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## **Global prevalence of diabetes mellitus in active tuberculosis: a systematic review and meta-analysis of data from 2.3 million patients with tuberculosis**

Jean Jacques Noubiap, MD<sup>1</sup>, Jobert Richie Nansseu, MD<sup>2</sup>, Ulrich Flore Nyaga, MD<sup>3</sup>, Jan René Nkeck, MD<sup>3</sup>, Francky Teddy A. Endomba, MD<sup>3</sup>, Arnaud D. Kaze, MD<sup>4</sup>, Valirie N. Agbor, MD<sup>5,6</sup>, Jean Joel Bigna, MD<sup>7,8\*</sup>

- 1- Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa
- 2- Department of Public Health, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon
- 3- Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon
- 4- Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
- 5- Ibal sub-divisional Hospital, Oku, North-west Region, Cameroon
- 6- Department of Clinical Research, Health Education and Research Organization (HERO), Cameroon
- 7- Department of Epidemiology and Public Health, Centre Pasteur of Cameroon, Yaoundé, Cameroon
- 8- Faculty of Medicine, University of Paris Sud XI, Le Kremlin-Bicêtre, France

E-mail addresses: JJN: [noubiapjj@yahoo.fr](mailto:noubiapjj@yahoo.fr); UFN: [nyagaflore@gmail.com](mailto:nyagaflore@gmail.com); VNA: [nvagbor@gmail.com](mailto:nvagbor@gmail.com); JRN: [jobertrichie\\_nansseu@yahoo.fr](mailto:jobertrichie_nansseu@yahoo.fr); FTAE: [franckyteddyea@gmail.com](mailto:franckyteddyea@gmail.com); ADK: [kazearnaud@yahoo.fr](mailto:kazearnaud@yahoo.fr); JJB: [bignarimjj@yahoo.fr](mailto:bignarimjj@yahoo.fr); JRNkeck: [jrnkeck@gmail.com](mailto:jrnkeck@gmail.com)

\*Corresponding author: Dr Jean Joel Bigna. Department of Epidemiology and Public Health, Centre Pasteur of Cameroon, Yaoundé, Cameroon. Email: [bignarimjj@yahoo.fr](mailto:bignarimjj@yahoo.fr)

**Keywords:** tuberculosis; diabetes; hyperglycaemia; global health

## Summary

**Background:** Although diabetes mellitus (DM) and poor glycaemic control significantly increase the risk of tuberculosis (TB) and adversely affect TB treatment outcomes, the global burden of DM in the course of TB remains unknown. Hence, we conducted a systematic review and meta-analysis to estimate the prevalence of DM among TB patients at global, regional, and country levels.

**Methods:** An extensive search of PubMed, Excerpta Medica Database, Web of Science, and Global Index Medicus was run to identify studies published between January 01, 1986 and June 15, 2017 on the prevalence of DM in patients with active TB, with no language restriction. Criteria to diagnose TB and DM concurred with WHO guidelines. Methodological quality of eligible studies was assessed, and random-effect models meta-analysis served to obtain the pooled prevalence estimate of DM among patients with active TB, globally. Heterogeneity ( $I^2$ ) was assessed via the  $\chi^2$  test on Cochran's Q statistic. Review registration: PROSPERO CRD42016049901.

**Findings:** In total, we screened 7,565 records of which 200 studies (2,229,571 people with active TB) were included in meta-analyses. The pooled prevalence of DM was 15.3% (95% predictive interval 2.5-36.1;  $I^2$  99.8%), varying from 0.1% in Latvia to 45.2% in Marshall Islands. Sub-group and meta-regression analyses for identifying sources of heterogeneity showed that four International Diabetes Federation (IDF) regions [North America & Caribbean (19.7%), Western Pacific (19.4%), South-East Asia (19.0%), Middle East & North Africa (17.5%)] had significantly higher prevalence estimates than the three others [Africa (8.0%), South & Central America (7.7%), and Europe (7.5%)],  $p < 0.0001$ . In addition, the prevalence increased with age and was higher in males and in countries with low TB burden. On the other hand, the prevalence of DM was lower in low income and low Human

Development Index countries. Moreover, the form of TB infection and presence of HIV seemed not to influence the prevalence of DM among patients with active TB.

**Interpretation:** This study suggests a high burden of DM among patients with active TB with disparities according to age, sex, regions, level of countries income and development. Cost-effective strategies to curb the burden of DM among patients with active TB are needed.

**Funding:** None.

## **Introduction**

Tuberculosis (TB) remains a major contributor to global burden of disease. In 2016, it is estimated that 10.4 million people developed active TB (new and relapse cases), and 1.3 million people died from the disease among HIV negative people and 374,000 among HIV-positive people, mostly from low-income and middle-income countries.<sup>1</sup> “This high burden is fuelled by major risk factors including HIV, substance abuse, advanced kidney disease, malnutrition, treatment with corticosteroids or immunosuppressant, and diabetes mellitus (DM).”<sup>2</sup> Indeed, DM triples the risk of developing TB and poor glycaemic control adversely affects TB treatment outcomes such as prolongation of culture conversion, treatment failure, relapse and death.<sup>3-5</sup> Furthermore, DM accounted for 10.6% of global TB deaths among HIV-negative individuals in 2015.<sup>6</sup> With 425 million people affected by DM globally in 2017 and a predicted 48% increase up to 629 million people who would have DM in 2045, it is foreseeable that the TB epidemic would also be on rise.<sup>6</sup> Unfortunately, the regions with the current highest burden of tuberculosis would also experience the uppermost increment in DM prevalence: +162.5% for Africa and +84% for South-East Asia for instance.<sup>6</sup>

Accordingly, the crucial need to curb the global DM epidemic as part of the strategy to tackle the burden of TB has led to the creation of the Collaborative Framework for Care and Control of Tuberculosis and Diabetes which aims to guide national programs, clinicians and other caregivers on how to establish effective integrated care for both diseases, at organizational and clinical levels.<sup>7</sup> The Collaborative Framework recommends the screening for DM and glycaemic control as essential parts of the management of TB patients.<sup>7</sup> In this context, data on the prevalence of DM in patients with active TB are important for health care planning and resources allocations. Hence, we conducted the first systematic review and meta-analysis on the prevalence of DM in patients with active TB at the global, regional and country levels.

## **Methods**

### **Search strategy and selection criteria**

In this systematic review with meta-analysis, we searched PubMed, Excerpta Medica Database (EMBASE), Web of Science, and Global Index Medicus to identify all relevant abstracts published from January 01, 1986 to June 15, 2017 on the prevalence of DM in patients with active TB globally, without language restriction. The search strategy for each database is available in the Appendix (Supplementary Tables 1-4). The main keywords for search strategy included “tuberculosis”, “TB”, “mycobacterium”, and “diabetes”, “diabetic”, “hyperglycaemia” and “glucose intolerance”. To supplement the bibliographic database searches and identify potential additional data sources, we scrutinized the reference list of all relevant articles.

We included cross-sectional, case-control or cohort studies conducted in patients suffering from pulmonary or extra-pulmonary drug-susceptible or resistant TB and reporting on the prevalence of DM or providing enough data to compute this estimate. The diagnosis of DM had to be made by a physician, or defined based on measured fasting plasma glucose, oral glucose tolerance test according to WHO criteria, or self-reported.<sup>8</sup> An amendment from the published protocol<sup>9</sup> was done to also include studies in which DM was diagnosed based on A1c haemoglobin.<sup>10</sup> TB cases must have been diagnosed based on WHO criteria.<sup>11</sup> We excluded letters, case series with small sample size (less than 50 participants), reviews, commentaries, and editorials.

Titles and abstracts of articles retrieved from literature search were independently screened by two investigators (JJN and JJB), and the full-texts of those potentially eligible were obtained and further assessed for final inclusion. Disagreements were resolved through consensus.

### **Data analysis**

A preconceived and standardized data extraction form was used to collect information on first author's name, study country, year of publication, period of participants' recruitment, study design (cross-sectional, cohort or case-control), setting (population-based vs hospital-based), sampling method, timing of data collection (prospectively vs retrospectively), source of data (from medical files, database, directly from patients), method used to diagnose DM, method used to diagnose TB, number of participants, mean or median age of the population, proportion of males, proportion of participants with extra-pulmonary TB, proportion of participants with drug-resistant TB, proportion of participants with HIV, and the number/prevalence of participants with DM. In case of multinational studies, data were separated to show the estimate within individual countries. Two pairs of investigators (UFN, VNA, EFTA and JRNkeck) independently extracted the data from individual studies, and all extracted data were crosschecked by a fifth investigator (JJN) with disagreements being resolved through consensus.

Methodological quality of included studies was evaluated using the tool developed by Hoy and colleagues.<sup>12</sup> A score of 1 (yes) or 0 (no) was assigned for each item, and scores summed across items to generate an overall quality score that ranged from 0 to 10 (Supplementary Table 5, Appendix). Studies were then classified as having a low (>8), moderate (6–8), or high ( $\leq$ 5) risk of bias. Two pairs of investigators (UFN, VNA, EFTA and JRNkeck) independently assessed study methodological quality of a quarter of included studies for each of them, and all assessments were independently reviewed by a fifth investigator (JJN) with disagreements being resolved through consensus.

Data were analysed using the '*meta*' and '*metafor*' packages of the statistical software R (version 3.5.1, The R Foundation for statistical computing, Vienna, Austria). Unadjusted prevalence was recalculated based on the information of crude numerators and denominators provided by individual studies. Prevalence was reported with their 95% confidence interval

and 95% prediction interval. Following the crude overall prevalence, we conducted a sensitivity analysis including only studies with low risk of bias to assess the robustness of our findings. To keep the effect of studies with extremely small or extremely large prevalence estimates on the overall estimate to a minimum, the variance of the study-specific prevalence was stabilized with the Freeman-Tukey double arcsine transformation before pooling the data with the random-effects meta-analysis model.<sup>13</sup> Funnel plots and Egger's test served for detecting the presence of publication bias.<sup>14</sup> A p-value < 0.10 on Egger test was considered indicative of statistically significant publication bias. Heterogeneity was evaluated by the  $\chi^2$  test on Cochrane's Q statistic,<sup>15</sup> which was quantified by H and I<sup>2</sup> values. The I<sup>2</sup> statistic estimates the percentage of total variation across studies due to true between-study differences rather than chance. In general, I<sup>2</sup> values greater than 60-70% indicate the presence of substantial heterogeneity.<sup>16</sup>

Subgroup analyses was performed for the following subgroups: period of recruitment, countries, regions according to the International Diabetes Federation (IDF) (Africa, Europe, Middle East & North Africa, North America & Caribbean, South & Central America, South-East Asia, Western Pacific), TB burden in the country of recruitment (high [countries that ranked first to twenty second in terms of their estimated number of incident cases, which accounted for approximately 80% of the global total of estimated new cases of TB] vs low TB burden country),<sup>17</sup> level of country income (low, lower-middle, upper-middle, high),<sup>18</sup> human development index (HDI: low, medium, high, very high),<sup>19</sup> study site (hospital- versus population-based), and population (adults, children  $\leq$  18 years). Univariable and multivariable meta-regression analyses were used to test for an effect of study and participants' characteristics (period, regions, TB burden in the country, level of income of the country, HDI, population, proportion of participants with extra-pulmonary TB, proportion of participants with diagnosed HIV infection, mean or median age, and proportion of males) on



the prevalence estimate. We used stepwise backward manual selection excluding variables with p value > 0.20. For categorical variables, the global p value was considered for inclusion in multivariable models. A p value < 0.05 was considered statistically significant. Inter-rater agreements between investigators for study inclusion and methodological quality assessment were assessed using Kappa Cohen's coefficient.<sup>20</sup>

The protocol was registered in the PROSPERO International Prospective Register of systematic reviews (registration number CRD42016049901) and published in a peer-reviewed journal.<sup>9</sup>

### **Role of the funding source**

There was no funding source for this study. The corresponding author had full access to all study data and had final responsibility for the decision to submit the paper for publication.

## **Results**

### **The review process and study characteristics**

We initially identified 7,565 records. After elimination of duplicates, 4,224 records remained. We screened the titles and abstracts and excluded 3,796 irrelevant records. Agreement between investigators on abstract selection was  $\kappa = 0.82$ . We scrutinized full-texts of the remaining 428 papers for eligibility, of which 229 were excluded. Finally, 199 full texts (200 studies) were included in the meta-analysis (Supplementary Figure 1). The inter-rater agreement for study inclusion and data extraction between investigators was  $\kappa = 0.94$  and  $0.72$  respectively. Reference list of all included studies is available in the Appendix.

Of the 200 included studies, 88 (44.0%), 81 (40.5%), and 31 (15.5%) had low, moderate, and high risk of bias respectively. Supplementary Tables 6 and 7 (Appendix) summarise characteristics of included studies. Most of studies were cross-sectional (57.0%), hospital-

based (87.5%) used consecutive sampling (75.5%), retrospectively collected data (51.5%), included only adults (84.0%), were conducted in countries with low TB burden (59.5%).

### **Global prevalence of diabetes mellitus in people with active tuberculosis**

In total, 2,229,571 people with active tuberculosis from 50 countries were included. The DM prevalence in this population varied widely across countries. The prevalence varied from 1.9% (Benin) to 32.4% (Ethiopia) in Africa (Figure 1), from 0.1% (Latvia) to 22.9% (Portugal) in Europe (Figure 2), from 6.1% (Libya) to 22.8% (Egypt) in Middle East & North Africa (Figure 3), from 14.0% (Guyana) to 29.5% (Mexico) in North America & Caribbean (Figure 4), from 4.8% (Peru) to 32.4% (Chile) in South & Central America (Figure 5), from 10.6% (Bangladesh) to 24.1% (Sri Lanka) in South-East Asia (Figure 6), and from 7.5% (Thailand) to 45.2% (Marshall Islands) in Western Pacific (Figure 7).

Table 1 presents overall and subgroups analyses. The global prevalence of DM in TB was 15.3% (95% predictive interval 2.5-36.1), with substantial heterogeneity (Table 1). The prevalence of the sensitivity analysis including only studies with low risk bias was very close to that of the crude analysis: 16.9% (95% predictive interval 2.6-39.7). Funnel plot suggested publication bias with missing small studies reporting high prevalence (Supplementary Figure 2), confirmed by the Egger test (Table 1).

### **Subgroup prevalence and analysis**

Table 1 presents subgroup analyses. The prevalence of DM in TB was higher in Western Pacific, North America & Caribbean, South-East Asia, Middle East & North Africa compared to Africa, Europe, and South & Central America ( $p < 0.0001$ ) (Table 1 and Supplementary Figure 4). This prevalence was slightly higher in countries with low TB burden ( $p = 0.036$ ) (Table 1 and Supplementary Figure 5). The prevalence was higher in studies including both adults and children compared to studies including only children ( $p = 0.0008$ ) (Table 1 and Supplementary Figure 6). The prevalence was lower in countries with low level of income ( $p$

= 0.0003) (Table 1 and Supplementary Figure 7) and low HDI compared to others ( $p < 0.0001$ ) (Table 1 and Supplementary Figure 8). The prevalence was not different between periods of recruitment of participants (Table 1 and Supplementary Figure 9) and between hospital and population-based studies (Table 1 and Supplementary Figure 10).

### **Sources of heterogeneity of the global prevalence**

In univariate analysis, all findings of subgroup analysis were confirmed with the following explained heterogeneity: IDF regions (36.9%), population (35.6%), TB burden in the country (19.1%), level of income of the country (0.01%), and human development index of the country (0.01%). In addition, the prevalence increased with age (19.1%) and proportion of males (0.01%). The diagnosis method of DM explained 49.3% of the heterogeneity of pooled prevalence estimate. There was no association with proportion of participants with resistant TB, with extra-pulmonary TB, and with HIV infection. In the final multivariable meta-regression model, all variables included in the model explained 59.6% of the 99.3% residual heterogeneity. The prevalence of DM in TB was higher in Western Pacific, North America & Caribbean, South-East Asia, Middle East & North Africa compared to Africa, Europe, and South & Central America), higher in low TB burden countries, lower in low-income and low-HDI countries (Supplementary Table 8).

### **Discussion**

This first systematic review and meta-analysis on the global prevalence of DM among patients with active TB compiled data from about 2.3 million patients and revealed an estimate of 15.3% (95% prediction interval 2.5-36.1). We observed a wide variability in the estimate across countries, ranging from 0.1% in Latvia to 45.2% in Marshall Islands. The substantial heterogeneity found between studies was mainly explained by the fact that DM was more than two-times more prevalent in four IDF regions (Western Pacific, North

America & Caribbean, South-East Asia, Middle East & North Africa) than in the three other regions (Africa, Europe, and South & Central America); additionally, the prevalence of DM tended to increase with age and was higher in males and in countries with low TB burden. On the other hand, the prevalence of DM was lower in low income and low HDI countries. The form of TB infection (resistant, extra-pulmonary) or presence of HIV had no influence on the estimate. We did not find any difference between hospital-based and community-based studies. This lack of difference could be explained by the fact that although the study is hospital-based, most of participants were outpatients and therefore close to the patients in the community.

This global prevalence of DM among patients with TB is almost twice higher than what has recently been reported by the IDF for the global adult general population in 2017, at 8.8%.<sup>6</sup> This finding reinforces the fact that DM represents a major risk factor for TB occurrence.<sup>2</sup> Men with TB tended to have higher prevalence estimates of DM than women in univariable meta-regression analysis, corroborating the IDF Diabetes Atlas' findings pointing a prevalence of DM of 9.1% among males and 8.4% among females.<sup>6</sup> Likewise, the increase in DM prevalence with age concurs with what has been seen in the general population, from less than 2% at 20-24 years old to 18.8% at 65-99 years old.<sup>6</sup>

Interestingly, the regional disparities we found aligns to the regional disparities reported for the general population,<sup>6</sup> even though the number of eligible studies we included was disproportionally represented across IDF regions. Indeed, the four regions with higher DM prevalence among patients with active TB were the same than that in the general population: North America & Caribbean (19.7 vs 13.0%), Western Pacific (19.4 vs 9.5%), South-East Asia (19.0 vs 8.5%), and Middle East & North Africa (17.5 vs 9.6%). This was also the case for regions with lower prevalence estimates: Africa (8.0 vs 3.3%), Europe (7.5 vs 8.8%), and South & Central America (7.7 vs 8.0%).<sup>6</sup> At exception of the two latter regions, the regional

prevalence among patients with TB was almost the double of that in the general population, in line with what was found for the global prevalence. As a matter of fact, it clearly appears that the prevalence of DM among patients with active TB is driven by the DM epidemic in the general population. As it is expected a huge increment in the DM prevalence particularly in some IDF regions such as Africa (+162.5%), Middle East & North Africa (+110%), South East Asia (+84%), and South & Central America (+62%),<sup>6</sup> the number of people affected by TB is also expected to rise exponentially. Therefore, reducing the TB burden would require to curb the DM epidemic. Four areas of effective action plan have been identified by the IDF to control DM: (i) promoting high quality research on diabetes epidemiology; (ii) prioritizing diabetes care and control through capacity building of primary care professionals and interdisciplinary collaboration; (iii) implementing national plans and strategies to reduce diabetes burden, and (iv) extending health promotion to reduce diabetes and its complication through educational and locally-adapted comprehensive lifestyles programmes.<sup>6</sup>

Another striking result figuring out from this review was the higher prevalence of DM in countries with low vs high TB burden, in high income vs low income countries, and in countries with medium to very high vs low HDI; these countries appear to be mainly represented by developed countries, where the burden of HIV is the lowest.<sup>17</sup> Put together and remembering that HIV remains the major risk factor for TB,<sup>1</sup> our findings suggest that DM might be a more important driver of the burden of TB in developed countries where the prevalence of DM in the general population is higher and that of HIV is lower,<sup>1,6</sup> as compared to in countries such as those in sub-Saharan Africa where the prevalence of DM in the general population is lower and the burden of HIV is the highest.<sup>1</sup> The WHO End TB Strategy aimed at reducing TB deaths by 95% and new cases by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic expenses due to TB.<sup>21</sup> Hence, strategies to combat TB should consider being integrated and targeting all major risk factors for TB

including DM and HIV.<sup>7</sup> WHO recommends as pillars to curb the burden of TB: integrated, patient-centered care and prevention, bold policies and supportive systems, and intensified research and innovation.<sup>21</sup> Furthermore, our data suggest that contextualized strategies against TB should be implemented depending on the burden of TB in individual countries. For instance, the TB Elimination framework proposed by Lönnroth and colleagues can be very useful for low-income countries where TB burden is the highest. This framework in its four main dimensions of TB elimination recommend to: i) ensure universal access to high-quality TB service with a focus on groups at highest risk; ii) reduce underlying vulnerability by considering health in all policies; iii) ensure political commitment to domestic TB strategy and iv) support implementation of the global TB strategy.<sup>22</sup> An important question that our findings might raise is whether a systematic screening for DM in patients with TB would be indicated. In the context of high income countries where the prevalence of DM in TB patients as well as in the general population is high, and where resources are available, systematic screening for DM in TB patients seems appropriate. Patients with newly diagnosed DM would therefore receive appropriate treatment for DM and avoid poor TB treatment outcomes related to poor glyceemic control. Studies would be needed to determine the appropriate timing of such a screening strategy. However, in low-income countries where the burden of DM is lower both in the general population and in patients with TB, as compared to high-income countries, systematic screening for DM in TB patients is questionable, especially in the context of limited resources. Evidence on the cost-effectiveness of adding systematic screening for DM in TB patients on the already stretched health system and TB program in low-income countries are highly needed to inform health policies. This is supported by the potential benefit of treating DM and improving glyceemic control on TB treatment outcomes.<sup>3-</sup>

This study should however be interpreted in the context of some drawbacks. First, we included 200 studies among which 81 (40.5%) and 31 (15.5%) had a moderate and high risk of bias, respectively. This may have affected the precision of our estimate; nevertheless, when pooling only the 88 (44.0%) studies having a low risk of bias in a meta-analysis, the overall estimate did not change considerably: 16.9% (95% predictive interval 2.6-39.7). Second, majority of studies were retrospective (51.5%), hospital-based (87.5%) or collected their data on a consecutive basis (75.5%); these factors may have led to an underestimation or overestimation of this prevalence estimate. Furthermore, most of the studies used plasma glucose to diagnose DM. Unfortunately, in many of these studies, after a positive screening test, no confirmation test was done to exclude transient hyperglycaemia among newly diagnosed TB patients. This could have led to an overestimation of the prevalence of DM. Third and most common to meta-analyses of this type, we found a huge heterogeneity between studies for which we undertook a meta-regression analysis which explained more than two-thirds of this heterogeneity. Most of the important sources of heterogeneity included the methods used to diagnose DM. This may explain the high disparity of DM prevalence in TB among countries in the same region in this review. Fourth, the various geographic regions and countries were variably represented, with some countries with only one small-sampled study or even no studies, which could affect the generalizability of our findings.

Despite these limitations, this study is the first systematic review and meta-analysis providing a clear summary of the existing knowledge on the global prevalence of DM among patients suffering from TB. A protocol had been published before, and we used rigorous methodological and statistical procedures to obtain and pool data from about 2.3 million patients with active TB. Furthermore, subgroup analyses and univariable and multivariable meta-regression analyses were conducted to investigate the various factors likely affecting our estimate.

This systematic review and meta-analysis compiled data from 2.3 million people suffering from active TB and pointed a high prevalence of DM, at 15.3%. This estimate seemed higher in some IDF regions, in older people, in males and in countries with low TB burden, and lower in low income and low HDI countries. These data suggest that systematic screening for DM in patients with TB might be recommended in high-income settings where the prevalence of DM is higher in the general population and in patients with TB. However, in low-income countries which have a high TB burden, and where the prevalence of DM in the general population and in patients with TB is lower, and considering the limited resources available, cost-effectiveness studies are needed to inform policies regarding the appropriateness of systematic screening for DM in patients with TB.

## **Research in context**

### **Evidence before this study**

Diabetes mellitus (DM) and poor glycaemic control significantly increase the risk of Tuberculosis (TB) and adversely affect TB treatment outcomes. It is estimated that DM accounted for 10.6% of global TB deaths among HIV-negative individuals in 2016. However, there are no available data presenting a clear estimate of the global burden of DM among patients suffering from TB.

### **Added value of this study**

This study is the first systematic review and meta-analysis figuring-out a comprehensive summary of the existing knowledge on the prevalence of DM among patients with active TB, worldwide. Our study suggests a high prevalence of DM in TB patients globally, at 15.3%. This prevalence estimate tends to be two-times higher in some IDF regions (Western Pacific, North America & Caribbean, South-East Asia, Middle East & North Africa) than in others



(Africa, Europe, and South & Central America). Furthermore, it seems to increase with age and be higher in males and in countries with low TB burden; by contrast, it seems to be lower in low income and low HDI countries, and not to be influenced by the form of TB infection as well as presence of the HIV.

### **Implications of all the available evidence**

Our findings call for cost-effective strategies to curb the burden of DM among patients with active TB. In high-income countries where the prevalence of DM is particularly high in the general population, and in patients with TB as shown by this review, systematic screening for DM in patients with TB should be recommended. Good glycaemic control would improve TB treatment outcomes in such patients with newly diagnosed and treated DM. However, in low-income countries which have a high TB burden, and where the prevalence of DM in the general population and in patients in TB is lower, and considering the limited resources available, cost-effectiveness studies are needed to inform policies regarding the appropriateness of systematic screening for DM in patients with TB.

### **Contributors**

JJN, JJB and JRNansseu conceived the study and, together with FTAE and ADK developed the protocol. JJN and JJB did the literature search. JJN and JJB selected the studies and UFN, FTAE, JRNkeck and VNA extracted the relevant information. JJB and JJN synthesised the data. JJN, JJB and JRNansseu wrote the first draft of the paper. JJN, JJB, JRNansseu, UFN, VNA, FTAE and JRNkeck critically revised successive drafts of the paper and approved its final version. JJN is the guarantor of the review.

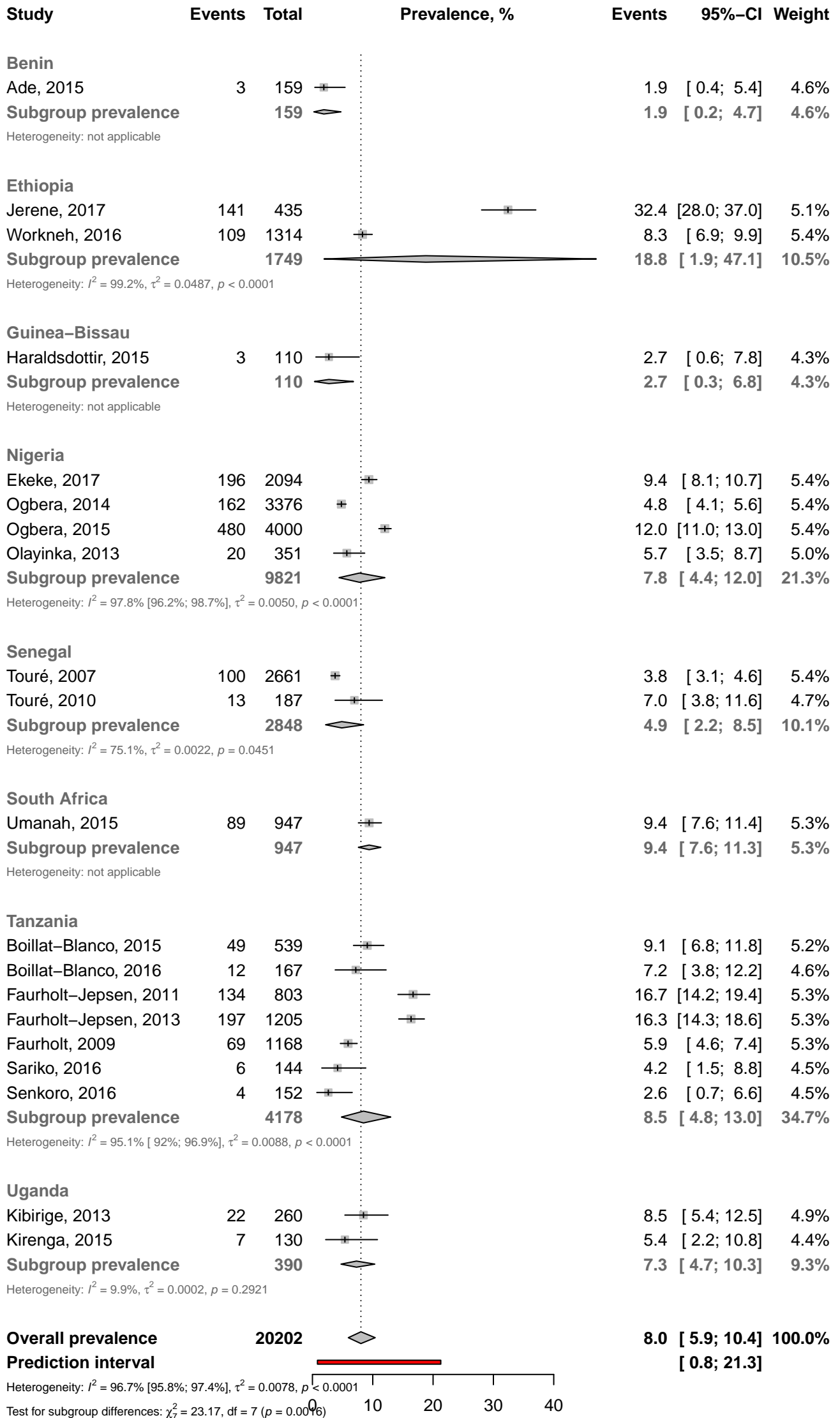
### **Declaration of interests**

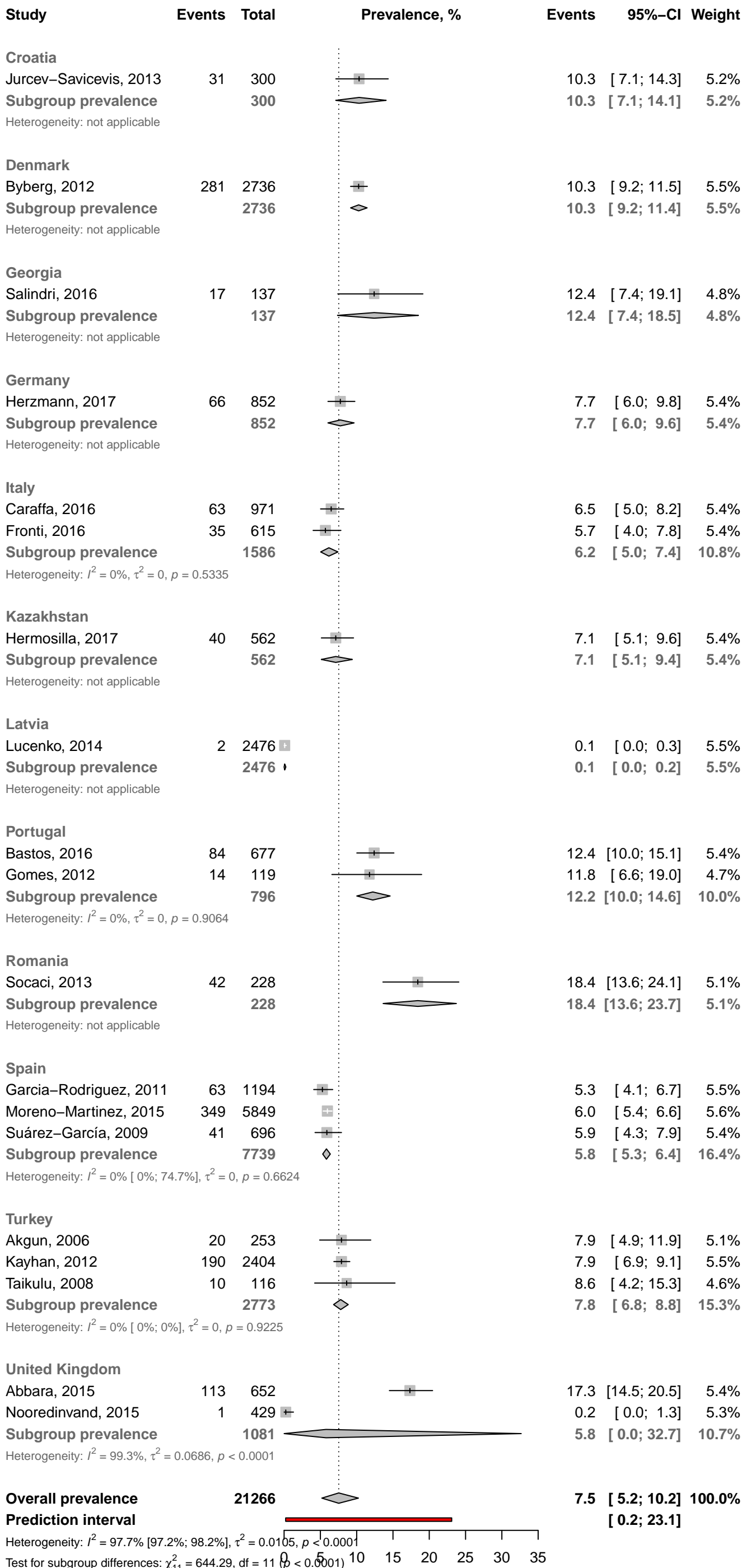
We declare no competing interests.

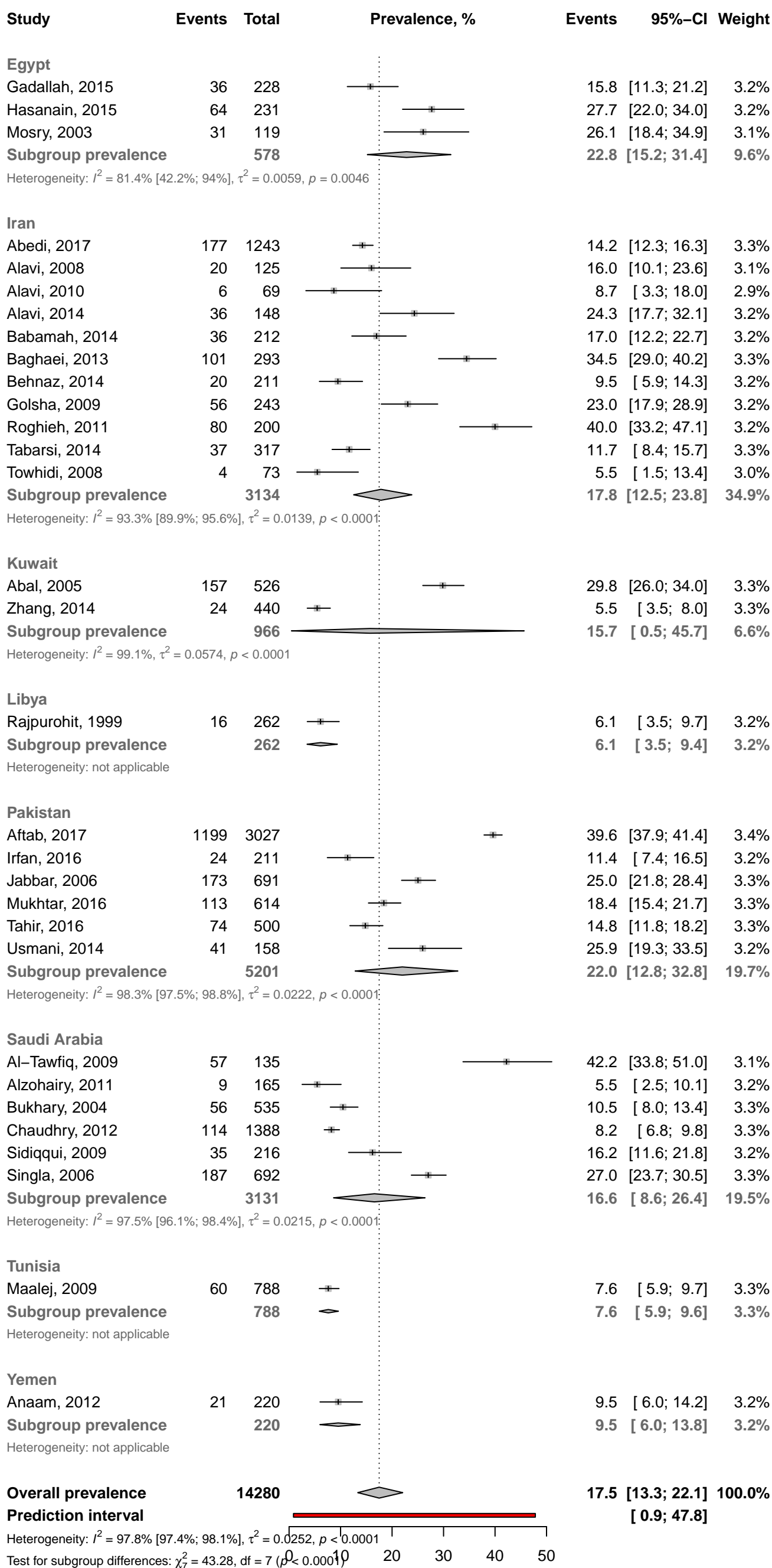
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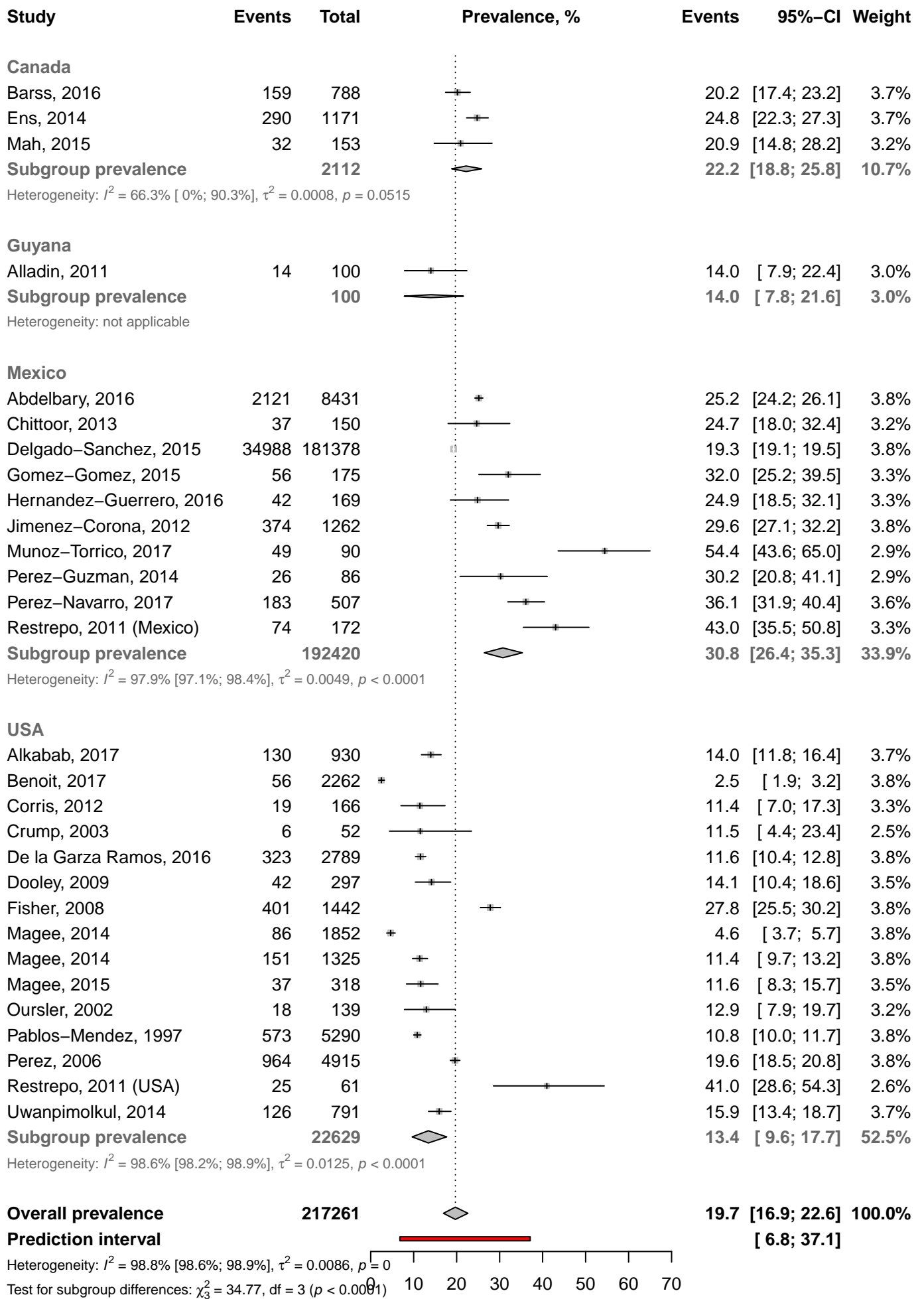
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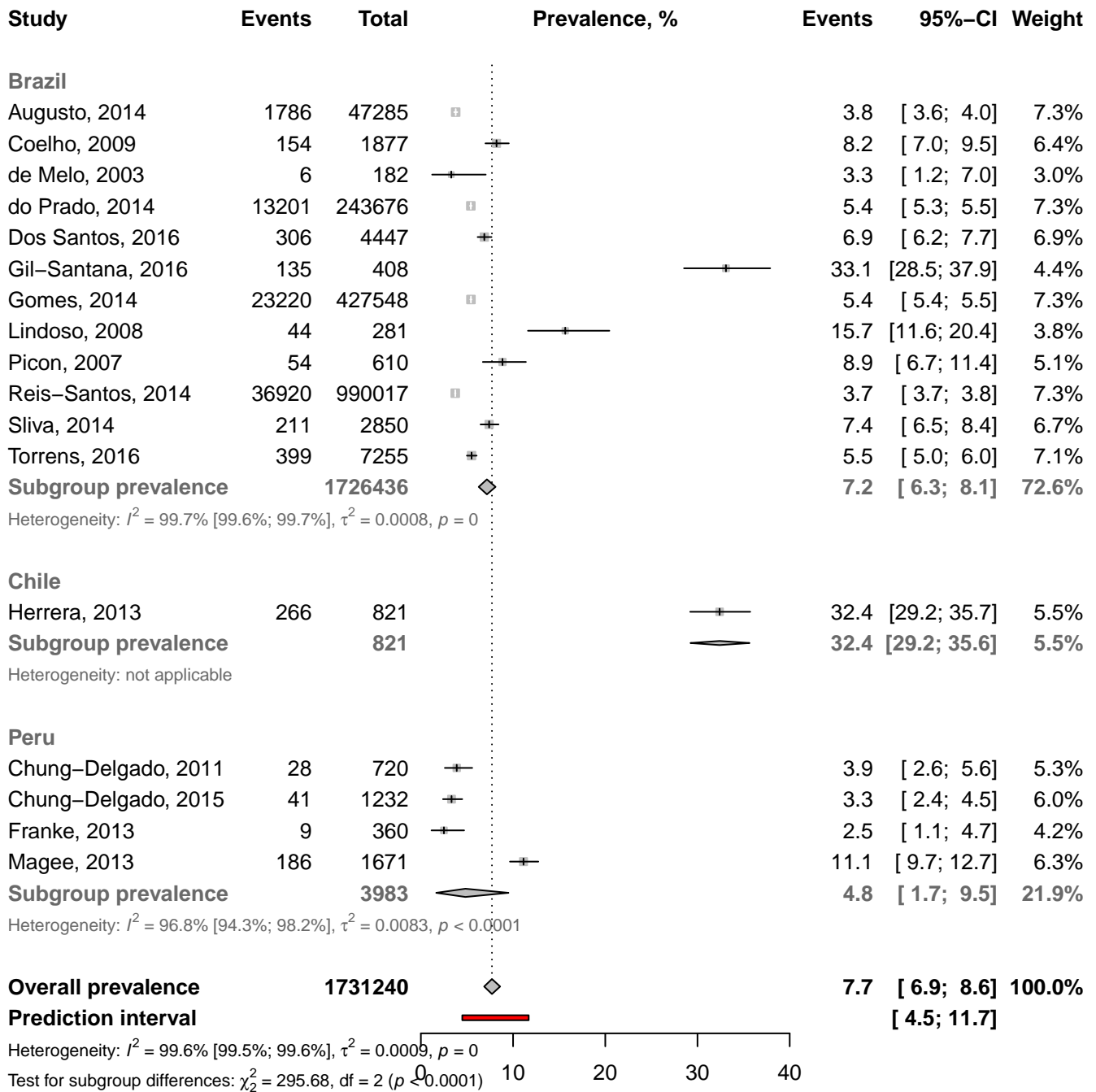
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Study	Events	Total	Prevalence, %	Events	95%-CI	Weight
<b>Bangladesh</b>						
Hossain, 2014	11	100		11.0	[ 5.6; 18.8]	2.9%
Rifat, 2014	83	1000		8.3	[ 6.7; 10.2]	3.6%
Sarker, 2016	245	1910		12.8	[11.4; 14.4]	3.6%
<b>Subgroup prevalence</b>		<b>3010</b>		<b>10.6</b>	<b>[ 7.2; 14.5]</b>	<b>10.1%</b>

Heterogeneity:  $I^2 = 85.9\%$  [59.1%; 95.2%],  $\tau^2 = 0.0021$ ,  $p = 0.0008$

Study	Events	Total	Prevalence, %	Events	95%-CI	Weight
<b>India</b>						
Achanta, 2013	19	374		5.1	[ 3.1; 7.8]	3.4%
Adwani, 2016	25	227		11.0	[ 7.3; 15.8]	3.3%
Charkha, 2016	24	74		32.4	[22.0; 44.3]	2.7%
Dave, 2013	36	556		6.5	[ 4.6; 8.9]	3.5%
Duraisamy, 2015	60	179		33.5	[26.7; 40.9]	3.2%
Gupta, 2010	64	207		30.9	[24.7; 37.7]	3.2%
Gupta, 2011	61	192		31.8	[25.3; 38.9]	3.2%
India TB-DM Group, 2013	1084	8109		13.4	[12.6; 14.1]	3.7%
Jali, 2013	109	307		35.5	[30.2; 41.1]	3.4%
Khanna, 2013	66	458		14.4	[11.3; 18.0]	3.5%
Kornfeld, 2016	113	209		54.1	[47.1; 61.0]	3.3%
Kumar, 2013	1084	8109		13.4	[12.6; 14.1]	3.7%
Kumpatla, 2013	84	779		10.8	[ 8.7; 13.2]	3.5%
Lisha, 2012	23	224		10.3	[ 6.6; 15.0]	3.3%
Manjareeka, 2016	24	101		23.8	[15.9; 33.3]	2.9%
Marak, 2016	8	110		7.3	[ 3.2; 13.8]	2.9%
Naik, 2013	62	358		17.3	[13.5; 21.6]	3.4%
Nair, 2013	298	920		32.4	[29.4; 35.5]	3.6%
Nandakumar, 2013	667	2794		23.9	[22.3; 25.5]	3.6%
Prakash, 2013	47	510		9.2	[ 6.8; 12.1]	3.5%
Rawat, 2011	52	156		33.3	[26.0; 41.3]	3.1%
Sidiqqi, 2016	50	316		15.8	[12.0; 20.3]	3.4%
Subhash, 2003	72	361		19.9	[15.9; 24.4]	3.4%
Tang, 2013	80	586		13.7	[11.0; 16.7]	3.5%
Vasudevan, 2014	63	217		29.0	[23.1; 35.6]	3.3%
Vaswanathan, 2012	209	827		25.3	[22.3; 28.4]	3.6%
<b>Subgroup prevalence</b>		<b>27260</b>		<b>19.9</b>	<b>[16.8; 23.2]</b>	<b>87.0%</b>

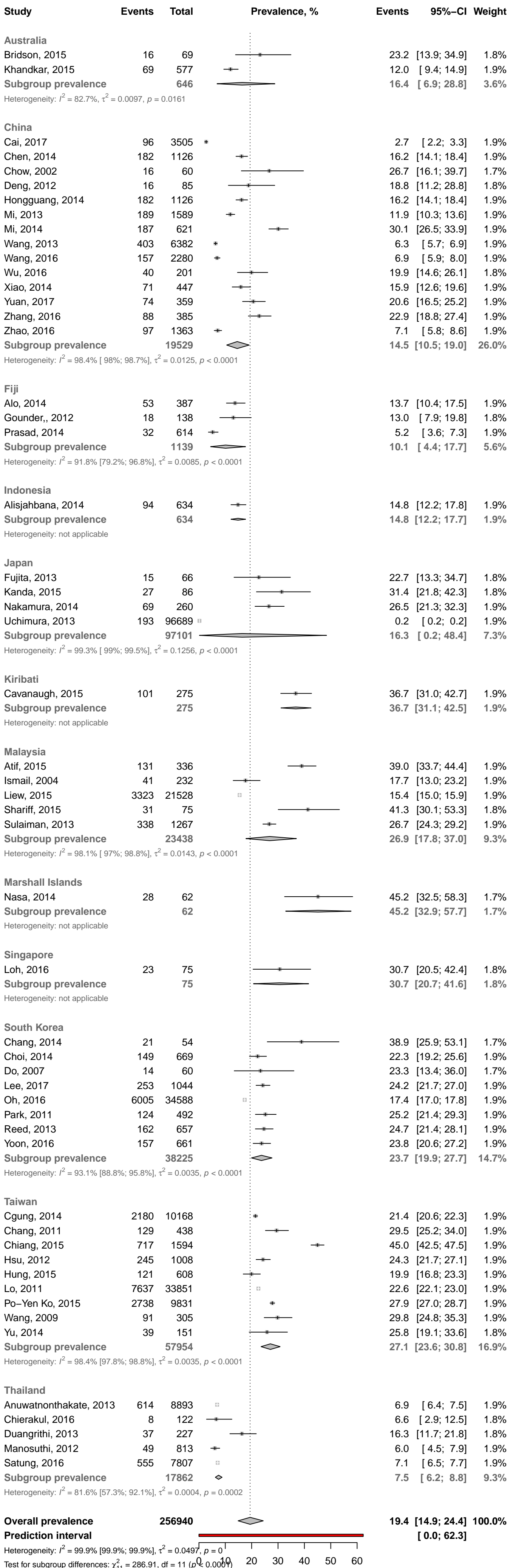
Heterogeneity:  $I^2 = 97.2\%$  [96.6%; 97.7%],  $\tau^2 = 0.0100$ ,  $p < 0.0001$

<b>Sri Lanka</b>						
Rajapakshe, 2015	27	112		24.1	[16.5; 33.1]	3.0%
<b>Subgroup prevalence</b>		<b>112</b>		<b>24.1</b>	<b>[16.6; 32.5]</b>	<b>3.0%</b>

Heterogeneity: not applicable

<b>Overall prevalence</b>		<b>30382</b>		<b>19.0</b>	<b>[16.2; 21.9]</b>	<b>100.0%</b>
<b>Prediction interval</b>					<b>[ 6.0; 36.9]</b>	

Heterogeneity:  $I^2 = 97.0\%$  [96.4%; 97.5%],  $\tau^2 = 0.0093$ ,  $p < 0.0001$   
 Test for subgroup differences:  $\chi^2 = 16.22$ ,  $df = 2$  ( $p = 0.0003$ )



**Table 1. Summary statistics of meta-analysis of the global prevalence of diabetes mellitus in people with active tuberculosis**

	<b>Prevalence, % (95% confidence interval)</b>	<b>95% prediction interval</b>	<b>N Studies</b>	<b>N Participants</b>	<b>H (95% confidence interval)</b>	<b>I<sup>2</sup> (95% confidence interval)</b>	<b>p heterogeneity</b>	<b>p Egger</b>	<b>p difference</b>
<b>Overall</b>	15.4 (14.1-16.6)	2.5-36.1	200	2291571	22.7 (22.4-23.0)	99.8 (99.8-99.8)	< 0.0001	< 0.0001	-
<b>Low risk of bias studies</b>	16.9 (14.9-19.0)	2.6-39.7	88	1144774	14.8 (14.4-15.2)	99.5 (99.5-99.6)	< 0.0001	< 0.0001	-
<b>By period of recruitment</b>									
- 2001 and more	14.9 (13.6-16.4)	2.4-35.1	155	2245245	25.0 (24.6-25.3)	99.8 (99.8-99.8)	< 0.0001	< 0.0001	0.946
- Less than 2000	14.7 (10.4-20.0)	2.5-35.4	13	9566	5.3 (4.6-6.2)	96.5 (95.2-97.4)	< 0.0001	0.423	
<b>By IDF region</b>									
- North America and Caribbean	19.7 (16.9-22.6)	6.8-37.1	29	217261	9.0 (8.4-9.7)	98.8 (98.6-98.9)	< 0.0001	0.629	< 0.0001
- Western Pacific	19.4 (14.9-24.4)	0.0-62.3	54	256940	28.0 (27.3-28.6)	99.9 (99.9-99.9)	< 0.0001	0.007	
- South-East Asia	19.0 (16.2-21.9)	6.0-36.9	30	30382	5.8 (5.3-6.4)	97.0 (96.4-97.5)	< 0.0001	0.070	
- Middle East and North Africa	17.5 (13.3-22.1)	0.9-47.8	31	14280	6.7 (6.2-7.3)	97.8 (97.4-98.1)	< 0.0001	0.103	
- Africa	8.0 (5.9-10.4)	0.8-21.3	20	20202	5.5 (4.9-6.2)	96.7 (95.8-97.4)	< 0.0001	0.921	
- South and Central America	7.7 (6.9-8.6)	4.5-11.7	17	1731240	15.5 (14.5-16.5)	99.6 (99.5-99.6)	< 0.0001	0.079	
- Europe	7.5 (5.2-10.2)	0.2-23.1	19	21512	6.6 (6.0-7.4)	97.7 (97.2-98.2)	< 0.0001	0.308	
<b>By TB burden in the country</b>									
- Low	16.5 (13.9-19.2)	0.0-52.5	119	474944	22.2 (21.9-22.7)	99.8 (99.8-99.8)	< 0.0001	0.260	0.036
- High	13.6 (12.7-14.5)	6.8-22.2	81	1816627	13.4 (13.0-13.9)	99.4 (99.4-99.5)	< 0.0001	< 0.0001	
<b>By level of income of the country</b>									
- Low	7.9 (4.9-11.5)	0.0-26.9	15	9434	5.6 (4.9-6.5)	96.8 (95.8-97.6)	< 0.0001	0.782	0.0003
- Lower-middle	17.7 (15.1-20.5)	3.4-40.6	48	48036	7.6 (7.1-8.1)	98.3 (98.0-98.5)	< 0.0001	0.148	
- Upper-middle	14.4 (12.8-16.0)	3.6-30.6	75	1994027	26.5 (26.0-27.0)	99.9 (99.9-99.9)	< 0.0001	0.006	
- High	16.6 (12.4-21.2)	0.0-60.9	62	240074	26.2 (25.6-26.8)	99.9 (99.8-99.9)	< 0.0001	0.006	
<b>By human development index</b>									
- Low	8.0 (5.9-10.4)	0.7-21.6	20	19475	5.5 (4.9-6.2)	96.7 (95.8-97.4)	< 0.0001	0.911	< 0.0001
- Medium	19.5 (16.6-22.5)	4.3-41.9	42	38005	7.0 (6.5-7.5)	97.9 (97.6-98.2)	< 0.0001	0.242	
- High	15.2 (13.5-17.0)	3.4-34.4	81	2050529	29.3 (28.8-29.9)	99.9 (99.9-99.9)	< 0.0001	0.001	
- Very high	14.8 (10.8-19.2)	0.0-56.0	56	183500	21.2 (20.6-21.8)	99.8 (99.8-99.8)	< 0.0001	0.0001	
<b>By site</b>									
- Hospital-based	15.7 (14.2-17.2)	1.6-39.8	175	1227780	20.9 (20.6-21.3)	99.8 (99.8-99.8)	< 0.0001	0.0002	0.309
- Population-based	12.9 (8.9-17.5)	0.7-36.5	15	58473	12.9 (11.9-14.0)	99.4 (99.3-99.5)	< 0.0001	0.448	
- Both	11.6 (5.4-19.6)	0.0-49.8	5	4859	6.8 (5.4-8.5)	97.8 (96.6-98.6)	< 0.0001	0.101	
<b>By population</b>									
- Adults	16.0 (14.5-17.5)	2.1-39.0	168	693012	15.3 (15.0-15.6)	99.6 (99.6-99.6)	< 0.0001	0.039	0.0008
- Adults and children	12.1 (10.6-13.8)	4.6-22.9	32	1598559	22.1 (21.3-22.9)	99.8 (99.8-99.8)	< 0.0001	0.090	

IDF: International Diabetes Federation, NA: not applicable, TB: tuberculosis; NA: not applicable