Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: A systematic review

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Abstract

Introduction

The dual burden of tuberculosis (TB) and diabetes mellitus (DM) has become a major global public health concern. There is mounting evidence from different countries on the burden of TB and DM comorbidity. The objective of this systematic review was to summarize the existing evidence on prevalence and associated/risk factors of TBDM comorbidity at global and regional levels.

Methods

Ovid Medline, Embase, Global health, Cochrane library, Web of science and Scopus Elsevier databases were searched to identify eligible articles for the systematic review. Data were extracted using standardized excel form and pilot tested. Median with interquartile range (IQR) was used to estimate prevalence of TBDM comorbidity. Associated/risk factors that were identified from individual studies were thematically analyzed and described.

Results

The prevalence of DM among TB patients ranged from 1.9% to 45%. The overall median global prevalence was 16% (IQR 9.0%-25.3%) Similarly, the prevalence of TB among DM patients ranged from 0.38% to 14% and the overall median global prevalence was 4.1% (IQR 1.8%-6.2%). The highest prevalence of DM among TB patients is observed in the studied countries of Asia, North America and Oceania. On the contrary, the prevalence of TB among DM patients is low globally, but relatively higher in the studied countries of Asia and the African continents. Sex, older age, urban residence, tobacco smoking, sedentary lifestyle, poor glycemic control, having family history of DM and TB illness were among the variables identified as associated/risk factors for TBDM comorbidity.

Conclusion

This systematic review revealed that there is a high burden of DM among TB patients at global level. On the contrary, the global prevalence of TB among DM patients is low.
Assessing the magnitude and risk/associated factors of TBDM comorbidity at country/local level is crucial before making decisions to undertake TBDM integrated services.

Introduction

Diabetes mellitus (DM) and tuberculosis (TB) are major killers of mankind across the globe [1]. The World Health Organization (WHO) global report for 2015 indicates that, there were 10.4 million new cases and 1.4 million deaths resulting from TB [2]. In the same year, 415 million cases and 5.0 million deaths due to DM were registered [3]. About 95% of TB and 75% of the DM cases live in low- and middle income countries. The rising prevalence of DM is a potential threat to TB control. Poorly controlled DM increases the risk of TB and leads to unfavorable TB treatment outcomes [4–5].

WHO has recommended a collaborative framework for the clinical management and control of TBDM comorbidity. Three important intervention strategies namely, establishing mechanisms of collaboration between TB and DM control programs, detection and management of TB in patients with DM, and detection and management of DM in TB patients have been recommended [6]. Some countries in Asia (China and India) have piloted the TBDM collaborative framework and have demonstrated that bi-directional screening for both diseases is feasible [7–10]. It may also be important if other countries implement this strategy to reduce the dual burden of TBDM comorbidity. However, for policy making and implementation of this strategy, it is crucial to primarily understand the magnitude and associated factors of TBDM comorbidity particularly in low- and middle-income countries.

Former studies conducted in various parts of the world have shown that TBDM comorbidity has become a major public health problem. A wide range of estimates on the burden and associated factors of the two comorbid conditions and impact of DM on TB treatment outcome were reported [11–13]. For example, a previous systematic review of bidirectional screening for TBDM comorbidity reported high prevalence of DM among TB patients ranging from 1.9% to 35%. TB prevalence among DM patients ranged from 1.7% to 36% [11]. Similarly, another systematic review done on 13 observational studies reported that DM was associated with an increased risk of TB [relative risk (RR) = 3.11, 95% confidence interval (C.I.) 2.27–4.26] [12].

Several reasons motivated us to do the current systematic review. Firstly, the risk/associated factors of TBDM comorbidity were not included in the previous systematic reviews. Secondly, the numbers of individual studies on TBDM comorbidity conducted after 2010 have increased by 78% compared to the number of studies done before 2010. Thirdly, unlike the periods before six years, bi-directional screenings of TB and DM studies have been emerging from different African countries. Therefore, an updated synthesis of the prevalence and associated factors of the two comorbid conditions is important for policy making, planning and development of TBDM integrated services. This systematic review was thus conducted to summarize the existing evidence on prevalence and associated/risk factors of TBDM comorbidity.

Methods

Eligibility criteria

In this systematic review, we included all full text articles that involved human subjects of any age, and that determined either prevalence and risk/associated factors of DM among TB patients or prevalence and associated factors of TB among DM patients. Type of DM was not an inclusion/exclusion criteria and therefore both types were included. Studies reporting prevalence of
DM among latent TB patients, prevalence of impaired glucose tolerance among TB patients and incidence of TB among DM patients were excluded from the review. In addition, pharmacological studies related to TBDM comorbid conditions, articles written other than English language, conference papers, abstracts without full texts, articles that didn’t describe journal’s name and corresponding author, articles that reported prevalence/incidence of the two comorbidity conditions stratified by socio-demographic and clinical parameters were excluded from the study.

Search strategy and selection of studies
We searched Ovid Medline from 1946 to March 09/2016, Embase from 1947 to March 09/2016, Global health from 1973 to March 09/2016, Cochrane library from 1992–March 09/2016, Web of science from 1900-March 09/2016 and Scopus elsevier from 1996-March 09/2016 using the following medical subject heading (MeSh) and text terms (Table 1). The full strategy was run in Endnote software. We also used hand searching to look for relevant reference lists and journals.

Data extraction and risk of bias assessment
A standardized form using excel sheet was used to extract relevant information. The standardized form was pilot tested in twenty selected articles included in the study. A number of variables including study locations, years of publications, study periods, study designs, number of patients included in the study, and prevalence of TBDM and associated/risk factors were extracted from all studies included in the systematic review. The risk of bias for each study was assessed using study design, sampling technique and sample size determination methods as important domains. In addition, we considered “type of screening method used” and “time of screening” for studies that assessed prevalence of DM among TB patients. For studies that analyzed TB prevalence among DM patients, “type of TB screening method used” was considered as an important domain (Table 2). Some of the above domains were also used in the previously conducted systematic review (12). One reviewer (MHW) searched, extracted the data and assessed the risk of bias. Any ambiguity in the extracted and assessed information was resolved through discussion with the other author (SAY).

Data analysis and syntheses
Descriptive statistics (range and median with interquartile range (IQR)) were used to summarize prevalence rates estimated from individual studies. Due to the observed wide variations in prevalence, and sample sizes used in the reviewed articles, we reported median prevalence rate based on geographical regions. The summaries were described into two groups, i.e. prevalence of DM among TB patients and prevalence of TB among DM patients. Data analyses were performed using Statistical Package for Social Science (SPSS) version 22 Armonk, New York 10504 IBM Corp. The risk/associated factors were grouped into main themes and described accordingly. In addition, findings of the studies were grouped into the different geographical regions of the world depending on where the individual studies were conducted. Each domain assessed for the risk of bias was categorized as either low or high risk of bias depending on the findings of each study. We scored 0 and 1 for low and high risk of bias, respectively. Accordingly, for studies that determined prevalence of DM among TB patients, the overall risk of study bias was calculated out of five total score points. While those with a total point of 2 were considered low risk, studies with a total value of 3–4 and 5 were considered to have moderate and high risk of bias, respectively. Similarly, for studies that analyzed prevalence of TB among DM patients, the overall risk of study bias was calculated out of four total score points. Consequently, studies that scored a total of 1 were considered low risk, and those with a total value of 2 and 3–4 were evaluated to have moderate and high risk of bias, respectively.
Results

A total of 1845 literatures were initially selected for screening. These included 1765 literatures identified from the electronic database search, 59 identified by hand search and 21 literatures identified by reference check (Fig 1). After removing 780 duplicate articles form the total 1845 literatures, 1065 articles remained for further screening. Additional screening by title and
abstract resulted in the exclusion of 877 articles and we were left with 188 articles for further
screening. We performed full text screening on 188 articles and found that 94 articles were eli-
gible for final analysis [9–10, 14–105]. The criteria for exclusion of the different studies are
listed in Fig 1.

The 94 studies selected for final analysis had applied different study designs. Majority 36
(38.3%) were cross-sectional studies, 11 (11.7%) were prospective cohort, 9 (9.6%) applied ret-
rospective cohort study design, 21 (22.3%) were medical record reviews, four (4.3%) studies
used prospective observational (not clearly specified) method, three (3.2%) used case-controls
study design and 10 (10.6%) studies did not describe the type of study design used. The studies
represented 33 countries globally and were divided into six regions. Of the total studies
included in the analysis, 74 (78.7%) were published between 2011 and 2016, 12 (12.8%) studies
were published from 2000 to 2010, and 8 (8.5%) studies were reported between 1957 to 1999
(Table 3).

### Risk of bias

The value of risk of bias ranged from 1 to 5 for 78 studies that determined prevalence of DM
among TB patients. Based on this assessment, 23 (29.5%) studies were assessed to have low
risk of bias, 49 (62.8%) studies had moderate risk of bias and 6 (7.7%) studies were evaluated
as having high risk of bias. The risk of bias for 19 studies that analyzed prevalence of TB
among DM patients ranged from 0 to 4. Accordingly, 3 (15.8%) studies were assessed to have

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**Table 2. Risk of bias assessment tools.**

| Variable                        | Methods used by the studies                                                                 | Risk of bias |
|---------------------------------|---------------------------------------------------------------------------------------------|--------------|
| Study design                    | Prospective cohort, cross-sectional or descriptive, case control, observational, population based study designs | 0            |
|                                 | Retrospective cohort, record review and studies that did not report study design             | 1            |
| Sampling methods                | Random selection                                                                          | 0            |
|                                 | Consecutive enrollment of all eligible patients & studies that did not describe sampling methods | 1            |
| Sample size determination       | Sample size determined                                                                     | 0            |
|                                 | Sample size not determined or studies that did not report how sample size was estimated      | 1            |
| Methods of DM screening among TB patients | Use of blood test alone, or use of combination methods (blood test either with urine glucose, self-report or medical record review) | 0            |
|                                 | Studies that reported the use of self-report, urine glucose, record review methods alone or in combination, and studies that did not report methods of DM screening | 1            |
| Timing of DM screening          | Studies that screened at the time of TB diagnosis or before TB treatment was started and both before and after anti-TB treatment was started | 0            |
|                                 | Studies that screened after TB treatment was initiated, or at the middle of TB treatment, or at the end of TB treatment period or both, and studies that did not report timing of DM screening | 1            |
| Methods of TB screening among DM patients | Use of WHO or National TB Control Program diagnostic methods of the respective country, use of either combination or individual screening methods of either of the following methods: microbiologically determined (sputum microscopy or sputum culture), PCR, Xpert/RIF-TB test or QFT-G. Use of clinical sign and symptoms, response to treatment, chest x-ray, tuberculin skin test, histopathology in combination with one of the above mentioned diagnostic methods | 0            |
|                                 | Studies that used ICD code, self-report, medical record review, clinical sign and symptoms, response to treatment, chest x-ray, tuberculin skin test, histopathology, broncho-alveolar lavage alone or in combination and studies that did not report methods of TB screening | 1            |

0 = low risk, 1 = high risk, DM = diabetes mellitus, TB = tuberculosis, WHO = World Health Organization, PCR = Polymerase chain reaction, Xpert MTB/RIF-TB = GeneXpert Rifampicin-TB, QFT-G = QuantIFERON-TB Gold, ICD = International classification of diseases

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low risk of bias, 8 (42.1%) studies were evaluated as having moderate risk of bias and 8 (42.1%) studies were assessed to have high risk of bias (S1 Table, Assessment of risk of bias of the studies).

Prevalence of DM among TB patients

Out of the total 94 studies, 78 studies reported DM prevalence among TB patients. Except one study, all reported the total number of observed DM cases among enrolled TB patients. Accordingly, the prevalence of DM among TB patients ranged from 1.9% in Cotonou-Benin to 45% in Ebeye-Marshall Islands [68,103]. This amounted to an overall global median DM prevalence of 16% (IQR 9.0–25.3%). Among the 78 studies, 48 (61.5%) studies were conducted in countries of Asia and showed prevalence rates ranging from 5.1% in Saluru-South India to 44% in Kerala-India [14, 18]. The overall median prevalence of DM among TB patients in Asia was calculated to be 17% (IQR 11.4%-25.8%). Thirteen (16.7%) studies conducted in countries of Africa showed prevalence rates ranging from 1.9% in Cotonou-Benin to 16.7% in Tanzania [68, 70]. This resulted in an overall median prevalence of 6.7% (IQR 4.1%-10.4%) in the studied countries of Africa. Eight (10.3%) studies that were done in countries of North America showed a prevalence rates ranging from 11.4% in Georgia [93] to 39.0% in South Texas [92]. The median prevalence in North America was 23.6% (IQR 17.3%-35.4%). There were five (6.4%) studies from Oceania that showed prevalence rates ranging from 12% in Fiji [104] to 45% in Ebeye-Marshall Islands [103] and the overall median prevalence in this area was 23.2%
Table 3. Profile of reviewed articles.

| Region | First author and publication year | Country | Study period | Study design | Reference |
|--------|-----------------------------------|---------|--------------|-------------|-----------|
| Asia   | India group et al. 2013           | India   | Jan-Sep/2012 | Prospective observational | [9]       |
|        | China group et al. 2012           | China   | 1 Sep 2011–31 March 2012 | Prospective observational | [10]      |
|        | Achanta et al. 2013               | Saluru-South India | Jan–Sep/2012 | Cross-sectional | [14]      |
|        | Alavi et al. 2012                 | Iran    | 2008–2010 | Medical record review | [15]      |
|        | Alisjahbana et al. 2006           | Indonesia | 2001–2005 | Case-control | [16]      |
|        | Bagheli et al. 2015               | Tehran-Iran | May 2012-May 2013 | Prospective cohort | [17]      |
|        | Balakrishnan et al. 2012          | Kerala-India | June-July/2011 | Cross-sectional | [18]      |
|        | Dave et al. 2013                  | Gujarat -India | Jan-Sep/ 2012 | Cross-sectional | [19]      |
|        | Jawad et al. 1995                 | Nazimabad-Pakistan | NR | NR | [20]      |
|        | Lin et al. 2015                   | Taiwan  | Sep-Nov/2012 | Cross-sectional | [21]      |
|        | Pandya et al. 1991                | Riyadh  | July 83-August 87 | Medical record review | [22]      |
|        | Raghuraman et al. 2014            | Puducherry | NR | Cross-sectional | [23]      |
|        | Rajapakse et al. 2015             | Sri Lanka | Jan 2013-Oct 2014 | Cross-sectional | [24]      |
|        | Shidam et al. 2015                | Pondicherry, India | Jan- Dec /2013 | Cross-sectional | [25]      |
|        | Thapa et al. 2015                 | Nepal   | 15th of Sep - 23rd of Nov/2013 | Cross-sectional | [26]      |
|        | Usmani et al. 2014                | Lahore-Pakistan | 1st July-30th Sep /2011 | Cross-sectional | [27]      |
|        | Viswanathan et al. 2012           | India   | Jan-March/2011 | NR | [28]      |
|        | Nagar et al. 2015                 | India   | Oct 2013-March 2014 | Cross-sectional | [29]      |
|        | Wang et al. 2013                  | China   | Sep 2010-Dec 2012 | Prospective community based cohort | [30]      |
|        | Sarvamangala et al. 2014          | India   | Jan 2012-Aug 2012 | Cross-sectional | [31]      |
|        | Deshmukh et al. 1984              | India   | NR | NR | [32]      |
|        | Chachra et al. 2014               | Ghaziabad -India | NR | Cross-sectional | [33]      |
|        | Wang et al. 2000                  | Taiwan  | 1993–1996 | Retrospective cohort | [34]      |
|        | Chaudhry et al. 2012              | Filipino-Saudi-Arabia | Jan. 2003-June 2010 | Retrospective/medical record | [35]      |
|        | Duangritthi et al. 2013           | Thailand | April 2010 -July 2012 | Prospective | [36]      |
|        | Jabbar et al.2006                 | Pakistan | Jan 1992-Dec 1996 | Retrospective descriptive (Medical record review) | [37]      |
|        | Jali et al. 2013                  | India   | Feb-Sep/2012 | Cross-sectional | [38]      |
|        | Magee et al. 2015                 | Georgia- Tbilisi | Oct 2011-May 2014 | Prospective cohort | [39]      |
|        | Mi et al. 2013                    | Guangzhou, China | 1 Sep. 2011–30 June 2012 | Cross-sectional and retrospective cohort study (medical record review) | [40]      |
|        | Mi et al. 2014                    | Beijing -China | 1 Jan 2011–30 June 2012 | Cross-sectional and retrospective record review | [41]      |
|        | Pablo-Villamor et al.2014         | Philippines | July 2011-Nov.2012 | Prospective observational cohort study | [42]      |
|        | Park et al.2012                   | Korea   | Jan 2005-Dec 2009 | Retrospective (medical record review) | [43]      |
|        | Roghieh et al.2011                | Iran    | 2004–2008 | Retrospective cross-sectional (review of medical record) | [44]      |
|        | Mehta et al. 2015                 | India   | 2012–2013 | Cross-sectional | [45]      |
|        | Shaikh et al. 2003                | Saudi-Arabia | Jan1998-Dec1999 | Retrospective (medical record) | [46]      |
|        | Siddiqui et al. 2009              | Saudi-Arabia | Jan 2002-Dec 2007 | Retrospective (medical record review) | [47]      |
|        | Sulaiman et al. 2013              | Malaysia | Jan 2006-Dec 2007 | Retrospective cohort | [48]      |
|        | Zhang et al. 2009                 | China   | 2008–2009 | Retrospective | [49]      |
|        | Chen et al. 2014                  | China   | Jan 2010-Dec 2011 | Cross-sectional | [50]      |
|        | Jali et al. 2013                  | India   | Feb 2012-Sep 2012 | Prospective observational study | [51]      |
|        | Kumpatla et al. 2013              | India   | Mar-Dec/ 2012 | Descriptive (review of record) | [52]      |

(Continued)
| Region     | First author and publication year | Country       | Study period             | Study design                      | Reference |
|------------|-----------------------------------|---------------|--------------------------|-----------------------------------|-----------|
| India      | Tripathy et al. 1984              | India         | 1st Jan. 1978-31st Dec.1982 | Prospective study                | [53]      |
|            | Wu et al. 2015                    | China         | 2007–2008                | Retrospective population based study | [54]      |
| Pakistan   | Naeem et al. 2016                 | Pakistan      | Feb 2013-Dec 2014        | Prospective observational         | [55]      |
| Kerala     | Nair et al. 2013                  | Kerala-India  | March-Sep/2012            | Descriptive study                 | [56]      |
| Pakistan   | Tahir et al.2014                  | Kohat-Pakistan| NR                       | Cross-sectional                   | [57]      |
| India      | Jain et al. 2015                  | NR            | Cross-sectional          | [58]      |
| Pakistan   | Amin et al. 2011                  | Pakistan      | 1st Aug 2010-31st July 2011 | NR                                | [59]      |
|            | Prakash et al.2013                | India         | 1 March-30 Sep 2012      | Descriptive study                 | [60]      |
| Pakistan   | Qayyum et al.2004                 | Pakistan      | Jan.2001 –Dec 2001       | NR                                | [61]      |
| Jammu      | Sangrati et al.2012               | Jammu-India   | 2009–2010                | NR                                | [62]      |
| Indonesia  | Alisjahbana et al.2007            | Indonesia     | Oct 2000-Dec 2005        | Prospective cohort                | [63]      |
| Iran       | Kermansari et al.2014             | Iran          | April 2010-Dec 2011      | Cross-sectional                   | [64]      |
| India      | Padmalatha et al. 2014            | India         | May 2014-Oct 2014        | Cross-sectional                   | [65]      |
| Kerala     | Kottarath et al. 2015             | Kerala-India  | Aug.2014-July 2015       | Descriptive                       | [66]      |
| Hyderabad  | Rao et al. 2015                   | Hyderabad-India| June-July/2014         | Cross-sectional                   | [67]      |
| Tanzania   | Ade et al. 2015                   | Cotonou-Benin | June-July/2014           | Cross-sectional                   | [68]      |
| Ethiopia   | Amare et al. 2013                 | Ethiopia      | Feb-April/2012           | Cross-sectional                   | [69]      |
| Tanzania   | Faurholt-Jepsen et al. 2011       | Tanzania      | April 2006-Jan 2009      | Case control                      | [70]      |
| Guinea-Bissau | Haraldsdottir et al. 2015    | Guinea-Bissau | July 2010-July 2011      | NR                                | [71]      |
| Uganda     | Kibirige et al. 2013              | Uganda        | Sep 2011- Feb 2012       | Cross-sectional                   | [72]      |
| Tanzania   | Mtwangambate et al. 2014           | Tanzania      | Sep 2011-March 2012      | Prospective cohort                | [73]      |
| Lagos-Nigeria | Ogbera et al. 2014               | Lagos-Nigeria | Sep 2010 –March 2012    | Cross-sectional                   | [74]      |
| Lagos-Nigeria | Olayinka et al. 2013             | Lagos-Nigeria | NR                      | Cross-sectional                   | [75]      |
| Ethiopia   | Workneh et al. 2016               | Ethiopia      | Sep 2103–Sep 2014        | Cross-sectional                   | [76]      |
| Ethiopia   | Feleke et al. 1999                | Ethiopia      | Sep 1989–1996            | Cross-sectional based on the retrospective analysis of data review record | [77]      |
| Tanzania   | Swai et al. 1990                  | Tanzania      | 1 June 1981–31 May 1977  | NR                                | [78]      |
| South-Africa | Webb et al. 2009                 | South-Africa  | 10 Sept 2006–31 Jan 2007 | Cross-sectional                   | [79]      |
| Kenya      | Kirui et al. 2012                 | Kenya         | Jan 2007-Feb 2011        | Descriptive study from routine record data | [80]      |
| Ethiopia   | Tiroro et al. 2015                | Ethiopia      | Jan 2010-Jan 2014        | Retrospective study (medical record) | [81]      |
| Lagos-Nigeria | Ogbera et al. 2015               | Lagos-Nigeria | March 2011-July 2012    | Descriptive observational study | [82]      |
| Ethiopia   | Getachew et al. 2014              | Ethiopia      | Oct.2011-August 2012     | Cross-sectional                   | [83]      |
| Ethiopia   | Damte et al. 2014                 | Ethiopia      | Feb.2014-May 2014        | Cross-sectional                   | [84]      |
| Guinea     | Balad et al. 2006                 | Guinea        | 1 Feb 30-June 2002       | NR                                | [85]      |
| Antananarivo-Madagascar | Rakotonirina et al. 2014     | Antananarivo-Madagascar | July15,2013—Oct 30,2013 | Descriptive                       | [86]      |
| Tanzania   | Mugusi et al. 1990                | Tanzania      | NR                      | NR                                | [87]      |
| Europe     | Moreno-Martinez et al. 2015       | European city- Barcelona | 1 Jan 2000–31 Dec 2013 | Retrospective, population based cross-sectional | [88]      |
| Britain    | Warwick et al. 1957               | Britain       | 1 Jan 1940-Dec 31,1954  | Medical record review             | [89]      |
| Mexico     | Ponce-de-leon et al. 2004         | Mexico        | 1995–2003               | Population based cohort study     | [90]      |

(Continued)
Three (3.8%) studies conducted in South America indicated prevalence rates ranging from 6.1% in Brazil to 14% in Guyana [98,101]. This amounted to an overall median prevalence of 11.1% (IQR 6.1%-14.0%). There was only one study from Europe that showed a prevalence rate of 5.9% (Fig 2).

![Fig 2. Map showing median prevalence of DM among TB patients by region. (NB: There is only one study reported in Europe). IQR: Interquartile range (Source of the map: https://www.flickr.com/photos/blatantworld/5052373414/, Accessed March 20/2017).](https://doi.org/10.1371/journal.pone.0175925.g002)

**Table 3.** (Continued)

| Region     | First author and publication year | Country                  | Study period                  | Study design                          | Reference |
|------------|-----------------------------------|--------------------------|-------------------------------|---------------------------------------|-----------|
| South America |                                   |                          |                               |                                       |           |
|            | Restrepo et al. 2007              | Texas-Mexico            | Mexico (1998–2003) / Texas (1996–2002) | Medical record review                | [91]      |
|            | Restrepo et al. 2011              | South-Texas & North-eastern Mexico | March 2006-Sep 2008            | Cross-sectional                      | [92]      |
|            | Magee et al. 2014                 | Georgia-US              | Jan 2009- Sep 2012            | Retrospective cohort                 | [93]      |
|            | Suwanpimolkul et al. 2014         | USA-San Francisco       | April 2005-March 2012         | Retrospective                        | [94]      |
|            | Delgado-Sánchez et al. 2015       | Mexico                  | 2000–2012                    | TB registry review retrospective analysis | [95]      |
|            | Castellanos-Joya et al. 2014      | Mexico                  | July 2012—April 2013          | Prospective observational cohort      | [96]      |
|            | Jiménez-Corona et al. 2013        | Southern-Mexico         | 1995 to 2010                  | Prospective cohort                   | [97]      |
|            | Alladin et al. 2011               | Guyana                  | May-June/2006                 | Cross-sectional                      | [98]      |
|            | Magee et al. 2013                 | Peru                    | Jan,2005-May 2008             | Medical record                       | [99]      |
| Oceania    | Reis-Santos et al. 2013           | Brazil                  | 2009                         | Disease notification information system | [100]     |
|            | Bridson et al. 2015               | Australia               | 1995–2014                    | Retrospective                        | [101]     |
|            | Viney et al. 2015                 | Kiribati-Pacific Island | June 2010-March 2012          | Case control (unmatched)             | [102]     |
|            | Nasa et. al. 2014                 | Ebeye-Marshall Islands  | July 2010-December 2012      | Retrospective cohort                 | [103]     |
|            | Prasad et al. 2014                | Fiji                    | 2010–2012                    | Retrospective descriptive (TB register) | [104]     |
|            | Gounder et al. 2012               | Fiji                    | Jan-March/2012                | Cross-sectional medical record review | [105]     |

NR = Not reported, TB = tuberculosis.

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Of the 78 studies included in this systematic review, only ten (12.8%) studies reported number needed to screen (NNS). The NNS indicates the number of TB patients that must be screened to get a single case of DM. The NNS ranged from four cases in Kerala India [18] to 56 in Sri Lanka [23]. Only 42 (53.8%) studies described the number of new DM patients obtained by screening TB patients. The number of new DM cases obtained after screening ranged from one case in Cotonou-Benin [68] to 402 cases in India [9] (Table 4).

Prevalence of TB among DM patients

Out of the total 94 studies, 19 studies reported TB prevalence among DM patients. The studies were conducted in 11 countries distributed in four geographic regions of the world. The prevalence of TB among DM patients ranged from 0.38% in Taiwan [21] to 14% in Pakistan [59], and the overall median prevalence was 4.1% (IQR 1.8%-6.2%). Among the 19 studies, ten (52.6%) were from four countries of the Asian Region and the prevalence ranged from 0.38% in Taiwan [21] to 14% in Pakistan [59]. This amounted to an overall median TB prevalence of 3.5% (IQR 0.9%-10.5%) among DM patients in the studied countries of Asian Region. Seven (36.8%) prevalence studies were conducted in four countries of the African Region, and the prevalence ranged from 1.3% in Tanzania [73] to 6.2% in Ethiopia [69]. The overall median TB prevalence among DM patients in the Africa studies was 5.6% (IQR 3.5%-5.8%). There was only one study in North America (Mexico) that showed a prevalence rate of 4.9% [96]. There was also one prevalence study from Europe that showed prevalence rate of 1.82% [89] (Fig 3). Only two study reported the NNS and NNS reported to screen DM patients to get one TB case ranges 71 DM patients in Mexico [96] to 812 in India [60] (Table 4).

Risk factors for TBDM comorbidity

The risk/associated factors for TBDM comorbidity were heterogeneous. Both sexes, age, family history of DM, pulmonary form of TB (PTB) and positive sputum smear were the most frequently mentioned factors in the majority of the studies. The studies used different measures of association to analyze the factors. Out of the 94 reviewed articles, 11 (11.7%) studies applied chi square test. Twenty two (23.4%) studies reported TBDM risk/associated factors using odds ratio, relative risk or hazard ratio. Conversely, 61 (64.9%) studies did not report either associated or risk factors for TBDM coexistence. This might be due to that most of the studies did not have adequate sample size and almost all studies mentioned neither in their objective nor in the limitation part about the risk factors of TBDM comorbidity. The following is a brief thematic description of the associated/ risk factors that were identified in the different studies.

1. Socio-demographic and economic factors. A number of studies concluded that both males [18, 21, 94] and females [76, 91, 95] were at increased risk for TBDM comorbidity. Men were more likely to develop TBDM comorbidity compared to women [15]. Twenty two studies reported that older age increased the risk of TBDM comorbidity [14–15, 17–19, 23, 25–26, 28, 30, 48, 54, 56, 65–67, 76, 81, 86, 91, 96, 100]. Urban residence and having an education level beyond primary schooling were associated factors for TBDM comorbid conditions [31, 69]. Place of birth, ethnicity, high-income status and sedentary occupation were risk factors associated with TBDM comorbidity [21, 26, 28, 30, 48, 86, 91, 94].

2. Behavioral factors. Illicit drug use, and sedentary lifestyle were reported as behavioral factors associated with TBDM comorbidity [15, 85]. Cigarette smoking [21] and being alcohol drinker [23] were identified as an increased risk factors for TBDM coexistence. Practicing frequent outdoor activity was reported as a low behavioral risk factor for TBDM comorbidity [30].
Table 4. Prevalence of TBDM comorbidity.

| Region | First author and publication year | Country | Prevalence of DM among TB patients | Prevalence of TB among DM patients | Reference |
|--------|----------------------------------|---------|-----------------------------------|-----------------------------------|-----------|
|        |                                  |         | Enrolled TB patients | Total DM case | Prevalence of DM (%) | Type of DM status and prevalence | NNS Enrolled DM patients | Total TB cases | Prevalence of DM (%) | NNS |
|        |                                  |         | New N (%) | Known N (%) |                       |                        |                       |                        |                       |         |
| Asia   | India group et al. 2013          | India   | 8109     | 1084       | 13                      | 402 (5) | 682 (8) | NR |
|        | China group et al. 2012          | China   | 8886     | 1090       | 12.4                    | 227 (2.9) | 863 (9.7) | NR |
|        | Achanta et al. 2013              | Saluru-South India | 374 | 19 | 5.1 | 12 (3.2) | 7 (1.9) | 31 |
|        | Atavi et al. 2012                | Iran    | 148      | 36         | 24.3                    | NR | 36 (24.3) | NR |
|        | Alisjahbana et al. 2006          | Indonesia | 454 | 60 | 13.2 | 36 (60.0) | 24 (40) | NR |
|        | Baghaei et al. 2015               | Tehran-Iran | 293 | 101 | 34.5 | 45 (15.4) | 56 (19.1) | 5 |
|        | Balakrishnan et al. 2012         | Kerala-India | 552 | 243 | 44 | 115 (21) | 128 (23) | 4 |
|        | Dave et al. 2013                  | Gujarat-India | 553 | 36 | 6.5 | 22 (4) | 14 (2.5) | 25 |
|        | Jawad et al. 1995                | Nazimabad-Pakistan | 106 | 21 | 19.8 | NR | NR | NR |
|        | Lin et al. 2015                   | Taiwan  | 3,087    | 12         | 0.38                    | NR | NR | NR |
|        | Pandya et al. 1991               | Riyadh  | 1566     | 136        | 8.7                     | NR | NR | NR |
|        | Raghuraman et al. 2014            | Puducherry | 217 | 63 | 29 | 18 (8.3) | 45 (20.7) | NR |
|        | Rajapakshe et al. 2015            | Sri Lanka | 112 | 10 | 9 | 2 (1.8) | 8 (7.1) | 56 |
|        | Shidam et al. 2015                | Pondicherry-India | 570 | 121 | 21.2 | 52 (43) | 69 (57) | 11 |
|        | Thapa et al. 2015                 | Nepal   | 407      | 37         | 9.1                     | 9 (2.2) | 28 (6.9) | NR |
|        | Usmani et al. 2014                | Lahore-Pakistan | 158 | 41 | 25.9 | 9 (5.69) | 32 (20.3) | NR |
|        | Viswanathan et al. 2012           | India   | 827      | 209        | 25.3                    | 77 (9.3) | 132 (15.96) | NR |
|        | Nagar et al. 2015                 | India   | 220      | 34         | 15.4                    | 9 (4.09) | 25 (11.3) | NR |
|        | Wang et al. 2013                  | China   | 6382     | 403        | 6.3                     | 177 (43.9) | NR | NR |
|        |                                   | 6675 Non-TB controls | 313 | 4.7 | 136 (43.5) | NR | NR | NR |
|        | Sarvamangala et al. 2014          | India   | 200      | 28         | 14                     | NR | 18 (64.3) | NR |
|        | Deshmukh et al. 1984              | India   | 2434     | 138        | 5.6                     | 78 (56.6) | 60 (43.4) | NR |
|        | Chachra et al. 2014               | Ghaziabad-India | 700 | 88 | 12.6 | 64 (72.7) | 24 (27.3) | NR |
|        | Wang et al. 2000                  | Taiwan  | 2841     | 480        | 16.9                    | NR | NR | NR |
|        | Chaudhry et al. 2012              | Filipino-Saudi-Arabia | 1388 | 114 | 7.17 | NR | NR | NR |
|        | Duangrithi et al. 2013            | Thailand | 227 | 37 | 16.3 | 11 (29.7) | 26 (70.3) | NR |
|        | Jabbar et al. 2006                | Pakistan | 1458 | 173 | 11.9 | NR | NR | NR |

(Continued)
| Region | First author and publication year | Country          | CP | Prevalence of DM among TB patients | Prevalence of TB among DM patients | Reference |
|--------|----------------------------------|------------------|----|------------------------------------|-----------------------------------|-----------|
|        |                                  |                  |    | Enrolled TB patients               | Total DM case                     |           |
|        |                                  |                  |    | Prevalence of DM (%)               | Type of DM status and prevalence  | NNS       |
|        |                                  |                  |    | New N (%)                          | Known N (%)                       | Enrolled DM patients | Total TB cases | Prevalence of DM (%) | NNS |
|        |                                  |                  |    |                                    |                                   | Non-DM 40,9000 | 691 | 1.7           |      |
|        | Jali et al. 2013                 | India            | 307| 109                                | 35.5                              | NR          | NR | NR           | [38] |
|        | Magee et al. 2015                | Georgia- Tbilisi | 318| 37                                 | 11.6 (95% C.I. 8.4–15.5)          | 9 (24.3)    | NR | NR           | [39] |
|        | Mi et al. 2013                   | Guangzhou, China | 1589| 189                                | 12                                | NR          | NR | NR           | [40] |
|        | Mi et al. 2014                   | Beijing-China    | 621 | 187                                | 30                                | NR          | NR | NR           | [41] |
|        | Pablo-Villamor et al. 2014       | Philippines      | 38 | 7                                  | 18.4 (95% C.I. 7.7–34.3)          | NR          | NR | NR           | [42] |
|        | Park et al.2012                  | Korea            | 492| 124                                | 25.2                              | NR          | NR | NR           | [43] |
|        | Roghieh et al. 2011              | Iran             | 200| 80                                 | 40                                | NR          | NR | NR           | [44] |
|        | Mehta et al. 2015                | India            | 194| 22                                 | 11.3                              | NR          | NR | NR           | [45] |
|        | Shaikh et al. 2003               | Saudi-Arabia     | 692| 187                                | 27                                | 23 (12.3)   | NR | NR           | [46] |
|        | Siddiqui et al. 2009             | Saudi-Arabia     | 216| 35                                 | 16                                | NR          | NR | NR           | [47] |
|        | Sulaiman et al. 2013             | Malaysia         | 1267| 338                                | 26.7                              | NR          | NR | NR           | [48] |
|        | Zhang et al. 2009                | China            | 2141| 203                                | 9.5                               | NR          | NR | NR           | [49] |
|        | Chen et al. 2014                 | China            | 1126| 182                                | 16.2                              | 18 (1.6)    | 164 (14.6) | NR           | [50] |
|        | Jali et al. 2013                 | India            | 307| 109                                | 35.5                              | 49 (15.96)  | 60 (19.54) | 4118         | 111 | 2.70 | NR           | [51]* |
|        | Kumpatla et al. 2013             | India            | 7083| 50                                 | 0.7                               | NR          |      |              | [52] |
|        | Tripathy et al. 1984             | India            | 219| 9                                 | 4.1                               | NR          |      |              | [53] |
|        | Wu et al. 2015                   | China            | 201| 40                                 | 19.90                             | NR          | NR | NR           | [54] |
|        | Naeem et al. 2016                | Pakistan         | 95 | 17                                 | 16.75                             | NR          | NR | NR           | [55] |
|        | Nair et al. 2013                 | Kerala-India     | 920| 298                                | 32.4                              | 63 (7)      | 235 (26) | NR           | [56] |
|        | Tahir et al.2014                 | Kohat-Pakistan   | 253| 48                                 | 18.97                             | NR          | NR | NR           | [57] |
|        | Jain et al. 2015                 | India            | 189| 41                                 | 21.69                             | NR          | NR | NR           | [58] |
|        | Amin et al. 2011                 | Pakistan         | 100| 14                                 | 14                                | NR          |      |              | [59] |
|        | Prakash et al.2013               | India            | 510| 47                                 | 9.2                               | 15 (2.9)    | 32 (6.3) | 1670         | 47 | 2.8 | 812       | [60]* |
|        | Qasym et al.2004                 | Pakistan         | 95 | 9                                  | 9.5                               | NR          |      |              | [61] |
|        | Sangrul et al. 2012              | Jammu-India      | 280| 23                                 | 8.2                               | NR          | NR | NR           | [62] |
|        | Alijsjahbana et al. 2007         | Indonesia        | 634| 94                                 | 14.8                              | 57 (61.3)   | NR | NR           | [63] |
|        | Kermansarar et al. 2014          | Iran             | 400| 1                                  | 1                                 | NR          |      |              | [64] |

(Continued)
| Region | First author and publication year | Country | Prevalence of DM among TB patients | Prevalence of TB among DM patients | Reference |
|--------|----------------------------------|---------|-----------------------------------|------------------------------------|-----------|
|        |                                   |         | Enrolled TB patients | Total DM case | Prevalence of DM (%) | Type of DM status and prevalence | NNS | Enrolled DM patients | Total TB cases | Prevalence of DM (%) | NNS |
|        |                                   |         | 252 | 77 | 30.60 | 60 (77.8) | 17 (22.2) | NR | 65 |
|        |                                   |         | 147 | 29 | 19.7 | 16 (55) | 13 (45) | NR | 66 |
|        |                                   |         | 96 | 10 | 10 | NR | 67 |
|        |                                   |         | 159 | 3 | 1.9 | 1 (0.63) | 2 (1.26) | NR | 68 |
|        |                                   |         | 350 | Non-TB control | NR | 9.4 (95% C.I. 6.6–13.0) | NR | NR | 69 |
|        |                                   |         | 107 | 3 | 2.8 | NR | NR | NR | 70 |
|        |                                   |         | 531 | Non-TB control | 11 | 2.1 | NR | NR | 71 |
|        |                                   |         | 260 | 22 | 8.5 | NR | 5 (1.9) | NR | 72 |
|        |                                   |         | 803 | NR | 16.7 (95% C.I. 14.2–19.4) | NR | NR | NR | 73 |
|        |                                   |         | 3376 | 162 | 4.8 | 85 (52.5) | 77 (47.5) | NR | 74 |
|        |                                   |         | 351 | 20 | 5.7 | 10 (2.8) | NR | NR | 75 |
|        |                                   |         | 1314 | 109 | 8.3 | 64 (4.9) | 45 (3.4) | 19.8 | 76 |
|        |                                   |         | 1352 | 78 | 5.8 | NR | 77 |
|        |                                   |         | 1250 | 70 | 5.6 | NR | 78 |
|        |                                   |         | 258 | 9 | 3.48 | NR | 79 |
|        |                                   |         | 1376 | 77 | 5.6 | NR | 80 |
|        |                                   |         | 199 | 17 | 8.5 (95% C.I. 4.6–12.5) | 9 (53) | NR | NR | 81 |
|        |                                   |         | 199 | 17 | 8.5 (95% C.I. 4.6–12.5) | 9 (53) | NR | NR | 82 |
|        |                                   |         | 120 | 19 | 15.8 (95% C.I. 9.20–22.45) | 16 (84.2) | 3 (15.8) | NR | 83 |
|        |                                   |         | 388 | 13 | 3.35 (95% C.I. 1.35–5.35) | 4 (31) | NR | NR | 84 |
|        |                                   |         | 156 | 9 | 5.8 (95% C.I. 3.1–10.6) | NR | 4 (2.6) | NR | 85 |
|        |                                   |         | 506 | 34 | 6.7 | 25 (4.9) | 9 (1.8) | NR | 86 |
|        |                                   |         | 5849 | 349 | 5.9 | NR | NR | NR | 87 |
| Europe | Moreno-Martinez et al. 2015 |         | 5849 | 349 | 5.9 | NR | NR | NR | 88 |

(Continued)
3. Clinical factors. Both lower and higher body mass index (BMI), human immune–deficiency virus (HIV) coinfection, body weight loss and hypertension were reported as associated factors for TBDM comorbidity [15–16, 21, 26, 58, 65, 85]. Both lower and higher BMI were also reported as an increased risk factor for TBDM comorbidity [28, 81]. Pre-existing and long duration of DM [69, 81], poor glycemic control at the time of TB diagnosis [79], patients with liver cirrhosis [21] and history of high blood pressure [26] were identified as an increased risk factor for the development of TBDM comorbidity. DM with both positive [15] and negative

### Table 4. (Continued)

| Region          | First author and publication year | Country         | Prevalence of DM among TB patients | Prevalence of TB among DM patients | Reference |
|-----------------|-----------------------------------|-----------------|-----------------------------------|-----------------------------------|-----------|
|                 |                                    |                 | Enrolled TB patients | Total DM case | Prevalence of DM (%) | Type of DM status and prevalence | NNS | Enrolled DM patients | Total TB cases | Prevalence of DM (%) | NNS |
|                 |                                    |                 | NNS (%) | Known N (%)           |                   |                                      |     | NR | NR | NR | [89] |
| Warwick et al.  | 1957                               | Britain         | 1851 | 34 | 1.82 | NR | NR | NR | [90] |
| North America   |                                    |                 | Love | 1241 | 401 | 27.8 | NR | 401 (27.8) | NR | [91] |
| Restrepo et al. | 2011                               | South-Texas     | 61 | 24 | 39.0 | NR | NR | NR | [92] |
| Magee et al.    | 2014                               | Georgia-US      | 1325 | 151 | 11.4 | NR | NR | NR | [93] |
| Suwanpimkul et al. 2014 | USA-San Francisco | 791 | 126 | 15.9 | NR | NR | NR | [94] |
| Delgado-Sánchez et al. 2015 | Mexico | 181,378 | 34,988 | 19.29 | NR | 34,988 (19.29) | NR | [95] |
| Castellanos-Joya et al. 2014 | Mexico | 361 | 70 | 19.4 | 16 (22.9) | NR | 22 | 783 | 38 | 4.9 | 71 | [96]* |
| Jiménez-Corona et al. 2013 | Southern -Mexico | 1262 | 400 | 31.7 | 26 (2.1) | 374 (29.6) | NR | [97] |
| Magee et al.    | 2013                               | Peru            | 1671 | 186 | 11.1 | NR | NR | NR | [98] |
| Reis-Santos et al. 2013 | Brazil | 29,275 | 1797 | 6.1 (95% C.I. 6.9–6.4) | NR | NR | NR | [100] |
| Bridison et al. | 2015                               | Australia       | 69 | 16 | 23.2 | NR | NR | NR | [101] |
| Viney et al. 2015 | Kiribati-Pacific Island | 275 | 101 | 37 | 47 (17.1) | 54 (19.6) | 5 | [102] |
| Nasa et. al. 2014 | Ebeye-Marshall Islands | 62 | 28 | 45 | NR | NR | NR | [103] |
| Prasad et al. 2014 | Fiji | 567 | 68 | 12 | 8 (11.8) | 26 (38.2) | NR | [104]* |
| Gounder et al. 2012 | Fiji | 138 | 18 | 13 | NR | 18 (13) | NR | [105] |

* = bidirectional screening studies results  
θ = the types of DM status information for 34 (50%) patients was not documented  
DM = diabetes mellitus, TB = tuberculosis, NNS = number needed to screen, NR = not reported, C.I. = confidence interval.
HIV status were documented as associated and increased risk factor for TBDM comorbid condition. HIV coinfection and malnutrition were also reported as low risk factor for TBDM comorbidity [72, 95]. HIV coinfection with injection drug use (IDU) or without IDU was reported as low risk factor for TBDM coexistence [88]. TBDM comorbid patients were more likely to be PTB case, smear-positive, to have anti-TB drug resistance, to have cavitary lesions on chest x-ray, and to have high alanine transaminase (ALT) level [10, 25, 28, 30, 48, 54, 56, 88–89, 72, 76, 84, 88, 95, 100]. On the contrary, being an extra pulmonary TB (EPTB) case was reported as a low risk factor for TBDM comorbidity [100].

4. History of DM, TB illness & TB treatment. Having family history of DM, history of TB illness and treatment, experiencing more side effect of anti-TB treatment, type of TB treatment category, treatment for previous TB episode and extension of anti-TB treatment durations were reported as increased risk factor for TBDM comorbidity [23, 25–26, 28, 30, 54, 65, 69, 76, 88, 95]. Receiving TB treatment after abandonment was also identified as low risk factor for TBDM comorbidity [100].

5. Other factors. Contact with TB patient in the family was reported as associated/increased risk factor for TBDM comorbidity [16, 69, 79]. Being imprisoned was associated with TBDM comorbidity [15, 98]. TBDM comorbid patients may require hospitalization [88]. TBDM patients were more likely to die from TBDM comorbidity [100]. Being kept in certain institutions (prisons shelter, orphanage and psychiatric hospital) were documented as low risk factor for TBDM comorbidity [100] (Table 5).

Discussion
This systematic review revealed that the global burden of TBDM comorbidity is high, and is fueled by heterogeneous risk/associated factors. The observed global TBDM comorbidity
Table 5. Thematic analysis of risk/associated factors for TBDM comorbidity.

| Risk factor                                      | Associated factors | Risk factors |
|-------------------------------------------------|--------------------|--------------|
| **Socio-demography and economic factors**        |                    |              |
| **Sex**                                         |                    |              |
| Male                                            | [15]               | [18,21,94]   |
| Female                                          | [76,91,95]         |              |
| **Age**                                         | [14–15,17,19,65,67,98] | [18,23,25–26,28,30,48,54,56,76,81,88,91,100] |
| Old age                                         | [31]               | [69]         |
| **Urban residence**                             | [31]               |              |
| Education beyond primary schooling              |                    |              |
| Place of birth (Spanish born, Chinese, Philippines) | [48,88,94]         |              |
| Ethnicity (Hispanic)                            | [91]               |              |
| High-income status                              | [26,30]            |              |
| Sedentary occupation                            | [28]               |              |
| **Family size**                                 | [67]               |              |
| **Behavioral factors**                          |                    |              |
| **Illicit drug use**                            | [15]               | [21,26]      |
| Sedentary lifestyle                             | [85]               |              |
| **Smoking**                                     | [21,26]            | [85]         |
| Current alcohol drinker                         | [23]               | [30]         |
| Frequent outdoor activity                       | [30]               | [30]         |
| **Clinical factor**                             |                    |              |
| Body weight loss                                | [21]               | [21]         |
| **BMI** [17.7 kg/m² (range11.2–31.4), (<18.6kg/m²), (18.5–22.9 kg/m2), and (>18.5 kg/m²)] | [16] | [28,81] |
| Overweight or obese                             | [58,65,85]         | [58,65,85]   |
| **DM**                                          | [81]               | [81]         |
| **Long duration of DM**                         | [69,81]            | [69,81]      |
| **Poor glycemic control per unit increase in glycated hemoglobin (HbA1c)** | [79] | [79] |
| **DM in HIV negative status**                   | [70]               | [70]         |
| **HIV coinfection**                             | [15]               | [15]         |
| **HIV with injection drug use**                  | [88]               | [88]         |
| **HIV without injection drug use**               | [88]               | [88]         |
| Malnutrition                                    | [95]               | [95]         |
| Liver cirrhosis                                 | [21]               | [21]         |
| Hypertension                                    | [65]               | [26]         |
| **PTB**                                         | [28,48,56,76]      | [28,48,56,76]|
| **EPTB**                                        | [100]              | [100]        |
| **Drug resistance (in patient with antimicrobial susceptibility test)** | [95] | [95] |
| Positive sputum smear                            | [25,30,54,84,100]  | [25,30,54,84,100] |
| Cavitary on chest X-ray                         | [30,54,88]         | [30,54,88]   |
| **Raised serum ALT concentration**              | [72]               | [72]         |

(Continued)
The observed prevalence of TB among DM patients in this systematic review is low compared to the previous systematic review findings [11]. This might be related to the small number of similar studies conducted, the low sensitivity of diagnostic methods used to detect TB cases and the magnitude of TB prevalence in the studied countries. In addition, the language restriction criteria that we used may have resulted in underreporting bias. Hence, we must be

prevalence in the current systematic review is higher compared to the findings of the previous systematic review conducted in 2010 [11]. This might be related to the increasing number of studies addressing TBDM comorbidity in the last six years. A total of 74 studies have been published since 2011 which showed a threefold increase compared to the number of similar studies conducted before 2010. Contrary to the previous systematic review [12], where studies from the Africa Regions were not reported, our systematic review showed an increasing number of studies reporting high prevalence of DM among TB patients in some countries of the African Region.

The number of new DM patients identified by screening TB patients varied in the different studies. This variation might be due to differences in the screening methods used and variations in the prevalence of DM in the general population of the respective countries. However, the large proportion of newly identified DM patients suggests the identification of previously undiagnosed DM patients and highlights that screening TB patients for DM in the TB clinic is an important public health intervention [102].

The observed prevalence of TB among DM patients in this systematic review is low compared to the previous systematic review findings [11]. This might be related to the small number of similar studies conducted, the low sensitivity of diagnostic methods used to detect TB cases and the magnitude of TB prevalence in the studied countries. In addition, the language restriction criteria that we used may have resulted in underreporting bias. Hence, we must be
cautious in the interpretation of this finding. The prevalence of TB among DM patients in the studied countries of Asia and the African Regions were high compared to findings of other regions. This may be linked to the fact that countries in these continents are experiencing the fastest increase in DM prevalence along with the high burden of TB and HIV [27, 72].

We analyzed socio-demographic, behavioral, clinical and other factors associated with TBDM comorbidity. Male sex was identified as a risk/associated factor for TBDM comorbidity. Men usually practice smoking cigarettes and alcohol drinking which can predispose them to both diseases conditions [84]. Similarly, being women was found to be risk factor for TBDM comorbidity. The reason may be linked to poor health service utilization, care taking role of women for the sick, and influence of estrogen on cytokine production during TB infection that increases the vulnerability of women to TB and consequently to DM [76]. Old age was reported as associated/risk factor for TBDM comorbidity. The reason may be related to decrease in immune status in older age individuals that make them more susceptible to develop both TB and DM [48, 76, 81]. High-income status was also identified as risk factor for the two comorbid condition [26, 30]. Patients with high-income may spend much time in sedentary lifestyle activities than their counter parts and have better access for diagnostic and medical facilities [26]. Urban residence was reported as associated/risk factor for the development of TBDM comorbid condition [31, 69]. This might be due to the overcrowded living conditions, less physical activity and consumption of a high calorie rich diet among residents in urban areas [69]. In addition, urban residents have better access for the diagnosis of TB and DM.

Behavioral attributes such as tobacco smoking and alcohol drinking are associated with TBDM comorbidity [21, 23, 26]. Cigarette smoking results in inflammation and oxidative stress in body cells and increases the risk of developing DM [26]. In contrast, frequent outdoor activity was identified as protective factor for TBDM comorbidity [30]. This might be linked to the fact that increased physical activity results in increased peripheral insulin sensitivity which leads to more glucose uptake by body muscles [26].

Our systematic review identified various clinical factors associated with TBDM comorbidity. Patients BMI status was identified as increased as well as low risk factor for TBDM comorbid conditions. Previous studies showed that overweight and obesity were risk factors for DM but were protective against TB disease. However, weight loss due to poorly controlled DM and metabolic decomposition takes away this protection and becomes risk factor for TB [30, 81]. Existing DM was the other risk factor for TBDM coexistence. Long term DM is usually associated with uncontrolled DM and can impair the innate and adaptive immune response necessary to counteract the proliferation of TB [28, 69, 81]. Poor glycemic control and high blood pressure were reported as risk factors for TB among DM patients [79]. In resource poor settings, early diagnosis and adequate glycemic control is difficult and poor glycemic control may predispose DM patients to TB disease. In addition, hyperglycemia may provide a conducive environment for bacterial growth and increased virulence of various organisms [69–70, 79, 81]. The increased risk factor for TBDM related to high blood pressure may be linked to the fact that persons with DM were more likely to develop high blood pressure [26].

There is contradictory finding regarding the association of HIV with TBDM comorbidity [15, 70, 72, 88]. This might be linked to use of taking cotrimoxazole prophylaxis among HIV positive patients. Cotrimoxazole has been found to cause hypoglycemic effects in some patients [72]. The risk factor related to HIV infection could also be related to use of certain antiretroviral drugs that may predispose HIV infected patients to DM [106]. Having family history of DM was also identified as associated/risk factors for TBDM comorbidity. Family history of DM is a known risk factor for DM [3].

Contact with known TB patients was considered as risk factor for the development of TB among DM patients [16, 69, 79]. Frequent contact could lead to transmission of TB [69].
Patients with history of imprisonment were more likely to be exposed to TBDM comorbid conditions [15, 98]. This might indicate that the acquisition of both diseases during imprisonment period is very high [98] and might be related to overcrowded and stressful living conditions. It was also reported that TBDM comorbid patients usually become hospitalized [88]. DM patient more likely require hospitalization due to glycemic imbalance as a result of infection that may require taking insulin [88].

This systematic review has strengths and weaknesses. The comprehensive search strategy applied using multiple electronic databases and the inclusion of a large number of studies covering almost all geographic regions of the world are strengths of the study. Potential limitation of the study could be the exclusion of studies written in other languages except English. However, since our inclusion criteria was very broad and accommodated majority of the studies that assessed the magnitude and associated/risk factors of TBDM comorbidity, the effect of excluding non-English written articles in the generalizability of the study findings would be minimal. We could not be able to report age of study participants due to lack of uniformity in the way it was reported in the reviewed articles. We recommend future studies to address this important variable. One may question why we used prevalence rate to report the findings since all studies reviewed were not cross-sectional studies. However, majority of the articles included in this systematic review reported their findings as prevalence of either TB among DM or DM among TB patients. Some reported as the number of DM or TB patients obtained from screening TB or DM patients. The studies were observational studies and used cross-sectional and descriptive study designs. We thus have used prevalence rate as our effort was to relate it with what the reviewed articles reported. We did not exclude studies based on the level of risk of bias assessment as our main objective was to understand the global picture of the prevalence and associated/risk factors of TBDM comorbidity in a more comprehensive manner. We believe that this may not significantly affect the generalizability of the study as majority of the studies were evaluated as having low-moderate risk of bias. We did not perform metaanalysis because of methodological variations observed in the different studies included in our systematic review. The studies varied by type of study design used, methods of DM and TB screening, timing of DM screening and number of enrolled patients.

Conclusion

This systematic review revealed that there is a high burden of DM among TB patients at global level. The highest prevalence of DM among TB patients is observed in the studied countries of Asia, North America and Oceania. On the contrary, the prevalence of TB among DM patients is low globally, but relatively higher in the studied countries of Asia and the African continents. Factors associated with TBDM comorbidity included sex, older age, urban residence, illicit drug use, alcoholism, cigarette smoking, sedentary lifestyle, obesity, HIV coinfection, hypertension, long duration of pre-existing DM, poor glycemic control, being a PTB patient, and family history of DM.

The implementation of the WHO recommended TBDM integrated services is important to address the impact of TBDM comorbidity [6]. However, as implementing such a strategy is resource intensive, countries may benefit by first assessing the magnitude and risk/associated factors of TBDM comorbidity before making decisions to undertake such a big initiative.

Supporting information

S1 Prisma Checklist. This is prisima checklist for the prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: a systematic review.

(DOCX)
S1 Table. Assessment of risk of bias of the studies. (DOCX)

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Conceptualization: MHW GAB SAY.
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Supervision: GAB SAY.
Validation: MHW SAY.
Writing – original draft: MHW.
Writing – review & editing: MHW GAB SAY.

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