Effect of diabetes on tuberculosis control in 13 countries with high tuberculosis: a modelling study

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Summary

Background **Diabetes increases the risk of tuberculosis incidence and the risk of adverse treatment outcomes in patients with tuberculosis. Because prevalence of diabetes is increasing in low-income and middle-income countries where the burden of tuberculosis is high, prevention of diabetes carries the potential to improve tuberculosis control worldwide.**

Methods **We used dynamic tuberculosis transmission models to analyse the potential effect of diabetes on tuberculosis epidemiology in 13 countries with high tuberculosis burden. We used data for previous diabetes prevalence in each country and constructed scenarios to represent the potential ranges of future diabetes prevalence. The country-specific model was calibrated to the estimated trend of tuberculosis incidence. We estimated the tuberculosis burden that can be reduced by alternative scenarios of diabetes prevention.**

Findings **If the prevalence of diabetes continues to rise as it has been in the past decade in the 13 countries (base case scenario), by 2035, the cumulative reduction in tuberculosis incidence would be 8·8% (95% credible interval [CrI] 4·0–15·8) and mortality would be 34·0% (30·3–39·6). Lowering the prevalence of diabetes by an absolute level of 6·6–13·8% could accelerate the decline of tuberculosis incidence by an absolute level of 11·5–25·2% and tuberculosis mortality by 8·7–19·4%. Compared with the base case scenario, stopping the rise of diabetes would avoid 6·0 million (95% CrI 5·1–6·9) incident cases and 1·1 million (1·0–1·3) tuberculosis deaths in 13 countries during 20 years. If interventions reduce diabetes incidence by 35% by 2025, 7·8 million (6·7–9·0) tuberculosis cases and 1·5 million (1·3–1·7) tuberculosis deaths could be averted by 2035.**

Interpretation **The diabetes epidemic could substantially affect tuberculosis epidemiology in high burden countries. The communicable disease and non-communicable disease sectors need to move beyond conventional boundaries and link with each other to form a joint response to diabetes and tuberculosis.**

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Introduction

Tuberculosis remains a major global health challenge, with 9 million incident cases and 1·5 million deaths worldwide in 2013.[1] In the recently proposed global strategy and targets for tuberculosis control after 2015, WHO aims to reduce incidence of the disease by 90% and mortality by 95% by 2035.[2] However, incidence of tuberculosis decreased only 2% per year despite the implementation of DOTS (directly observed treatment, short-course) strategy for more than two decades. A crucial question for the global tuberculosis community is how to accelerate the decline of disease burden. Several risk factors and comorbidities increase the risk of tuberculosis and could contribute to the future trend of disease epidemiology.[3,4] Therefore, in addition to tackling active tuberculosis disease through improved diagnostics and treatments, primary prevention needs to be considered through management of risk factors in the post-2015 tuberculosis control plan.

Diabetes is a well-known risk factor for tuberculosis morbidity and mortality and is increasingly prevalent in low-income and middle-income countries such as India and China, where the burden of tuberculosis is still high.[5–7] The looming double epidemic of diabetes and tuberculosis can threaten the control of tuberculosis in these high-burden countries. Although diabetes was regarded as an important risk factor for tuberculosis prevention in the post-2015 global tuberculosis strategy, most countries do not have effective collaboration between tuberculosis and diabetes efforts.[2] The results of some studies have estimated the anticipated effect of diabetes on tuberculosis burden.[8–11] However, they all treated tuberculosis as a disease of the individual (such as stroke or heart disease that occur as a result of diabetes) and did not account for the effect of diabetes on tuberculosis transmission, hence underestimating the effect.[12] They also did not account for the trends of increasing diabetes prevalence over time, or changes in tuberculosis prevalence over time as a result of other control efforts (eg, DOTS), and hence cannot accurately inform future policy choices. Using a dynamic model of tuberculosis transmission, we projected the effect of diabetes on tuberculosis epidemiology in countries with the highest burden of tuberculosis worldwide.

Methods

Study population

Of the estimated 9 million new cases of tuberculosis in 2013 more than 80% were from 22 high-burden countries.[1]

We excluded countries with a generalised HIV epidemic (ie, prevalence of HIV infection >1%), because it is difficult to disentangle the potential effects of diabetes on tuberculosis in the presence of HIV. We included the remaining 13 countries (Afghanistan, Bangladesh, Brazil, Cambodia, China, India, Indonesia, Myanmar, Pakistan, Philippines, Russian Federation, Thailand, and Vietnam), which covered 60% of incident cases of tuberculosis in the world, in the analysis (appendix p 6).[1]

See Online for appendix

Analytical model

We constructed a compartmental model of tuberculosis transmission in the adult population (age >20 years). The model followed the conventions adopted by previous epidemic models of tuberculosis.[13,14] Additionally, the model incorporated the effects of diabetes on tuberculosis incidence, mortality, and treatment outcome based on previous epidemiological studies. The population was divided into mutually exclusive compartments based on the natural history of tuberculosis (susceptible, latent infection, infectious with active disease, and recovered; figure 1). Each of these model states were further stratified by diabetes status. We constructed one model for each of the 13 countries with high tuberculosis burden and calibrated the models to the estimated tuberculosis incidence in these countries. We took the Bayesian melding approach to calibrate the models and to account for uncertainty of input parameter values. We used Java SE 7 programming language for model simulations and R (version 3.0.0) for statistical analysis. The appendix shows details of model assumption, parameterisation, and calibration.

Estimating the effect of diabetes on tuberculosis epidemiology

We estimated the future burden of tuberculosis that can be reduced by alternative scenarios of diabetes (avoidable burden) and the reduction in present burden that would occur if the population had not been exposed to diabetes (attributable burden). The time horizon of the analysis was set to show the post-2015 global targets of tuberculosis control (2015–35).[2] We constructed diabetes scenarios that represent the potential ranges of future diabetes prevalence on the basis of estimated trends of diabetes in the 13 countries, the global non-communicable disease target for diabetes (halt the rise in diabetes), and the reported effect of intervention programmes on diabetes incidence (table 1 and figure 2). The analysis was mainly concerned with type 2 diabetes. As a base case scenario, we assumed that the age-specific prevalence of diabetes in each country would continue its present trend linearly if no intervention was implemented. We then used the age-specific diabetes prevalence and projected population structure to project the overall diabetes prevalence for 2015–35.[19] We also assumed that the present control efforts for tuberculosis (diagnosis and treatment for cases of active tuberculosis) would be maintained and no other major interventions for tuberculosis (eg, treatment for latent tuberculosis infection) would be introduced. Alternatively, we constructed two scenarios of diabetes control. In the moderate control scenario, we assumed the rise in diabetes prevalence would stop in 2015; in the aggressive control scenario, we assumed the incidence of diabetes would decrease by 35% between 2015 to 2025 via preventive control measures. Last, we set the worst case scenario (large rise in diabetes prevalence) and best case scenario (reduction of diabetes prevalence to background level) to represent that diabetes prevalence would increase or decrease to the highest or lowest possible values by 2035.

To calculate the avoidable burden, we applied the calibrated country-specific models to estimate the cumulative reduction of tuberculosis incidence and mortality under different scenarios of diabetes. We also computed the number of cases of incident tuberculosis and deaths from tuberculosis that can be avoided over the study period under alternative scenarios of diabetes. The future population size was based on the projected population by the UN Population Division.[19]

To calculate the attributable burden of tuberculosis due to diabetes, we used two different methods to estimate the population attributable fraction: the conventional Levin's formula, and the calibrated epidemic model. For both methods we computed the population attributable fraction of diabetes in the baseline year of 2015. The appendix shows details on estimation of the attributable burden.

Data sources

We obtained the trends of age-specific diabetes prevalence in the model countries from updates of global estimates.[7,20] The relative risks for diabetes and various stages of tuberculosis came from meta-analyses of previous epidemiological studies. In a meta-analysis of three cohort studies, Jeon and colleagues[5] reported a pooled relative risk (RR) of 3·11 for diabetes and active tuberculosis disease. Because there are no data suggesting an effect of diabetes on latent tuberculosis infection, we assumed that the recorded association between diabetes and active tuberculosis was because of an increased risk in tuberculosis progression in the latently infected population.[21] In a systematic review,

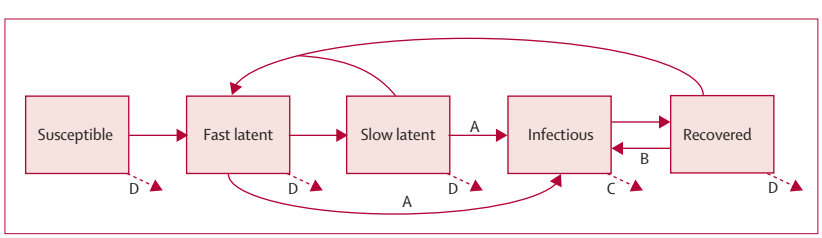

Figure 1: **Compartmental susceptible-latent-infectious-recovered model of tuberculosis transmission and the effects of diabetes on the pathogenesis of tuberculosis in the transmission model**
(A) Diabetes increases the risk of progression from latent infection to infectious active disease. (B) Diabetes increases the risk of relapse after treatment completion. (C) Diabetes increases the risk of death in individuals with active tuberculosis. (D) Diabetes increases the risk of death in the general population without active tuberculosis.

Baker and colleagues[6] noted that diabetes increased the risk of death in individuals with active tuberculosis (RR 1·89) and the risk of relapse after treatment completion (RR 3·89). Finally, diabetes is associated with increased risk of all-cause mortality because it affects a number of other disorders (RR 3·48).[22] We did not

	Definition	Average diabetes prevalence in 2035	Explanation
Large rise (worst case scenario)	Diabetes prevalence in 13 countries will reach 20·6% by 2035	20·6%	The upper bound of diabetes prevalence in all scenarios; diabetes prevalence is expected to increase worldwide because of ageing, urbanisation, and increased prevalence of obesity, physical inactivity, smoking, and unhealthy diet;[7,15] the diabetes prevalence of 20·6% is based on the finding in women in the Oceania region[7]
Continue current trend (base case scenario)	Diabetes prevalence will follow the present rising trend, with an upper bound of 20·6%	16·0%	Without further intervention the age-specific prevalence of diabetes will continue its present trend in each country
Stop rise	Diabetes prevalence will stop rising after 2015	9·4%	Assume the new global non-communicable disease target for diabetes will be reached by 2015[16]
Aggressive intervention	The incidence rate of diabetes will be reduced by 35% between 2015 and 2025	7·4%	Findings of previous studies showed that different intervention strategies can reduce the progression of pre-diabetes to diabetes[17,18]
To background level (best case scenario)	By 2035, diabetes prevalence will gradually decrease to the 1990 background level	2·2%	The lower bound and ideal scenario of diabetes prevalence; the background prevalence in 1900 was derived from external prediction with recorded diabetes prevalence in 1980–2008[7]

Table 1: **Scenarios of diabetes used in the analysis**

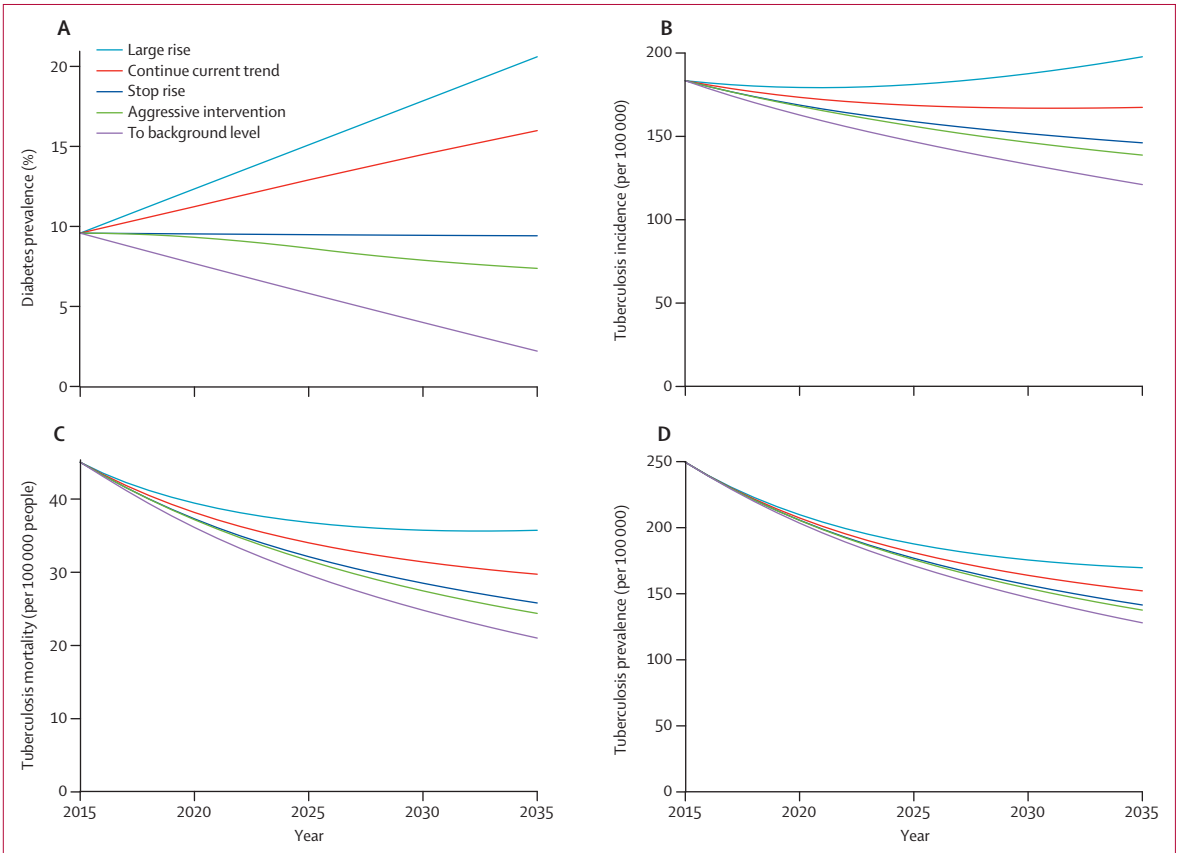

Figure 2: **Scenarios of diabetes prevalence aggregated for 13 countries with high tuberculosis burden (A) and projected tuberculosis incidence (B), mortality (C), and prevalence (D) in these countries under different scenarios of diabetes, 2015–35**

The lines in panels B, C, and D represent the means of posterior simulations from the calibrated models. Table 1 shows definitions of diabetes scenarios. The appendix shows country-specific results.

include the potential effect of tuberculosis on diabetes because it remains unclear whether tuberculosis indeed increases the risk of diabetes.[10]

Uncertainty and sensitivity analysis

The Bayesian calibration approach in our analysis accounted for uncertainty of all input parameters. Of the 100 000 posterior simulations from the Bayesian analysis, we reported the mean as the central estimates and their 2·5th and 97·5th percentiles as the 95% credible intervals (CrIs). We also did one-way sensitivity analyses by changing each parameter to see how it affected our results. The appendix shows details of the uncertainty and sensitivity analysis.

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

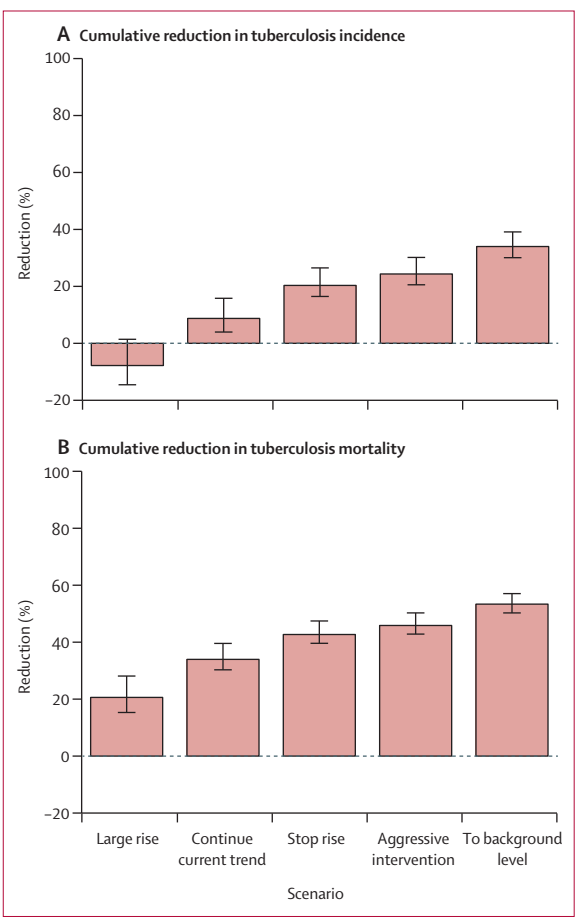

Figure 3: **Cumulative reduction of tuberculosis incidence (A) and mortality (B) in 13 countries with high tuberculosis burden under different scenarios of diabetes, 2015–35**

Table 1 shows definitions of diabetes scenarios. The uncertainty bounds represent 95% credible intervals.

Results

In the base case scenario, countries were assumed to continue the trend of diabetes prevalence. If the present efforts in diagnosis and treatment for active tuberculosis are maintained in these 13 countries and no other major interventions (eg, preventive therapy for latent infection) are introduced, the trend of tuberculosis morbidity and mortality is projected to decrease slowly (figure 2). The projected cumulative reduction by 2035 in tuberculosis incidence is 8·8% (95% CrI 4·0–15·8) and in mortality is 34·0% (30·3–39·6; figure 3).

If the 13 countries can stop the rise of diabetes prevalence and maintain it at 2015 levels, the reduction in tuberculosis by 2035 can be accelerated to 20·3% (95% CrI 16·5–26·5) for incidence and 42·7% (39·6–47·4) for mortality (figures 2 and 3). This change is equivalent to 6·0 million (5·1–6·9) fewer cases of incident tuberculosis during 20 years compared with the base case scenario, with most avoidable cases in India, China, Pakistan, and Bangladesh (75% of all avoidable cases). Similarly, stopping the rise of diabetes can prevent 1·1 million (1·0–1·3) tuberculosis deaths during 20 years (table 2); most avoidable deaths would also be in India, China, Bangladesh, and Pakistan (74% of all avoidable deaths; figure 4 and table 2).

If aggressive interventions decrease diabetes incidence in the 13 countries by 35% by 2025, the decline of tuberculosis incidence can be further accelerated to 24·4% (95% CrI 20·6–30·2), and mortality 45·9% (42·8–50·3) by 2035 (figures 2 and 3). This will translate into 7·8 million (6·7–9·0) fewer cases of incident tuberculosis and 1·5 million (1·3–1·7) fewer tuberculosis deaths during 20 years compared with the base case scenario (table 2). The effect on tuberculosis epidemiology would be the greatest if diabetes prevalence can be gradually lowered to the level of 2·2% (the lower bound of diabetes prevalence; table 1). By 2035, this improvement would accelerate the reduction of tuberculosis incidence to 34·0% (95% CrI 30·1–39·1) and mortality to 53·4% (50·3–57·1), preventing 13·2 million (11·3–15·2) cases of tuberculosis and 2·6 million (2·2–3·0) tuberculosis deaths in the 13 countries.

In the worst case scenario, in which diabetes prevalence in the 13 countries rises to reach 20·6% by 2035, the declining trend of incidence of tuberculosis will be reversed (figure 2). The cumulative increase in tuberculosis incidence over 20 years will be 7·8% (95% CrI −1·4–14·5) and the cumulative reduction in tuberculosis mortality will be 20·6% (15·3–28·1; figures 2 and 3).

In the analysis of attributable burden, the conventional method showed that 11·9% (Vietnam) to 19·7% (Thailand) of cases of tuberculosis could be attributed to the risk factor of diabetes (appendix p 9). When we used the calibrated epidemic model to account for the transmission in cases of tuberculosis, the estimated population attributable fractions increased in all countries, ranging from 21·2% (Cambodia) to 53·5% (Thailand).

In sensitivity analyses, we found that the effect of reducing diabetes prevalence on tuberculosis incidence and mortality was most sensitive to the relative risks for relapse and progression for patients with diabetes (compared with patients without diabetes), transmission parameter, partial immunity, and tuberculosis-specific mortality rate (appendix pp 19–22).

Discussion

With a calibrated, multi-country epidemic model, we investigated the effect of diabetes prevalence on the present and future epidemiology of tuberculosis. We found that the single risk factor of diabetes could substantially affect the trajectory of tuberculosis morbidity and mortality in 13 countries with high tuberculosis burden in the next 20 years (panel). Prevention of diabetes provides an opportunity to accelerate the decline of tuberculosis incidence and mortality in countries with the highest tuberculosis burdens. Insufficient attention to the rising prevalence of diabetes in countries with a high tuberculosis burden could undermine the global effort to control tuberculosis, or even reverse the declining trend of tuberculosis incidence.

In our base case scenario in which we assumed that diabetes prevalence would continue the present upward trend and tuberculosis intervention would only focus on diagnosis and treatment of active disease, by 2035, the incidence of tuberculosis would only decrease by 8·8% and mortality by 34·0% in 13 high tuberculosis burden countries. Despite increased access to diagnosis and treatment for tuberculosis, the level of latent tuberculosis infection would remain high for several decades in these countries (appendix p 23), and an increasing proportion of cases of tuberculosis would arise as a result of endogenous reactivation rather than recent transmission. Therefore, the recorded decline of tuberculosis is expected to slow down if the control programme only focuses on treating patients with active tuberculosis (ie, reducing recent transmission). Prevention of diabetes has the potential to lower the risk of reactivation in patients with latent tuberculosis infection[23] and could complement the strategy of treatment of active cases. Indeed, the findings of our analysis showed that reduction of the prevalence of diabetes to different levels could accelerate the decline of tuberculosis but would not be sufficient to achieve the post-2015 targets. Our results strongly support the new global tuberculosis control strategy, and that a multifaceted approach including integrated patient care for all forms of tuberculosis, actions on risk factors for tuberculosis (such as diabetes), and introduction of new vaccines and prophylaxis will be needed if a large reduction of tuberculosis is to be achieved.

Previous studies used the conventional population attributable fraction analysis to assess the effect of the diabetes epidemic on tuberculosis incidence. Stevenson and colleagues[9] estimated the population attributable fraction of diabetes on the incidence of tuberculosis in India, stratified by age, sex, and urbanicity. The researchers noted that diabetes accounted for 14·8% of pulmonary tuberculosis and 20·2% of smear-positive tuberculosis in the country. In another population attributable fraction analysis of 22 countries with high tuberculsosis burden, 3·4%–15·9% of adult tuberculosis cases were estimated to be attributable to diabetes.[4] Finally, with a population attributable fraction model that incorporates the exponential decline of tuberculosis in each WHO region, Odone and colleagues[8] estimated that a large rise in diabetes prevalence (by 25%) worldwide would increase incidence of tuberculosis by 8% by 2035. As also noted by Odone and colleagues, the population attributable fraction analysis is suitable only for assessing the effect of a risk factor on chronic diseases in which the risk for disease in individuals can be deemed independent (eg, diabetes and stroke). In the present study, we did two separate population attributable fraction analyses, one with the conventional method and the other with the calibrated epidemic model to account for the dependence of disease risk in individuals in the population (appropriate for an infectious disease such as tuberculosis). We found that the conventional method tended to underestimate the effect of the risk factor. Our analytic approach can be the basis for future studies on the population level effect of risk factors on infectious diseases.

In our analysis, we took a simplified approach to divide the population into those with diabetes and those without. In reality, people with diabetes might have different levels of glycaemic control, and their risk of tuberculosis might

	Incident cases of tuberculosis (thousands)		Deaths caused by tuberculosis (thousands)	
	Stop rise*	Aggressive intervention*	Stop rise*	Aggressive intervention*
Afghanistan	70 (45–94)	95 (62–128)	18 (12–25)	25 (16–34)
Bangladesh	518 (349–704)	650 (438–883)	137 (93–185)	171 (116–232)
Brazil	28 (18–37)	40 (26–52)	4 (3–5)	5 (4–7)
Cambodia	99 (66–133)	119 (79–160)	17 (11–23)	20 (14–27)
China	1649 (1090–2263)	1926 (1278–2636)	207 (136–287)	241 (158–333)
India	1795 (1207–2363)	2629 (1773–3462)	364 (252–506)	530 (368–738)
Indonesia	395 (242–572)	514 (315–743)	76 (48–108)	97 (62–139)
Myanmar	197 (135–258)	252 (173–330)	34 (24–47)	44 (30–59)
Pakistan	530 (354–696)	701 (469–918)	128 (82–174)	169 (108–230)
Philippines	222 (148–296)	309 (207–413)	42 (28–59)	58 (38–82)
Russian Federation	55 (47–70)	82 (70–104)	11 (10–13)	16 (14–20)
Thailand	172 (115–224)	213 (143–277)	37 (25–48)	46 (32–59)
Vietnam	247 (165–332)	303 (203–407)	55 (38–75)	68 (46–92)
Total	5976 (5128–6927)	7833 (6716–9035)	1129 (970–1300)	1489 (1274–1725)

Data are n (95% credible interval). The reference (base case scenario) assumes that diabetes prevalence will continue to follow the present rising trend. *Table 1 gives a detailed description of scenarios for diabetes prevalence.

Table 2: **Avoidable cases of tuberculosis and deaths from tuberculosis by reducing diabetes prevalence in 13 high burden countries, 2015–35**

not be homogeneous. We chose this simplified approach because most epidemiological studies of diabetes and tuberculosis only considered diabetes as a dichotomous exposure (diabetes *vs* no diabetes); therefore, information about the relative risk for diabetes and tuberculosis was confined to this dichotomous level. Although glycaemic

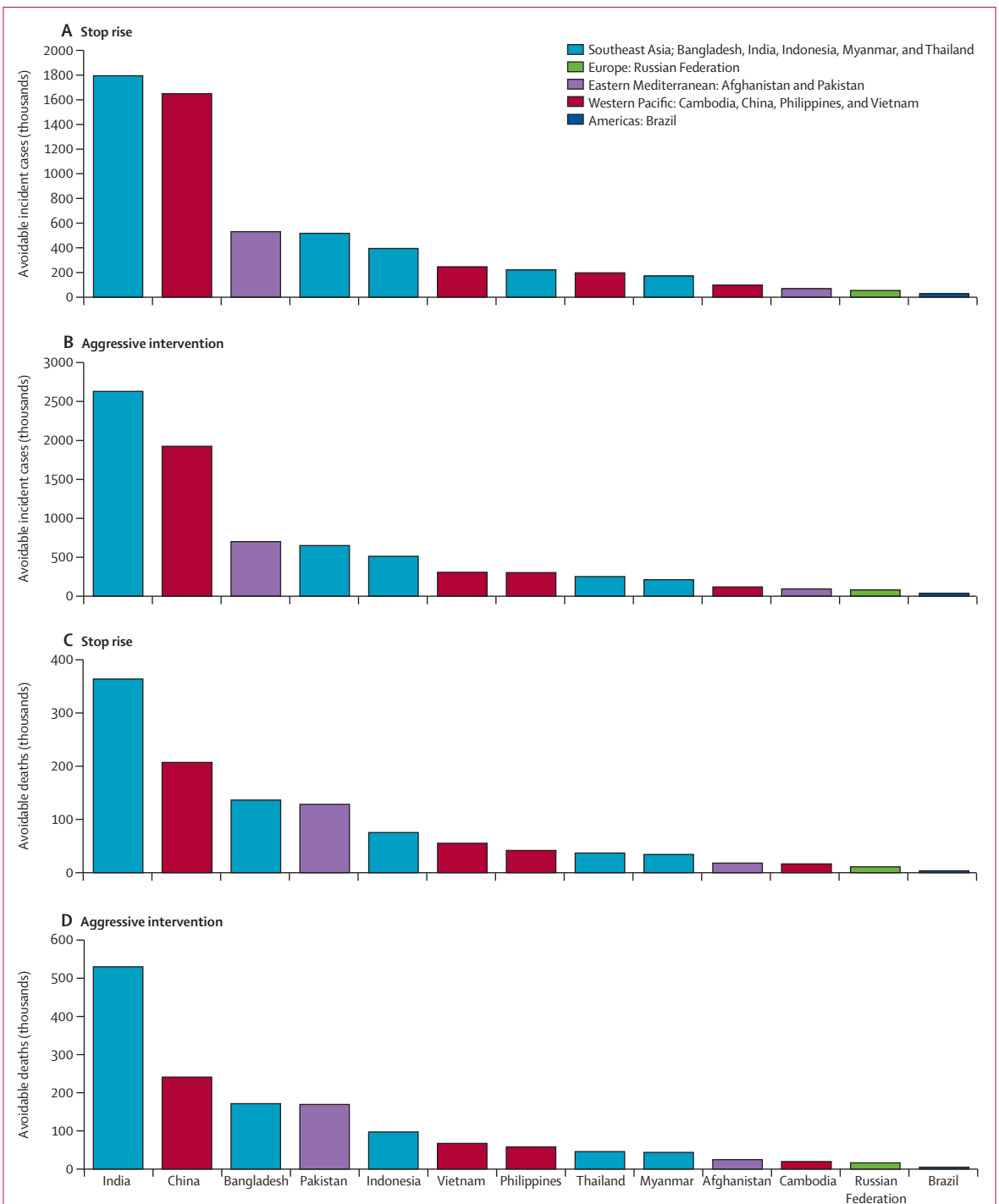

Figure 4: **Avoidable cases of incident tuberculosis and tuberculosis deaths in 13 countries with a high burden of tuberculosis if the rising prevalence of diabetes is stopped in 2015 (A and C) and if the incidence of diabetes is reduced by 35% (aggressive intervention) by 2025 (B and D)**
Numbers presented are cumulative cases or deaths from 2015 to 2035. The base case (reference) scenario assumes that the prevalence of diabetes will continue the present rising trend.

control has the potential to reduce or even reverse the risk of diabetes on tuberculosis, evidence on the effect of glycaemic control on tuberculosis is still limited.[23] Future analysis should explore the effect of diabetes management (glycaemic control) on tuberculosis when relevant evidence becomes available.

In addition to prevention and management of diabetes as a means of tuberculosis control, we note that diabetes can be the entry point for tuberculosis control in several ways. First, improved management and follow-up of patients with concurrent tuberculosis and diabetes might reduce mortality, relapse, and transmission of tuberculosis. Second, screening for latent tuberculosis infection in people with diabetes, followed by subsequent management in those with latent infection (including prophylactic treatment and glycaemic control), provides an additional opportunity to prevent active tuberculosis disease in a high-risk population. Further research is needed to explore the effects of these approaches.

One limitation of dynamic modelling is that the results can be affected by the assumptions on model structure and uncertainties in various model parameters. The values of input parameters might also change as a result of tuberculosis control and societal factors. To explore the effect of uncertainty in parameter values, we did multivariable uncertainty analysis to estimate the 95% CrI in the model outputs. However, additional sources of uncertainty could exist. For example, several important risk factors for tuberculosis, including HIV and nutritional status (usually measured by BMI) were not included in the model. With the increasing availability of anti-retroviral therapies globally, the HIV epidemic might change substantially in the near future.[24] Thus, the results might not be generalisable to countries with a high HIV burden. Being overweight and obese decreases the risk of tuberculosis but increases the risk of diabetes.[25] If future increases in diabetes prevalence are accompanied by increased BMI at the population level, the negative effect of diabetes on tuberculosis might be offset by the positive effect of increased BMI. Further studies are needed to address the interaction between BMI, diabetes, and tuberculosis.[8]

Additionally, the age effect was incorporated in our analysis only implicitly, and there was no explicit age structure in the model (appendix). When projecting the future trends of diabetes prevalence under the base case scenario, we assumed that the age-specific diabetes prevalence would increase linearly, as in the previous 10 years. If the trend rises more quickly in future the linear trend, our estimated effect of diabetes prevention on tuberculosis incidence and mortality could be an underestimate, and the actual effect might be even greater. Previous data suggested that diabetes might be associated with increased frequency of cavitary lesion (ie, the highly infectious form of tuberculosis) in patients with tuberculosis.[26] In the present model, we assumed that patients with diabetes and tuberculosis were as infectious as patients with tuberculosis without diabetes because quantitative information about differential infectiousness was not available. Therefore our analysis could have underestimated the overall effect of diabetes on tuberculosis. Finally, we considered different scenarios of diabetes prevalence instead of specific interventions for diabetes. Further research is needed to understand the cost-effectiveness of diabetes interventions on reducing tuberculosis burden.

Our analysis has crucial implications for global tuberculosis control and on the Sustainable Development Goal on health, which aims to reduce premature deaths from communicable and non-communicable diseases. With the rising trend of non-communicable diseases, low-income and middle-income countries will soon be confronted with the challenge of dual epidemics of communicable and non-communicable diseases. Interventions that tackle active tuberculosis (eg, adherence to the DOTS strategy and introduction of new diagnostics and new treatment regimens) are still the cornerstone of tuberculosis control in these countries. However, individuals saved by tuberculosis interventions could die prematurely from non-communicable diseases if their rising trend continues. Prevention and management of diabetes promises to reduce the disease burden from tuberculosis and non-communicable diseases simultaneously. So far the disease management programmes in most countries are vertical and driven by highly specialised health sectors.[27] It is time to think outside the box and reach beyond the domain-oriented

***Panel:* Research in context**

Systematic review

We searched PubMed for articles published in English on the effect of diabetes on tuberculosis epidemiology up until Sept 21, 2014. We used the search terms "tuberculosis" and "diabetes" and "epidemiology" and restricted the search to studies of human beings. All the studies identified in the review estimated the effect of diabetes on tuberculosis with a non-dynamic modelling approach (eg, Lonnroth and colleagues, Odone and colleagues, and Stevenson and colleagues). We did not find any study that assessed the effect of diabetes on tuberculosis and accounted for the effect of diabetes on transmission.

Interpretation

Our analyses provide the first assessment of the effect of diabetes on tuberculosis epidemiology by use of a dynamic transmission model. Our results support the post-2015 global tuberculosis control strategy that prevention and control of diabetes could be an important component in tuberculosis control. Importantly we found that non-dynamic models tend to underestimate the population level effect of risk factors on infectious diseases like tuberculosis. Our research provides a methodological framework for future studies on the population level effect of risk factors on infectious diseases.

approach for disease control and prevention. In practice, this approach means that the communicable disease sector and the non-communicable disease sector need to break the conventional boundary and link with each other to make integrated national health policies for issues like diabetes and tuberculosis.[28] Examples include bidirectional screening of diabetes and tuberculosis in primary health care centres and adapting the well-established DOTS framework to non-communicable disease management in resource-limited settings.[29]

Contributors

S-CP and H-HL designed the study. S-CP, C-CK, and DK did data analysis. S-CP, C-TF, ME, and H-HL wrote the first draft of the manuscript. All authors reviewed and approved the final report.

Declaration of interests

We declare no competing interests.

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References

1 WHO. Global tuberculosis report 2014. 2014 [cited 2014 Nov. 1]; Available from: http://www.who.int/tb/publications/global_report/en/.

2 WHO. Global strategy and targets for tuberculosis prevention, care and control after 2015. 2013 [cited 2014 July 25]; Available from: http://www.who.int/tb/post2015_TBstrategy.pdf?ua=1.

3 Dye C, Lönnroth K, Jaramillo E, Williams BG, Raviglione M. Trends in tuberculosis incidence and their determinants in 134 countries. *Bull World Health Organ* 2009; **87:** 683–91.

4 Lönnroth K, Castro KG, Chakaya JM, et al. Tuberculosis control and elimination 2010–50: cure, care, and social development. *Lancet* 2010; **375:** 1814–29.

5 Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 2008; **5:** e152.

6 Baker MA, Harries AD, Jeon CY, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med* 2011; **9:** 81.

7 Danaei G, Finucane MM, Lu Y, et al, and the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Glucose). National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. *Lancet* 2011; **378:** 31–40.

8 Odone A, Houben RMGJ, White RG, Lönnroth K. The effect of diabetes and undernutrition trends on reaching 2035 global tuberculosis targets. *Lancet Diabetes Endocrinol* 2014; **2:** 754–64.

9 Stevenson CR, Forouhi NG, Roglic G, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. *BMC Public Health* 2007; **7:** 234.

10 Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. *Lancet Infect Dis* 2009; **9:** 737–46.

11 Dye C, Bourdin Trunz B, Lönnroth K, Roglic G, Williams BG. Nutrition, diabetes and tuberculosis in the epidemiological transition. *PLoS One* 2011; **6:** e21161.

12 Murray M, Oxlade O, Lin HH. Modeling social, environmental and biological determinants of tuberculosis. *Int J Tuberc Lung Dis* 2011; **15** (suppl 2)**:** S64–70.

13 Cohen T, Lipsitch M, Walensky RP, Murray M. Beneficial and perverse effects of isoniazid preventive therapy for latent tuberculosis infection in HIV-tuberculosis coinfected populations. *Proc Natl Acad Sci USA* 2006; **103:** 7042–47.

14 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.

15 Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world--a growing challenge. *N Engl J Med* 2007; **356**: 213–15.

16 WHO. Draft comprehensive global monitoring framework and targets for the prevention and control of noncommunicable diseases. March 13, 2013. http://apps.who.int/gb/ebwha/pdf_files/WHA66/A66_8-en.pdf (accessed Feb 12, 2015).

17 Lindström J, Ilanne-Parikka P, Peltonen M, et al, and the Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006; **368:** 1673–79.

18 Tuomilehto J, Lindström J, Eriksson JG, et al, and the Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; **344:** 1343–50.

19 UN Population Division. World population prospects, the 2010 revision. http://esa.un.org/wpp/Excel-Data/population.htm (accessed Feb 19, 2015).

20 Kontis V, Mathers CD, Rehm J, et al. Contribution of six risk factors to achieving the 25×25 non-communicable disease mortality reduction target: a modelling study. *Lancet* 2014; **384:** 427–37.

21 WHO and The International Union Against Tuberculosis and Lung Disease. Collaborative framework for care and control of tuberculosis and diabetes. Geneva, Switzerland: World Health Organization, 2011.

22 Roglic G, Unwin N, Bennett PH, et al. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. *Diabetes Care* 2005; **28:** 2130–35.

23 Leung CC, Lam TH, Chan WM, et al. Diabetic control and risk of tuberculosis: a cohort study. *Am J Epidemiol* 2008; **167:** 1486–94.

24 Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009; **373:** 48–57.

25 Lönnroth 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.

26 Wang JY, Lee LN, Hsueh PR. Factors changing the manifestation of pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2005; **9:** 777–83.

27 Nigatu T. Integration of HIV and noncommunicable diseases in health care delivery in low- and middle-income countries. *Prev Chron Dis* 2012; **9:** E93.

28 Marais BJ, Lönnroth K, Lawn SD, et al. Tuberculosis comorbidity with communicable and non-communicable diseases: integrating health services and control efforts. *Lancet Infect Dis* 2013; **13:** 436–48.

29 Harries AD, Jahn A, Zachariah R, Enarson D. Adapting the DOTS framework for tuberculosis control to the management of non-communicable diseases in sub-Saharan Africa. *PLoS Med* 2008; **5:** e124.