Diabetes and tuberculosis 3

The effect of diabetes and undernutrition trends on reaching 2035 global tuberculosis targets

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This is the third paper in a Series of three papers about diabetes and tuberculosis

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To achieve the post-2015 global tuberculosis target of 90% reduction in tuberculosis incidence by 2035, the present rate of decline must accelerate. Among factors that hinder tuberculosis control, malnutrition and diabetes are key challenges. We review available data to describe the complex relationship between tuberculosis, diabetes, and nutritional status. Additionally, we review past trends, present burden, and available future global projections for diabetes, overweight and obesity, as well as undernutrition and food insecurity. Using a mathematical model, we estimate the potential effect of these factors on tuberculosis burden up to 2035. Great potential exists for reduction of worldwide tuberculosis burden by combination of improved prevention and care of diabetes with reduction of undernutrition. To achieve this combination will require joint efforts and strong cross-programme links, enabling synergistic effects of public health policies that promote good nutrition and optimum clinical care for tuberculosis and diabetes.

Introduction

In May 2014, the 67th World Health Assembly passed a resolution on the global strategy and targets for tuberculosis prevention, care, and control after 2015.[1] During the past two decades, global efforts to control tuberculosis have resulted in cure of 56 million patients and reduced tuberculosis mortality substantially.[2] However, tuberculosis remains a major global public health concern, accounting for 8·6 million new cases, 1·3 million deaths,[2] and more than 49 million disability-adjusted life-years (DALYs) lost every year.[3] Additionally, the tuberculosis epidemic has vast social effects, with a particularly high burden on the poor,[2] which is not captured by mortality, incidence, and DALY indicators.

The three pillars of the new global tuberculosis strategy are: integrated, patient-centred care and prevention; bold policies and supportive systems; and intensified research and innovation. The strategy has a renewed focus on prevention, and its components include, among others, management of comorbidities, action on tuberculosis risk factors and underlying determinants, and treatment of latent tuberculosis infection (LTBI) for people at high risk.[4] Undernutrition and diabetes are identified as among the main challenges for effective tuberculosis care and prevention.[4] Both factors increase the risk of development of active tuberculosis by about three times; they also increase risk of poor tuberculosis treatment outcomes, including death, treatment failure, and relapse.[5–9] At the same time, these factors are linked elements of individuals' nutritional profiles. Changes in the prevalence and distribution of diabetes and under-nutrition at the global level—in the context of the ongoing epidemiological transition—are likely to affect future tuberculosis burden.[10,11]

The post-2015 global tuberculosis targets include reduction of tuberculosis incidence by 90% by 2035.[4] To achieve this target, an acceleration of the present rate of tuberculosis decline is needed.[12,13] Thus, it is crucial to understand how changing trends in important tuber-culosis determinants such as diabetes and undernutrition will affect progress towards the new targets. Additionally, it is important to determine what actions are needed to move towards integration of tuberculosis control with improved nutrition and prevention and management of non-communicable diseases (NCDs);[14] such actions will likely include strengthening of health systems at many levels and social protection.[13]

Actions to address diabetes and undernutrition are already incorporated into the post-2015 global tuber-culosis strategy.[1,13] However, the potential effect of those actions on global tuberculosis epidemiology has not previously been assessed. In this Series paper, we first review epidemiological and biological evidence to describe the complex relationship between tuberculosis, diabetes, and nutritional status. We then review at the global level: past trends; present burden and future projections in diabetes, overweight, and obesity; and undernutrition and food insecurity. Last, we estimate how different scenarios (table; panel 1) of future trends for diabetes and undernutrition could affect tuberculosis epidemiology until 2035, and discuss implications for synergistic actions to address these determinants.

Nutritional status, diabetes, and tuberculosis

Solid epidemiological evidence indicates that poor nutritional status is a risk factor for tuberculosis,[8,9] and the biological basis of the relationship has been well described.[8] Data from studies in humans and animals show that vulnerability to progression from tuberculosis infection to active tuberculosis is related to macronutrient deficiencies that induce impairment of cellular immunity, and that this impairment is rapidly reversed with nutritional rehabilitation.[8] Improved nutritional status has contributed to the decrease in tuberculosis burden in industrialised countries during the past century,[15,16] and is contributing to the present global decline. Historical

	Short description	Parameters			
		Diabetes prevalence	RR of tuberculosis by diabetes status (95% CI)*	Undernutrition prevalence	RR of tuberculosis by undernutrition status (95% CI)*
Baseline	Present trajectory	-	-	-	-
1	Increase in diabetes prevalence and no change in undernutrition	Projected increase†	3·11 (2·27–4·26)[6]	2013 prevalence unchanged‡	3·2 (3·1–3·3)[7]
2	Increase in diabetes prevalence and undernutrition	Projected increase†	3·11 (2·27–4·26)[6]	25% increase by 2035 as compared with 2013 prevalence‡	3·2 (3·1–3·3)[7]
3	Large increase in diabetes prevalence	Projected increase† + 25%	3·11 (2·27–4·26)[6]	2013 prevalence unchanged‡	3·2 (3·1–3·3)[7]
4	Undernutrition eradication	Projected increase†	3·11 (2·27–4·26)[6]	Reduced to 0% by 2035	3·2 (3·1–3·3)[7]
5	Effect of diabetes on tuberculosis mitigated	No impact of diabetes on tuberculosis	1·00	2013 prevalence unchanged‡	3·2 (3·1–3·3)[7]
6	Effect of diabetes on tuberculosis mitigated and undernutrition eradication	No impact of diabetes on tuberculosis	1·00	Reduced to 0% by 2035	3·2 (3·1–3·3)[7]

RR=relative risk. *Estimated as RR (95% CI).†As estimated in the 6th edition of the Diabetes Atlas published by the International Diabetes Federation (IDF); projected increases in prevalence are shown in figure 1B.[49] ‡As estimated by the UN Food and Agriculture Organization.[51]

Table: **Description and parameters of the baseline, three pessimistic, and three optimistic scenarios**

evidence and ecological studies show that tuberculosis incidence has increased during times of food insecurity, famine, and high prevalence of starvation.[8,9,15,17] Data from the sociomedical experiment at the Papworth Village Settlement in England during 1918–43 showed that provision of adequate nutrition to children reduced tuberculosis incidence and associated deaths.[16] Similarly, in the pre-chemotheraphy era, tuberculosis incidence in war camps was 93% lower among British soldiers receiving Red Cross nutritional supplementation compared with Russian prisoners who did not.[18]

A systematic review and meta-analysis quantified the association between undernutrition and tuberculosis by pooling data from six cohort studies with a total sample size of more than 2·5 million people.[9] The authors reported a dose–response relationship between BMI status and tuberculosis, with a reduction in tuberculosis incidence of 13·8% (95% CI 3·4–14·2) per unit increase in BMI.[9] With application of previously used assumptions for undernutrition (BMI <18·5 kg/m²),[19] the relative risk of tuberculosis in people with undernutrition compared with those without undernutrition is estimated to be 3·2 (95% CI 3·1–3·3).[7] Because tuberculosis disease leads to loss of appetite, changes in micronutrient and macronutrient status, and, ultimately, weight loss,[8] the temporal association between nutritional status and tuberculosis is difficult to ascertain; thus, studies with cross-sectional or case-control designs were not included in the systematic review. Some evidence suggests that low birthweight and exposure to malnutrition in early childhood might predispose to increased vulnerability to tuberculosis and other infections through a mechanism of compromised immune and thymic function.[16,20,21]

The systematic review[9] found not only that people with healthy weight have lower tuberculosis incidence than do people who are underweight, but also that people who are overweight have even lower tuberculosis incidence. This finding was consistent across all reviewed studies. Two of three studies that included obese (BMI 30 kg/m²) people found that obese people have even lower tuberculosis incidence than do those who are overweight. However, the confidence intervals for tuberculosis incidence in this BMI category were wide, and the third of three studies did not find further risk reduction in obese people compared with overweight people. The authors of the systematic review concluded that the dose–response relationship is clear

Panel 1: Scenarios for modelled effect on tuberculosis incidence

The baseline scenario for our model of projected tuberculosis disease incidence assumed that present declining trends (2011–12)[2] would continue between 2013 and 2035. The pessimistic scenarios explored what would happen if diabetes prevalence increased as predicted by the IDF[49] (scenario 1 and 2) or more (scenario 3), with either no progress assumed in eradication of undernutrition (scenarios 1 and 3), or undernutrition prevalence increasing (scenario 2). The optimistic scenarios explored the effect of eradication of undernutrition only (scenario 4), of complete mitigation of the effect of diabetes on tuberculosis (scenario 5), or both (scenario 6). The table describes the six scenarios.

Uncertainty and sensitivity analyses

We expressed the uncertainty in our results by:

i) Sampling the risk ratios for diabetes (R_d) and undernutrition (R_u) within the 95% confidence intervals 1 million times, and calculating the prediction interval of the estimated distribution in tuberculosis incidence. We assumed that the risk ratios followed a log-normal distribution, and reported the point estimates together with corresponding predictive intervals.

ii) Assuming trends in tuberculosis incidence decrease in the baseline scenario ($z[r]$) were equal to the annual decrease in tuberculosis incidence estimated by WHO for 2005–12 rather than 2011–12.[2]

up to BMI 30 kg/m², but uncertain above this. The possible biological mechanisms for the apparent protective effect of being overweight are not yet understood. Overweight and obesity might have a direct protective effect on tuberculosis risk, but an indirect detrimental effect through diabetes.

Being overweight or obese is associated with increased risk of type 2 diabetes[22] and diabetes-associated mortality.[23] Results of a meta-analysis[22] of prospective cohort studies showed that, overall, overweight people have almost three times the risk of developing type 2 diabetes than do people with a healthy weight (Relative Risk 2·99, 95% CI 2·42–3·72), and that obese people have more than seven times the risk (7·19, 5·74–9·00). Although results of a previous meta-analysis showed a dose–response relationship between increasing BMI and risk of diabetes,[24] evidence from other studies suggests that the relationship might not be linear, and that positive associations hold true only for high BMI values.[25,26] We speculate that the confounding effect of factors such as physical activity[27] might partly explain discrepancies between findings. Also, some results,[28] but not others,[29] suggest that abdominal obesity might be a better indicator of diabetes risk than is BMI. To further complicate matters, undernutrition might also be involved in the pathogenesis of diabetes, both directly (through progressive damage of β cells and consequent impairment of glucose tolerance) and indirectly (through increasing vulnerability to other diabetes risk factors, such as heredity, viruses, and dietary toxins).[30] Indeed, a high prevalence of diabetes has been reported in people with healthy or low weight in several low-income and middle-income countries.[31] Coexistence of undernutrition and diabetes might therefore be common among disadvantaged people, adding to the increased exposure of this population to other tuberculosis risk factors such as crowding, indoor air pollution, and poor living conditions. Possible synergistic effects between these risk factors have yet to be studied.[32]

Diabetes is associated with increased risk of active tuberculosis and with worse tuberculosis outcomes.[13,33] The most recent and comprehensive systematic review and meta-analysis that estimated the risk of tuberculosis associated with diabetes was based on 13 observational studies of adult populations, and presented results adjusted by age.[6] A pooled effect estimate was obtained through random-effects meta-analysis of three cohort studies, and showed that diabetes was associated with increased risk of active tuberculosis (RR 3·11, 95% CI 2·27–4·26).[6] Results of studies with other designs were not pooled because of a high degree of heterogeneity, but consistently showed positive associations (RRs ranged from 1·16 to 7·83).[6] Findings from another systematic review published one year earlier are similar;[34] both studies also reported higher relative risk of tuberculosis with younger age. Although few studies in Africa and other low-income settings were included in the reviews, evidence from original studies done in Tanzania, India, west Africa, and the Middle East showed similar findings.[35–39] Levels of hyperglycaemia associated with prediabetes have also been reported to correlate with increased risk of tuberculosis.[40] At the population level, a longitudinal analysis of 163 countries reported increased tuberculosis incidence and prevalence in settings where diabetes prevalence increased over time.[11] With regard to tuberculosis outcomes, Baker and colleagues[5] did a systematic review of work published until 2010 and reported that diabetes is associated with increased risk of death in patients with tuberculosis (RR 1·89, 95% CI 1·52–3·36, increasing to 4·95, 2·69–9·10 when restricting the analysis to studies that accounted for the confounding effect of age and other factors), or treatment failure, and relapse (RR 3·89, 2·43–6·23). This association not only has a negative effect on individual outcomes but also increases the risk of secondary transmission and, ultimately, incidence of tuberculosis disease.[5] The biological plausibility of the association between diabetes and tuberculosis outcomes observed at the individual and population level is supported by evidence from animal models, experimental studies on plasma cells, and epidemiological data that have shown that diabetes directly impairs both innate and adaptive immune responses.[41–46]

Global burden and past trends in the context of the ongoing epidemiological transition

12% of the global population is undernourished,[47] 37% of adults are overweight or obese,[48] and 8·3% of adults have diabetes.[49] The prevalence of global undernourishment decreased from 18·9% in 1990–92 to 12·0% in 2011–13, approaching the third target of the UN Millennium Development Goal 1, which was to halve the proportion of people who suffer from undernourishment between 1990 and 2015.[50] Although globally the number of undernourished people has reduced overall, different rates of progress across regions have led to changes in the distribution of undernourished people in the world.[47] The decrease between 1990–92 and 2011–13 has been highest in southeast Asia (–65·6%) and lowest in Oceania (–10·4%).[51] In Africa, undernourishment prevalence decreased by nearly 23% during the same study period, corresponding to an annual decrease of 1%.[51] Although undernourishment has been steadily decreasing in the past two decades, 870 million people worldwide—one in eight—still suffer from hunger.[16] The UN Food and Agriculture Organization estimates that a fifth of the population of Africa is undernourished—far from the food security goal (Goal 5) to end hunger proposed by the High-Level Panel of Eminent Persons for the Post-2015 Development Agenda.[52]

In the ongoing process of the epidemiological transition, global undernutrition burden coexists with increasing trends in overweight and obesity. An analysis of data from

199 countries and 9·1 million participants reported that mean BMI increased by 0·4 kg/m² per decade in men and 0·5 kg/m² per decade in women in the period 1980–2008.[53] A systematic analysis for the Global Burden of Disease, published in May, 2014, estimated that worldwide prevalence of overweight and obesity combined in adults increased by 27·5% in the period 1980–2013, reaching 36·9% in men and 38·0% in women, totalling 2·1 billion people in 2013.[48] However, regional and country differences exist. The prevalence of overweight and obesity is high and increasing not only in high-income countries;[54,55] a similar phenomenon is occurring in middle-income and low-income settings.[56–61] Additionally, whereas since 2006 the rate of increasing obesity prevalence has slowed in some high-income countries, in low-income and middle-income countries, where two-thirds of all obese individuals live, data suggest the rate is accelerating.[48]

Adult global diabetes prevalence has increased by 20% in less than 30 years.[62] The number of people with diabetes increased from 153 million (95% CI 127–182) in 1980 to 347 million (314–382) in 2008. About 70% of the 194 million additional diabetes cases that occurred between 1990 and 2008 are reportedly due to population growth and ageing, and 30% to increased prevalence of diabetes risk factors related to fetal and childhood nutritional status, diet, and physical inactivity affecting overweight and obesity rates.[62] The rate of change in diabetes prevalence varies by geographical setting. In particular, massive ongoing urbanisation in several African countries is changing lifestyles and dietary habits, and is one of the main reasons for increase in diabetes incidence.[63,64] The International Diabetes Federation (IDF) estimates that 382 million people have diabetes worldwide,[49] corresponding with an adult prevalence of more than 9% in European, American, and eastern Mediterranean regions (figure 1). 80% of people with diabetes live in low-income and middle-income countries.

The 66th World Health Assembly in 2013 endorsed the WHO Global Action Plan for the Prevention and Control of NCDs, which set the global target to halt the rise in diabetes and obesity between 2013 and 2020.[65] This endorsement represents an important commitment by the global community; however, in view of the fact that although some countries reported a levelling off of the obesity epidemic, especially in children and adolescents,[66] no countries have reported downward trends in overweight and obesity in the past three decades,[48] such a goal seems ambitious.

Projections of tuberculosis burden to 2035

The effect of diabetes

We created an analytical model to estimate the effect of diabetes and undernutrition on projected tuberculosis epidemiology until 2035 under different scenarios (panels 1 and 2). In 2011–12, tuberculosis incidence decreased globally by 2%;[2] if this small decrease persists in a linear way, by 2035 tuberculosis incidence will be decreased by about 40% compared with 2012. This would correspond with an annual disease incidence of about 72 per 100 000 people in 2035, which is far below the agreed 2035 targets of a 90% reduction and less than 10 per 100 000 people. At the regional level, if we assume the estimated 2011–12 tuberculosis incidence trend to persist linearly in all WHO regions, only the European region would meet the 90% reduction target by 2035; the African and American regions will reach only 50%, the western Pacific region 43%, the southeast Asian region 37% and the eastern Mediterranean region less than 10%. Figure 2 shows corresponding 2035 tuberculosis incidence absolute values in this baseline scenario for every region. Sensitivity analysis showed that if the assumed decline in tuberculosis incidence was based on 2005–12 annual trends, rather than on 2011–12 trends, the expected decline until 2035 would be even lower (appendix).

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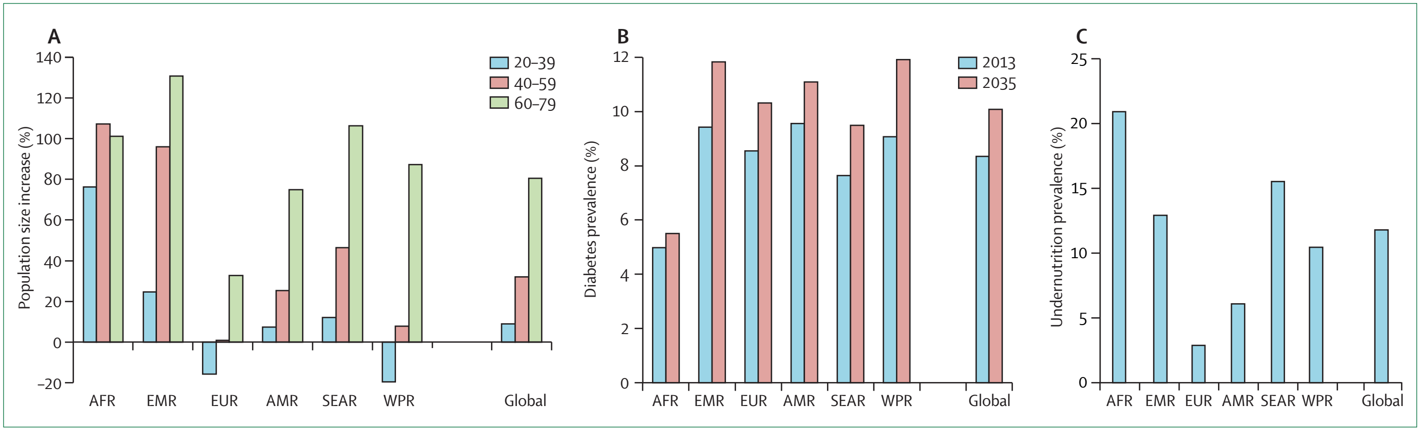

Figure 1: **Data on population size, diabetes prevalence, and undernutrition prevalence, globally and by WHO region**
Population size increase in 2013–35 by age group (years) and by WHO region (A). Diabetes prevalence in 2013 and 2035 in the adult population (20–79 years), by WHO region (B). Undernutrition prevalence in 2013 by WHO region (C). AFR=African region. EMR=eastern Mediterranean region. EUR=European region. AMR=Americas region. SEAR=southeast Asian region. WPR=western Pacific region. Data in A are from UN, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2012 Revision.[67] Data from B are from the International Diabetes Federation Atlas 2013.[49] Data from C are from the UN Food and Agriculture Organization, food security indicators.[51] All data are freely available online.

Panel 2: **The model**

We created an analytical model to estimate how future trends in diabetes and undernutrition prevalence could affect tuberculosis epidemiology until 2035. The model was parameterised from published data on present tuberculosis incidence, prevalence of diabetes and undernutrition, and risk of tuberculosis associated with diabetes and undernutrition. We fitted the model to match tuberculosis incidence in 2013 in the six WHO regions and at the global level, and then ran the model to 2035 to obtain tuberculosis incidence rates for each area under different pre-specified scenarios: a baseline, three pessimistic scenarios, and three optimistic scenarios (panel 2; table).

The appendix provides further details on source data we used.

We adapted a method previously applied by Dye and colleagues[10] to estimate the effect of diabetes and undernutrition on tuberculosis incidence ($I_{(a,r,t)}$) per person per year in different age groups (a), WHO regions (r), and over time (t) in various scenarios:

$$I_{(a,r,t)}=I_{0(r)}e^{-z(r)t}[1+U_{(r,t)}(R_u-1)][1+D_{(a,r,t)}(R_d-1)]$$

Where $I_{0(r)}e^{-z(r)t}$ is tuberculosis incidence per person between 2013 and 2035 among people not exposed to diabetes and undernourishment; $z(r)$ is the assumed rate of tuberculosis disease incidence decline in the baseline scenario; $U_{(r,t)}$ is the prevalence of undernutrition; and $D_{(a,r,t)}$ is the prevalence of diabetes in adults. In undernourished people, tuberculosis incidence is increased by relative risk R_u. In people with diabetes, tuberculosis incidence is increased by relative risk R_d.

We fitted the model to data on tuberculosis incidence in 2013 by adjusting I_0 so that the value of $I_{(a,r,t)}$ equalled that reported by the WHO Global Tuberculosis Report 2013.[2] $I_{(a,r,t)}$ was then estimated for the different scenarios and parameter values described here and in the table.

For each scenario, we calculated $I_{(a,r,t)}$ for three age groups (20–39 years, 40–59 years, and 60–79 years), six WHO regions (Africa region; Americas region; eastern Mediterranean region; Europe region; southeast Asia region; and western Pacific region), and the global level, between 2013 and 2035.

The figures for this baseline scenario do not take into account the expected increase in global diabetes prevalence. The IDF predicts that diabetes prevalence will increase in every region by 2035.[49] Globally, prevalence in 2035 will have increased by 21% compared with 2013 estimates, which will correspond to an overall diabetes prevalence in adults of more than 10%, and a total of almost 600 million cases of diabetes worldwide.[49] The expected increase will be highest in the western Pacific region (31·5%) and lowest in the African region (10·3%) (figure 1).

If we take those projections into account, we estimate that global tuberculosis incidence in 2035 would be 3% (prediction interval [PI] 2–4%) higher compared with the present downward baseline scenario. At the regional level, the present downward trend in tuberculosis incidence would be offset by 5% or less in all regions, with the smallest difference occurring in the African region (figure 3, scenario 1).

Although the negative effect of increasing diabetes prevalence seems small, these projections only take into account projected demographic changes (figure 1) and ongoing urbanisation as estimated by the UN Populations Division.[67] The projections are relatively conservative because no other risk factors for diabetes are taken into consideration.[68] If we assume an additional 25% increase in 2035 diabetes prevalence (12·5%)—accounting for increasing trends in overweight and other risk factors for diabetes—we estimate that the present downward trajectory in global tuberculosis incidence would instead be offset by 8% (PI 5–11%) by 2035, ranging from 4% (2–5%) in Africa to 10% (6–15%) in the western Pacific region (figure 3, scenario 3). As mentioned, overweight and obesity rates are on the rise in every country, with high rates in low-income and middle-income countries. In fact, the burden of diabetes is increasing most rapidly in Africa and Asia, the regions where tuberculosis is most prevalent.[49,62–64,69] In China, India, and other countries undergoing an epidemiological and demographic transition, levels of physical activity, diet, and burden of diet-related NCDs continue to change rapidly.[56–61,70,71] Different inter-related societal drivers are responsible for such epidemiological trends, including development and economic growth, industrialisation, and urbanisation.[10,11,56–61,63,64,10,11] This increase in diabetes might offset the positive effect of other factors, such as economic growth, on global tuberculosis incidence.

Although reduction of global diabetes prevalence is not plausible over the next two decades, the effect of diabetes on tuberculosis burden can, in theory, be mitigated through prompt diagnosis of diabetes and improved glucose control. Evidence suggests that tuberculosis risk increases with poor glucose control.[72] The IDF estimates that 46% of diabetes cases worldwide (around 175 million) are not diagnosed, with the highest proportions in Africa (62%, with peaks of 90% in rural settings)[73] and southeast Asia (54%),[49] where the greatest tuberculosis burden is concentrated. Globally, 84% of all people with undiagnosed diabetes live in low-income and middle-income countries,[49] and management of those who are diagnosed in these countries is rarely optimum. Although no randomised trials have been done to assess the role of glucose control on tuberculosis risk in patients with diabetes, observational data suggest that risk increases with poor glucose control;[74,75] however, such an effect needs to be empirically verified.[76] Substantial barriers to improving diabetes control can exist in low-income and middle-income settings, including poor health services integration, poor supply of effective antidiabetes drugs, little monitoring of and poor understanding of the risks associated with diabetes, little self-efficacy for management of diabetes, absence of health insurance, and poor quality of public services. Undiagnosed and poorly controlled diabetes could therefore be major contributing factors to diabetes-associated tuberculosis. Improvement of diagnosis and management of diabetes could diminish complications including impaired host defence against tuberculosis infection and disease.[74] As emerged from an expert meeting in 2009,[76] research efforts and resources should be focused on development and assessment of better point-of-care diagnostic and monitoring tests for diabetes.

Another way to minimise the tuberculosis risk in people with diabetes might be preventive treatment for those with LTBI.[33] However, although evidence exists for the efficacy of chemoprophylaxis in people with LTBI,[77] no proper randomised controlled trial has tested the efficacy and safety specifically in people with diabetes. Moreover, the accuracy of LTBI diagnosis is challenging.[76] A recent systematic review[72] identified two observational studies done in Germany[78] and Russia[79] that reported reduced incidence of active tuberculosis in patients with diabetes who received chemoprophylaxis compared with control patients who did not receive chemoprophylaxis; however, the small sample size and the absence of details on the intervention in both studies prevented authors of the systematic review from making conclusions about its efficacy. More research on LTBI diagnosis and management in patients with diabetes is needed.

If the effect of diabetes on tuberculosis risk could be removed (ie, such that the relative risk of tuberculosis due to diabetes was reduced from 3 to 1) through improved glucose control and chemoprophylaxis in people with LTBI, the model predicts a 15% (PI 9–21%) lower incidence of tuberculosis in 2035 compared with the baseline scenario, ranging from 17% (95% PI 10–23%) in the eastern Mediterranean and Americas regions to 10% (95% PI 6–14%) in the African region (figure 3, scenario 5).

The effect of undernutrition

If global changes in dietary patterns shift the BMI distribution to the right, we might note a positive tuberculosis-prevention effect from reduced undernutrition. Undernutrition is decreasing worldwide, but no global or regional projections of undernutrition prevalence through 2035 are available. The proposed food-security goal for the post-2015 development agenda is to end hunger.[52] If we assume that goal is achieved and undernutrition is eradicated, our model predicts that 2035 global tuberculosis incidence would be further reduced by 18% (PI 19–17%) compared with the baseline scenario based on the present trajectory of decline. The effect of eradication of undernutrition on tuberculosis burden would be highest in the African region (31%, PI 30–32%) and southeast Asian region (23%, PI 22–24%; figure 3, scenario 4).

Is such an optimistic scenario plausible? Prevalence of undernutrition has decreased by more than 60% in the past 20 years. To sustain this rate of decline would lead to a reduction to about 4% prevalence in 2035. Thus, the trajectory is promising but acceleration is needed to reach the proposed food security goal to end hunger set in the post-2015 development agenda. In the past two decades national governments, international organisations, and donors publicly committed to efforts to reduce undernutrition rates.[80] It has been agreed that three levels of intervention will enable reduction and ultimately elimination of undernourishment: enhancement and expansion of quality and coverage of nutrition-specific interventions with proven efficacy;[81] maximisation of nutrition-sensitive intersectoral interventions in the area of water and sanitation, agriculture, and social protection; and enhancement of political commitment, harmonisation within stakeholders, and resource allocation.[80]

A very optimistic and less realistic scenario is one in which both undernutrition was eradicated and the effect of diabetes on tuberculosis was eliminated. In this scenario, global tuberculosis incidence in 2035 would be 33% (PI 28–37%) lower than under the baseline scenario

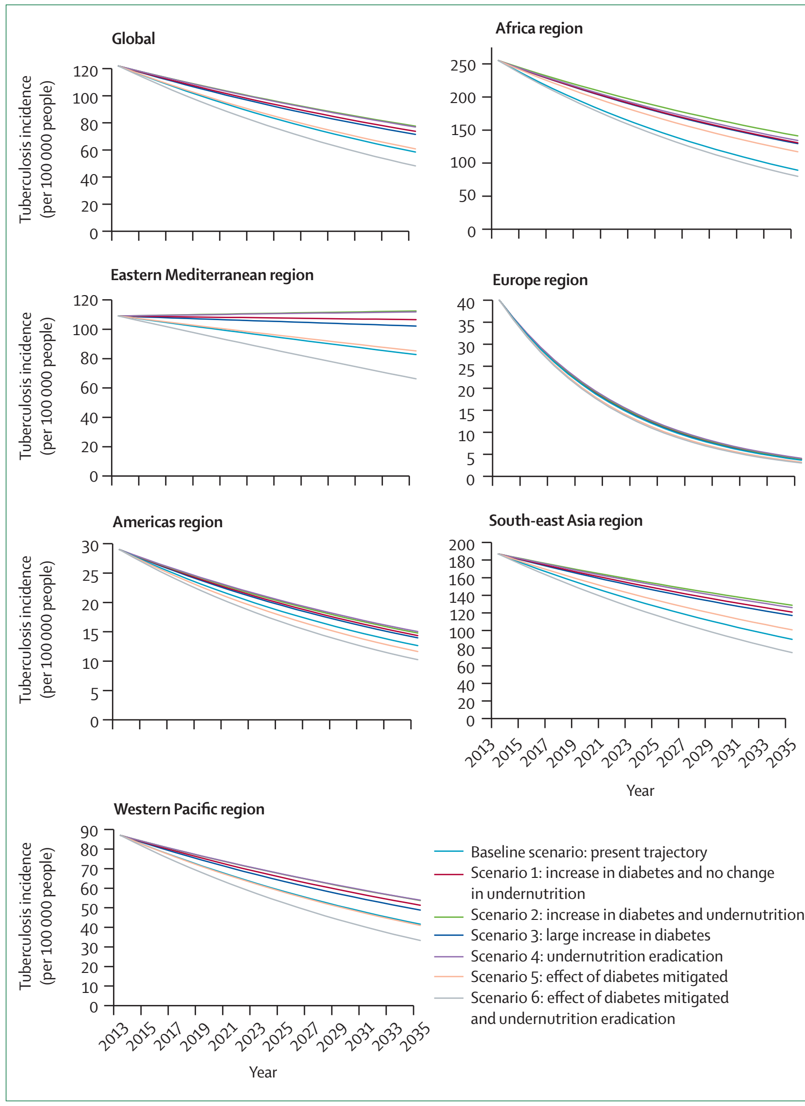

***Figure 2:* Estimated trends in tuberculosis incidence 2013–35**
Modelled effects of diabetes and undernutrition on tuberculosis incidence according to scenarios detailed in panel 2 and the table. Scales differ in each graph. Baseline annual percentage decrease in tuberculosis incidence: global 2·4%, African region 3·04%, Eastern Mediterranean region 0·29%, European region 10·15%, Americas region 3·27%, Southeast Asian region 2·11%, Western Pacific region 2·59%.

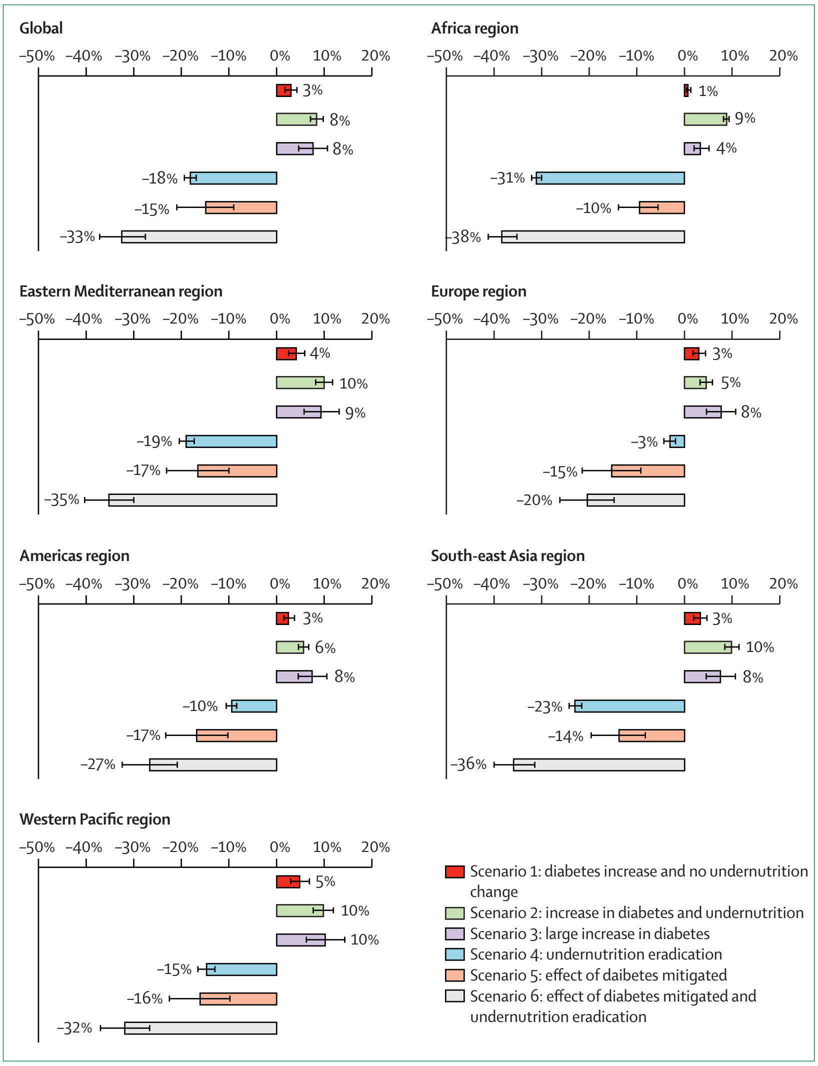

***Figure 3*: Effect of diabetes and undernutrition scenarios on tuberculosis incidence in 2035**
Percentage changes (with prediction intervals) in 2035 tuberculosis incidence, relative to baseline scenario, globally and by WHO region. Details of different scenarios are described in panel 2 and the table.

of the present rate of decline, ranging from 20% (PI 15–26%) in Europe to 38% (PI 35–41%) in Africa (figure 3, scenario 6).

Conversely, if we fail to fight undernutrition—that is, we assume a scenario in which undernutrition is at levels that occurred in the late 1990s—the decline in global tuberculosis incidence would be offset by 8% (PI 7–10%) by 2035, with greatest effect in the southeast Asian, eastern Mediterranean and western Pacific regions (figure 3, scenario 2). This scenario is alarming, but possible. In 2008 and 2013, *The Lancet* published two Series on maternal and child undernutrition. The Series papers offered a comprehensive overview of the main causes of undernourishment at the global level, and outlined various options to address this global public health challenge.[80] Various factors threaten further progress to reduced undernutrition, including climate change, natural disasters, war, social unrest, substantial population growth, reduced food availability, and decreased political commitment.[82–84] As reported in a review,[82] climate change is negatively affecting all four of the UN Food and Agriculture Organization's dimensions of food security: availability of sufficient quantities of food; access to adequate resources for acquiring appropriate foods; use of food through adequate diet, clean water, sanitation, and health care; and stability that allows access to adequate food at all times. Global warming also affects food availability, increasing rates of undernourishment through direct mechanisms—mainly reducing crop productivity—and indirectly, affecting household and individual-level income, capabilities, and rights.[82]

Strengths and limitations of the model

As we have stated,[85] in the context of increasingly poor resources, mathematical modelling can augment understanding and support policy for implementation of those strategies most likely to bring public health and economic benefits. Modelling of the effect of the diabetes epidemic on the tuberculosis epidemic is one of the ten key research questions identified by experts.[76] Previously published epidemiological models explored the association between diabetes and tuberculosis and the effect of diabetes prevalence on tuberculosis, focusing on specific countries including India[10,86] and Korea,[10] and on specific ethnic groups.[87] Only one study focused on the effect of both diabetes and nutrition on tuberculosis incidence,[10] but no previous study has made global predictions on future tuberculosis global burden. Mathematical modelling from Stevenson and colleagues[86] estimated that diabetes accounted for nearly 15% of incident tuberculosis in India and that increased diabetes prevalence was associated with nearly 11% greater tuberculosis incidence in urban compared with rural areas. In line with this modelling, Dye and colleagues[10] reported that nutritional and demographic changes had greater adverse effect on tuberculosis burden in India than in Korea. Increases in population size, urbanisation, and undernutrition in men living in rural areas in India were identified as main factors responsible for such a pattern.

We explored hypothetical optimistic scenarios to show the maximum positive effect of public health action, and pessimistic scenarios to warn against the potential detrimental consequences of failing to fight undernutrition or to control the diabetes epidemic. To our knowledge, our work is the first to make global predictions on future tuberculosis incidence rates focusing on several scenarios, looking towards 2035. Models are, by definition, simplifications of reality. We therefore acknowledge the uncertainties in our estimates and exhort caution in their interpretation. However, an urgent need exists for projections that can inform and inspire researchers and policy makers.[88]

Valuable examples of projections to 2020 and 2035 of different relevant public health outcomes—including life expectancy, neonatal and under-5 mortality, economic burden of overweight and obesity, and alcohol-related deaths—have been published.[88–91]

Our modelling exercise has limitations. First, we did not take into account dynamic effects of onward transmission from diabetes-associated and undernutrition-associated tuberculosis cases. Nor did we account for the effect of these factors on tuberculosis treatment outcomes, which could indirectly affect tuberculosis transmission. Therefore, our estimates of both positive and negative effects might be conservative. Second, we did not include assumptions about the varying diabetes and undernutrition risks of tuberculosis in different age groups, as age-stratified global data were not available. We identified three studies that reported age-specific relative risks for tuberculosis in patients with diabetes;[92–94] however, the findings were not generalisable to the global level, and we preferred to use effect estimates from rigorous systematic reviews and meta-analyses. Age-stratified prevalence data were available for diabetes, but not for undernutrition. Additionally, because of data availability constraints we could not account for varying degrees of undernourishment. Third, we did not model the direct effect of overweight and its role in the association between diabetes and tuberculosis. Overweight and obesity increase the risk of diabetes,[22] but tuberculosis risk diminishes with increasing BMI.[9] Data for the dose–response relationship between BMI and tuberculsosis are limited for BMI greater than 30 kg/m²; prevalence projections for global obesity to 2035 are not available. In view of the uncertainty of tuberculosis risk for high BMI values, we included only undernutrition as a binary variable in this analysis. Fourth, we did not model changes in other risk factors or interventions for tuberculosis. Fifth, WHO tuberculosis incidence estimates we used include children, whereas estimates of diabetes prevalence are for adults only. Last, when modelling the scenario of undernutrition elimination (scenarios 4 and 6), we did not take into account that continuous undernutrition for several years might have a long-term residual effect.[95] At the same time, very low birthweight might be associated with increased risk of diabetes;[96] these two factors negatively affecting tuberculosis are not captured by the model because of constraints of data availability.

Conclusion

Reduction of undernutrition and better prevention and care for diabetes could produce a large preventive effect on tuberculosis. Our analysis suggests that eradication of undernutrition would be especially effective in the African and southeast Asian regions, and lead to further decreases in 2035 tuberculosis incidence by 31% and 23%, respectively, compared with the present trajectory of decline. Better prevention and care for people with diabetes has the strongest potential to affect tuberculosis incidence in the European, American, and western Pacific regions.

If both the consequences of diabetes were fully mitigated and undernutrition eradicated, global tuberculosis incidence in 2035 would be 33% lower than under the baseline scenario of the present rate of decline. This hyper-optimistic scenario was modelled to show the maximum positive effect that could result from the most effective public health actions. We acknowledge that it would be very difficult to substantially improve food security without causing an increase in obesity and diabetes. Globally, the decrease in undernutrition and simultaneous increase in overweight and obesity, with diabetes in its wake, suggests an overall shift to the right in the BMI distribution. However, in many low-income and middle-income countries, where high rates of social and health inequalities persist, BMI distribution actually clusters around extremes values. In many of these countries, diabetes coexists with undernutrition, a situation with the potential to detrimentally affect tuberculosis burden. Public health efforts should aim to improve nutrition, rates of physical activity, and other lifestyle factors to ensure that as many people as possible are within the healthy weight-for-height range. We show that such measures would have a substantial positive effect also on tuberculosis prevention. However, failure to fight undernutrition would negatively affect future tuberculosis burden, offsetting present trajectory of tuberculosis incidence decline by up to 10% in some regions. In low-income settings where tuberculosis burden is highest, and where undernutrition and diabetes share common underlying social determinants,[97] failure to prevent, diagnose, and manage diabetes will further hinder tuberculosis control.

Search strategy and selection criteria

We searched Medline and Embase up to May 29, 2014, using combinations of free text and Mesh terms for “diabetes mellitus”, “nutritional status”, “malnutrition”, “overweight”, “obesity”, and “tuberculosis” in a comprehensive search strategy, without language restrictions. We applied no limits to the search strategy. Original studies of any design, narrative and systematic review, meta-analyses, expert consultation reports, consensus papers, and book chapters were considered. We prioritised the highest available level of evidence for each research question as defined by the Oxford Centre for Evidence-based Medicine.[101] Additional records were retrieved from reference listing of relevant papers and consultation with experts in the field. The effect estimate parameters for our model were taken from the most recent and comprehensive systematic reviews and meta-analyses that estimated the risk of tuberculosis disease associated with diabetes[6] and undernutrition,[9] and the risk of diabetes associated with overweight and obesity.[22]

The post-2015 global tuberculosis strategy incorporates collaborative activities to control infectious diseases and and NCDs. Our projections support the need for enhanced joint efforts between those working to control communicable diseases and those working to control non-communicable diseases[13,14,33] and strengthened cross-programme links,[98] particularly to enable synergistic effects between tuberculosis control, efforts to halt the rise in diabetes,[99] and proposed actions on under-nutrition.[52] In the first paper in this Series, Lönnroth and colleagues[13] discuss in detail the implications for policy and practice of operationalising the new post-2015 global tuberculosis strategy.

In times of epidemiological transition when the relative importance of different risk factors for tuberculosis is shifting, efforts should aim at diagonal[100] actions to address social determinants of health. Reduction of undernutrition and better prevention and care for diabetes, combined with improved access to prevention of infection, quality diagnosis, and treatment for all people with tuberculosis, are crucial to reach the post-2015 tuberculosis targets.

Contributors

AO, RMGJH, KL, and RGW designed the study. AO analysed the data, with RMGJH, and RGW. AO wrote the first draft of the Series paper. All authors contributed to writing the Series paper, and have seen and approved the final draft.

Declaration of interests

KL is an employee of WHO. The views expressed in this Series paper do not necessarily represent the decisions or policies of WHO. AO, RMGJH, and RGW declare no competing interests.

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