doi:10.1177/1472393X07081850

19 Faurel-Jepsen D, Range N, Praygod G, Kidola J, Faurel-Jepsen M, Aaby MG, et al. The role of diabetes co-morbidity for tuberculosis treatment outcomes: a prospective cohort study from Mwanza, Tanzania. BMC Infect Dis. 2012;12:165. Medline:22839693 doi:10.1186/1471-2334-12-165

20 Huangfu P, Ugarte-Gil C, Golub J, Pearson F, Critchley J. The effects of diabetes on tuberculosis treatment outcomes: an updated systematic review and meta-analysis. Int J Tuberc Lung Dis. 2019;23:783-96. Medline:31439109 doi:10.5588/ijtld.18.0433

21 Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. Indian J Endocrinol Metab. 2012;16 Suppl 1:527-36. Medline:22701840 doi:10.4103/2230-8210.94253

22 Geerlings SE, Hoepelman AIM. Immune dysfunction in patients with diabetes mellitus (DM). Fems Immunol Microbiol. 1999;26:259-65. Medline:10575137 doi:10.1111/j.1574-695X.1999.tb01397.x

23 Peleg AY, Weerarathna T, McCarthy JS, Davis TME. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. Diabetes Metab Res Rev. 2007;23:3-13. Medline:16960917 doi:10.1002/dmrr.682

24 Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. N Engl J Med. 1999;341:1906-12. Medline:10601511 doi:10.1056/NEJM199912163412507

25 Vardakas KZ, Siempos II, Falagas ME. Diabetes mellitus as a risk factor for nosocomial pneumonia and associated mortality. Diabet Med. 2007;24:1168-71. Medline:17888136 doi:10.1111/j.1464-5491.2007.0234.x

26 Restrepo BI, Camerlin AJ, Rahbar MH, Wang WW, Restrepo MA, Zarate I, et al. Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases. Bull World Health Organ. 2011;89:352-9. Medline:21556303 doi:10.2471/BLT.10.085738

27 Harrries AD, Lin Y, Satyanarayana S, Lonroth K, Li L, Wilson N, et al. The looming epidemic of diabetes-associated tuberculosis: learning lessons from HIV-associated tuberculosis. Int J Tuberc Lung Dis. 2011;15:1436-44. Medline:21902876 doi:10.5588/ijtld.11.0503

28 Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009;9:737-46. Medline:19926034 doi:10.1016/S1473-3099(09)70282-8

29 Viardot A, Grey ST, Mackay F, Chisholm D. Potential antiinflammatory role of insulin via the preferential polarization of effector T cells toward a T helper 2 phenotype. Endocrinology. 2007;148:346-53. Medline:17008395 doi:10.1210/en.2006-0686

30 Stalenhoef JE, Alisjahbana B, Nelwan EJ, van der Ven-Jongekrijg J, Ottenhoff TH, van der Meer JW, et al. The role of interferon-gamma in the increased tuberculosis risk in type 2 diabetes mellitus. Eur J Clin Microbiol Infect Dis. 2008;27:97-103. Medline:17962984 doi:10.1007/s10096-007-0395-0

31 Tsukaguchi K, Okamura I, Ikumo M, Kobayashi A, Fukuioka A, Takenaka H, et al. 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. 1997;72:617-22. Medline:9423299

32 Delamaire M, Maugendre D, Moreno M, Le Goff AJ, Rahbar MH, Wang WW, et al. The MathWorks Inc.; 2018. The MathWorks, Inc. MATLAB. The language of technical computing. 8.5.0.197613 (R2015a). Natick, MA, USA: ed:

33 Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Nechemias C, Smith H. Infection and diabetes: the case for glucose control. Am J Med. 1982;72:439-50. Medline:7036735 doi:10.1016/0002-9343(82)90511-3

34 Awad SF, Dargham SR, Omori R, Pearson F, Critchley JA, Abu-Raddad LJ. Analytical Exploration of Potential Pathways by which Diabetes Mellitus Impacts Tuberculosis Epidemiology. Sci Rep. 2019;9:8494. Medline:31186499 doi:10.1038/s41598-019-44916-7

35 Levin ML. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum. 1953;9:531-41. Medline:13124110

36 The MathWorks, Inc. MATLAB. The language of technical computing. 8.5.0.197613 (R2015a). Natick, MA, USA: ed: The MathWorks, Inc.; 2018.

37 Abu-Raddad LJ, Sabatelli L, Achterberg JT, Sugimoto JD, Longini IM Jr, Dye C, et al. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. Proc Natl Acad Sci USA. 2009;106:13980-5. Medline:19665950 doi:10.1073/pnas.0901720106

38 Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. Lancet. 1998;352:1886-91. Medline:9863786 doi:10.1016/S0140-6736(98)03199-7

39 World Health Organization. What is DOTS? A Guide to Understanding the WHO-recommended TB Control Strategy Known as DOTS. Available: http://apps.who.int/iris/bitstream/10665/65979/1/WHO_CDS_CPC_TB_99.270.pdf. Accessed: 01 February 2018.

40 Jan J. Barendregt. Ersatz Function Overview Version 1.35. Available: http://www.epigeart.com/index_files/Ersatz%20Function%20Overview.pdf. Accessed: 01 April, 2011.
REFERENCES

41 Chang JT, Dou HY, Yen CL, Wu YH, Huang RM, Lin HJ, et al. Effect of type 2 diabetes mellitus on the clinical severity and treatment outcome in patients with pulmonary tuberculosis: a potential role in the emergence of multidrug-resistance. J Formos Med Assoc. 2011;110:372-81. Medline:21741005 doi:10.1016/S0929-6646(11)60055-7

42 John NN, George JM, Narmadhia M. Study on the prevalence and incidence rates of diabetes mellitus in tuberculosis. Int J Pharm Chem Biol Sci. 2017;7:401-6.

43 Singla R, Khan N, Al-Sharif N, Ai-Sayegh MO, Shaikh MA, Osman MM. Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. Int J Tuberc Lung Dis. 2006;10:74-9. Medline:16466041

44 Chiang CY, Bai KJ, Lin HH, Chien ST, Lee JJ, Enarson DA, et al. The Influence of Diabetes, Glycemic Control, and Diabetes-Related Comorbidities on Pulmonary Tuberculosis. PLoS One. 2015;10:e0121698. Medline:25822974 doi:10.1371/journal.pone.0121698

45 Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg. 2009;80:634-9. Medline:19343691 doi:10.4269/ajtmh.2009.80.634

46 Restrepo BI, Fisher-Hoch SP, Crespo JG, Whitney E, Perez A, Smith B, et al. Type 2 diabetes and tuberculosis in a dynamic bi-national border population. Epidemiol Infect. 2007;135:483-91. Medline:16863600 doi:10.1017/S0950268806006935

47 Duangritthi D, Thanachartvet W, Desakorn V, Jitrukthai P, Phojanamongkolkij K, Renthong S, et al. Impact of diabetes mellitus on clinical parameters and treatment outcomes of newly diagnosed pulmonary tuberculosis patients in Thailand. Int J Clin Pract. 2013;67:1199-209. Medline:23750554 doi:10.1111/j.1742-1241.2012.02826.x

48 Suwanpimolkul G, Grinsdale JA, Jarlsberg LG, Higashi J, Osmond DH, Hopewell PC, et al. Association between diabetes mellitus and tuberculosis in United States-born and foreign-born populations in San Francisco. PLoS One. 2014;9:e114442. Medline:25478954 doi:10.1371/journal.pone.0114442

49 Young P, Wotton CJ, Critchley JA, Unwin NC, Goldacre MJ. Increased risk of tuberculosis disease in people with diabetes mellitus: record-linkage study in a UK population. J Epidemiol Community Health. 2012;66:519-23. Medline:21109542 doi:10.1136/jech.2010.114595

50 World Health Organization. WHO Global Health Observatory Data Repository. Available: http://apps.who.int/gho/data/node.main. Accessed: 21 December 2017.

51 International Diabetes Federation. IDF Diabetes Atlas. 3th edition. Brussels, Belgium (available at: https://www.idf.org/sites/default/files/Diabetes-Atlas-3rd-edition.pdf. Accessed on 10 Dec. 2015). 2006.

52 International Diabetes Federation. IDF diabetes atlas, sixth edition. Available: www.idf.org/diabetesatlas. Accessed: 15 September 2016.

53 International Diabetes Federation. IDF Diabetes Atlas. 7th edition. Brussels, Belgium (Available at:http://www.diabetesatlas.org. Accessed on 15 Sept. 2016). 2016.

54 Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract. 2014;103:137-49. Medline:24630390 doi:10.1016/j.diabres.2013.11.002

55 Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011;94:311-21. Medline:22079683 doi:10.1016/bres.2013.11.002

56 Anjana RM, Deepa M, Pradeepa R, Mahanta J, Narain K, Das HK, et al. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR-INDIAB population-based cross-sectional study. Lancet Diabetes Endocrinol. 2017;5:585-96. Medline:28601585 doi:10.1016/S2213-8587(17)30174-2

57 United Nations Department of Economic and Social Affairs, Population Division, Population Estimates and Projections Section. World population prospects, the 2017 revision. Available: https://esa.un.org/unpd/wpp/Download/Standard/Population/. Accessed: 01 April 2018.

58 Kim SJ, Hong YF, Lew WJ, Yang SC, Lee EG. Incidence of pulmonary tuberculosis among diabetics. Tuberc Lung Dis. 1995;76:529-33. Medline:8593374 doi:10.1016/0962-8479(95)00529-4

59 Nico JD. Nagelkerke. Courtesans and consumption. How sexually transmitted infections drive tuberculosis epidemics. The Netherlands (www.eburon.nl). Eburon, Delft. ISBN: 978-90-5972-603-1 (paperback), ISBN: 978-90-5972-604-8 (ebook); 2012.

60 Verver S, Warren RM, Beyers N, Richardson M, van der Spuy GD, Borgdorff MW, et al. Rate of reinfection tuberculosis after successful treatment is higher than rate of new tuberculosis. Am J Respir Crit Care Med. 2005;171:1430-5. Medline:15831840 doi:10.1164/rccm.200409-1200OC

61 Nagelkerke NJ, de Vlas SJ, Mahendradhata Y, Ottenhoff TH, Borgdorff M, et al. Effect of diabetes on tuberculosis control in 13 countries with high tuberculosis prevalence: a modelling study. Lancet Diabetes Endocrinol. 2015;3:323-30. Medline:25754415 doi:10.1016/S2213-8587(15)00042-X
REFERENCES

66 World Health Organization. Draft global strategy and targets for tuberculosis prevention, care and control after 2015. Available: http://apps.who.int/ibwha/pdf_files/WHA67/A67_11-en.pdf. Accessed: 01 April 2018.
67 International Union Against Tuberculosis and Lung Disease, World Diabetes Foundation. The Looming Co-epidemic of TB-Diabetes: A Call to Action. Available: https://www.theunion.org/what-we-do/publications/technical/low-resolution/25383_TCB_Report_LR.pdf. Accessed: 01 April 2018.
68 Kapur A, Harries AD, Lonroth K, Wilson P, Sulishtyowati LS. Diabetes and tuberculosis co-epidemic: the Bali Declaration. Lancet Diabetes Endocrinol. 2016;4:8-10. Medline:26620249 doi:10.1016/S2213-8587(15)00461-1
69 Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9:88. Medline:19320986 doi:10.1186/1471-2458-9-88
70 Lonnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. Int J Epidemiol. 2010;39:149-55. Medline:19820104 doi:10.1093/ije/dyp308
71 Lin HH, Wu CY, Wang CH, Fu H, Lonnroth K, Chang YC, et al. Association of Obesity, Diabetes, and Risk of Tuberculosis: Two Population-Based Cohorts. Clin Infect Dis. 2018;66:699-705. Medline:29029077 doi:10.1093/cid/cix852
72 Young F, Critchley JA, Johnstone LK, Unwin NC. A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and diabetes mellitus, HIV and metabolic syndrome, and the impact of globalization. Global Health. 2009;5:9. Medline:19751503 doi:10.1186/1744-8603-5-9
73 Levitt NS, Bradshaw D. The impact of HIV/AIDS on Type 2 diabetes prevalence and diabetes healthcare needs in South Africa: projections for 2010. Diabet Med. 2006;23:103-4. Medline:16409575 doi:10.1111/j.1464-5491.2006.01768.x
74 Paranjape RS, Challacombe SJ. HIV/AIDS in India: an overview of the Indian epidemic. Oral Dis. 2016;22 Suppl 1:10-4. Medline:27109267 doi:10.1111/odi.12457
75 Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. Epidemiol Infect. 1997;119:183-201. Medline:9363017 doi:10.1017/S0950268897007917
76 Owiti P, Keter A, Harries AD, Pastakia S, Wambugu C, Kirui N, et al. Diabetes and pre-diabetes in tuberculosis patients in western Kenya using point-of-care glycated haemoglobin. Public Health Action. 2017;7:147-54. Medline:28693089 doi:10.5588/pha.16.0114