GENDER DISPARITYOF TUBERCULOSISBURDENIN LOW-AND MIDDLE-INCOME COUNTRIES: A SYSTEMATIC REVIEW

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ABSTRACT

The tuberculosis burden is higher in the population from low- and middle-income countries (LMICs) and differently affects gender. This review explored risk factors that determine gender disparity in tuberculosis in LMICs. The research design was a systematic review. Three databases; Google Scholar, PubMed, and HINARI provided 69 eligible papers.The synthesized data were coded, grouped and written in a descriptive narrative style. HIV-TB co-infected women had a higher risk of mortality than TB-HIV-infected men. The risk of Vitamin-D deficiency-induced tuberculosis was higher in women than in men. Lymph node TB, breast TB, and cutaneous and abdominal TB occurred commonly in women whereas pleuritis, miliary TB, meningeal TB, pleural TB and bone and joint TB were common in men. Employed men had higher contact with tuberculosis patients and an increased chance of getting the disease. Migrant women were more likely to develop tuberculosis than migrant men. The TB programmers and policymakers should balance the different gaps of gender in TB-related activities and consider more appropriate approaches to be gender-based and have equal access to every TB-associated healthcare.

KEYWORDS

Tuberculosis, Gender Disparity, Determinant Factors, Low- and Middle-Income Countries

1. INTRODUCTION

Tuberculosis (TB) is one of the infectious communicable diseases causing illness and death around the world.In 1993, the World Health Organization (WHO) declared TB a critical global health issue due to concerns about the rapid spread of multidrug-resistant TB [1].It infects roughly one-quarter of the world's population, amounting to 127 cases per 100,000 people, with 1.3 million dying and an additional 214 000 dying among HIV-positive people [2].A wide range of determinant factors has influenced the likelihood of being exposed to tuberculosis, progressing to active tuberculosis, diagnosis and treatment, compliance, and outcome [3].Individual and behavioural factors, socioeconomic and cultural factors, and health system and program-related factors are all examples of determinant factors. Age, HIV infection, immunosuppressive medication use, diabetes mellitus, malnutrition, drug and alcohol abuse, smoking and its related illness, and prisoner are all individual and behavioural factors. Poor, homeless, illiterate, living in rural areas, migrants, overcrowding, indoor air pollution, poor ventilation, disadvantaged communities, and living or working conditions in high-incident environments are socioeconomic factors [4-7]. Diagnostic delay and limited access to health care services are health system and

program-related factors [8, 6].Many epidemiological studies have demonstrated that there is still a need for more discussion about the existence of gender disparities in the TB burden, diagnosis, treatment, and outcome, as well as in the outcomes of TB-related interventions such as prevention activity accomplishments. The difference ranges of gender differences in TB case notification were found across a wide range of LMICs. Overall, men had higher notification than women except in Uganda (Table 1). The differences depend on geographical context, and diagnostic and treatment capacities across countries [9-32].

Table1. Gender-specific notification ratio in LMICs

Country	**Year of Study**	**Total notified**	**Male notified**	**Female notified**	**ratio**
Uganda	2007-2008	133	67	66	1:1
Pakistan	2001–2010	571,958	292,551	279,407	1.1:1
Turkey	2005	86	44	42	1.1:1
Ethiopia	2003-2012	37,070	20,193	16,867	1.2:1
Cape Town, South Africa	2009	29,478	16,099	13,379	1.2:1
Tunisia	1995-2016	2,771	1,508	1,263	1.2:1
Kazakhstan	2012-2014	562	309	253	1.2:1
Argentina	2007	123	68	55	1.2:1
Nigeria	2011-2012	1,668	963	705	1.3:1
Morocco	2017-2018	211	125	86	1.4:1
Mexico	2010-2014	5,508	3,198	2,310	1.4:1
Indonesia	2019	543,870	313,640	230,230	1.4:1
The Philippines	2015 to 2016	338,376	224817	113,559	2.0:1
Brazil	2007-2011	243,670	164,909	78,761	2.1:1
Malaysia	2015-2019	1,211	837	374	2.2:1
Tanzania	2013-2015	513	353	160	2.2:1
India	1999-2005	3,605	2,498	1,107	2.3:1
Myanmar	2015-2018	147,328	103,008	44,320	2.3:1
Nepal	1997-1999	336	238	98	2.4:1
Bangladesh	2000	1,071	762	309	2.5:1
China	2013-2018	211,892	153,303	58,589	2.6:1
Russia	2005-2008	374	282	92	3.1:1
Egypt	2017	126	98	28	3.5:1
Vietnam	2006-2007	269	212	57	3.7:1

Adult men, for example, bear the greatest burden, accounting for 56% of all TB cases in 2020, compared to 33% for adult women [2].TB prevalence increased with age and was significantly higher in men than women of all ages [33, 30]. As a result, men have nearly double the tuberculosis burden, and the men-to-women ratio is 1.7:1, especially to have pulmonary tuberculosis and a positive smear [12,10]. The following gender-specific prevalence data showed the number of new and existing burdens of bacteriologically confirmed tuberculosis across the highest TB-burden countries in LMICs and generally foundthata higher prevalence of tuberculosis occurred in men [34-44] (Table 2).

Table 2. Prevalence of bacteriologically confirmed TB among men and women/100,000 population

Countries	Year of study	Men	Women	M: F Prevalence ratio
Pakistan	2010-2011	484	320	1.5:1
South Africa	2018	1,094	675	1.6:1
Nigeria	2012	751	359	2.1:1
Ethiopia	2011	352	162	2.2:1
Indonesia	2020	1,083	461	2.3:1
The Philippines	2016	1,713	627	2.7:1
China	1990-2010	183	64	2.9:1
Bangladesh	2007-2009	122	40	3.1:1
Yangon, Myanmar	2017-2018	1,026	287	3.6:1
Vietnam	2017-2018	522	133	3.9:1
India	2010-2012	571	140	4.1:1

Furthermore, men were more likely than women to have a higher failure rate of sputum conversion, a poor treatment outcome, and a higher TB mortality rate [16, 45, 2]. According to the available data across LMICs, women had a higher cure rate than men whereas men had a higher mortality rate and failure rate than women [11, 16, 23, 26, 29, 45-48] (Table 3).

Table 3. Gender disparities in type of TB treatment outcomes

Countries	Year	Cure %		Death %		Lost to follow-up %		Failure %	
		Men	Women	Men	Women	Men	Women	Men	Women
Mexico	1995-2003	79.6	88.0	NA	NA	11.95	4.89	NA	NA
Bangladesh	2000	88.7	92.6	7.7	4.8	NA	NA	NA	NA
India	1999-2005	85.8	89.4	4.1	2.9	4.5	3.3	2.4	1.8
Ethiopia	2003–2012	NA	NA	3.4	2.9	9.4	8	NA	NA
Nigeria	2011-2012	NA	NA	10.4	9.2	9.4	9.4	2.2	0.7
Kenya	2012-2015	89.4	91.2	10.6	8.8	NA	NA	NA	NA
Egypt	2017	70.4	60.7	4.1	3.6	4.1	28.6	NA	NA
Iran	2008-2017	46.5	52.0	14.5	9.2	NA	NA	39	38.8
Sierra Leone	2017	32.0	22.1	4.4	4.7	21.5	30.4	0.5	0.3

As well, exposure to tuberculosis risk factors differs between men and women due to differences in social positions, risk behaviour, and job nature. Travel, social contacts, and spending in tuberculosis-prone areas, for example, are higher in men [49, 50]. What's more, the barriers to tuberculosis diagnosis and treatment accessibility were differently experienced by gender, leading to gender disparities in tuberculosis burden [51].To summarize, men and women are affected differently by tuberculosis burdens, such as notification, incidence, prevalence, clinical presentations, treatment outcomes and complications. The goal of this review was to summarize the factors that contribute to the gender disparity in tuberculosis burden in low- and middle-income countries to provide effective gender-specific TB control methods.

2. MATERIAL AND METHOD

2.1. Research Design

Among four types of literature reviews; literature review as theoretical background in primary research articles, literature review in the thesis or dissertation of the student as a chapter, stand-alone literature review and systematic literature review [52],in this study, the systematic literature review study design was applied.All the findings were presented in the narrative description by synthesizing huge amounts of information and clarifying discrepancies. Further, the present review was executed to explore the generalized results of different targeted settings and large study populations as representatives of low-and-middle-income countries (LMICs).The research question was "What factors are determining gender disparity in tuberculosis burden in low-and middle-income countries?". This research question came to establish hypotheses and generate the review title. Therefore, the review title was “Factors determining gender disparity of tuberculosis burden in low-and middle-income countries: A systematic review”. Further, the PEOframework.Bettany-Saltikov, 2016 was used for framing the research question. The PEO is the acronym and stands for population or patients, exposure and outcomes. (Where P – Tuberculosis patient, E – Gender and O – Factors influencing gender disparity in tuberculosis burden) [53].The registration of this review was made at the University of York during the protocol stage and it has already been approved. Because of the registration, this review might be higher transparency and lower the risk of bias as well as avoid unintentional duplication.

2.2. Inclusion and Exclusion Criteria

Since systematic review aimed to summarize the existing evidence from primary studies, we included primary research studies and peer-reviewed ones for quality control. To obtain heterogeneously sound results, the studies designed with different methods: quantitative, qualitative or mixed methods were considered to include. As the review was to examine the tuberculosis burden between genders in LMICs, the studies focusing on tuberculosis, examining gender differences and conducted in LMICs were picked up. The language was limited to English as the authors were bilingual, English and native Myanmar. Studies published in 2006 and onwards were included because the STOP strategy was launched in 2006 as well as to get contemporary research studies.

2.3. Searching Strategy

The keywords were, ‘Gender disparity, ‘Tuberculosis’, ‘Factors’, ‘Determining’, ‘Low- and middle-income countries’ that derived from the research question and their synonyms were used for searching to obtain a sufficient number of studies.

Gender disparity: Synonyms of gender disparity were gender difference, sex difference, sex disparity, gender differential, sex differential, male-female difference and male-female differential.

Tuberculosis: The researcher identified similar words of Tuberculosis as TB and pulmonary tuberculosis.

Factors: Regarding factors, the researcher included individual and behavioural factors, socio-economic and cultural factors, and program and health system-related factors. Examples of individual and behavioural factors were age, sex, smoking, alcohol and drug abuse, imprisonment, commodities such as diabetes mellitus, HIV, undernutrition, etc. Examples of

socio-economic and cultural factors were education, literacy, poverty, income, occupation, employment, stigma, traditional belief, etc. Examples of program and health system-related factors were delayed diagnosis and treatment, under the notification, access to health care, the barrier to health care and treatment duration, etc.

Low-and-middle-income countries: The researcher used its acronym LMICs and each of the countries listed by the World Bank.
A Boolean search method was applied by its operators, 'AND', 'OR' and 'NOT' for the combined search of relevant search terms. This method was supplemented by hand search and reference checking of relevant studies to prevent missing out on relevant studies.Search engines and databases utilized for literature searches were Google scholar, PubMed, and HINARI.

2.4. Screening Strategy and Selecting Studies

There were two main strategies in the literature screening process and the whole process was guided by the Preferred Reporting Items for Systematic Reviews and Meth-Analyses (PRISMA) flow diagram. This process was done by two reviewers to prevent inter-rater reliability.

- Title/Abstract Screening: Through an initial search of pre-determined search terms in the online database, lots of potentially relevant studies were found, then titles and abstracts screening were done and relevant ones against inclusion and exclusion criteria were downloaded in Mendeley online library for further step. The two reviewers checked the potential downloaded studies each other and removed the duplicated ones.
- Full-text Screening: It was a more detailed task and needed filtering the individual text content of papers. The independently selected studies by two reviewers were checked again and agreed with the final selection.

A list of all selected studies was kept and sorted in Mendeley online library again with reasons of inclusion criteria and exclusion.

2.5. Quality Appraisal

The methodological quality of selected studies was assessed by using the Mixed Methods Appraisal Tool (MMAT) designated for the appraisal stage of systematic mixed studies reviews. It was the final stage of the study selection process and was essential for the reliable, accurate and generalizable conclusion of this review. The quality of studies was calculated using the MMAT and the score was mentioned using descriptor (%). The score was provided as 20 % to 100% depending on the meeting of criteria [54]. As all the selected studies had publication standards, any of the studies were excluded due to quality issues.

2.6. Data Extraction

Data extraction was done by using a spreadsheet, Microsoft Excel (version 2016) that was a reference to the Cochrane data collection form (Cochrane, 2014) and adapted according to research questions and objectives. Operational definitions of each variable were set up to increase the consistency of data extraction between two reviewers.

2.7. Ethical Consideration

For the current review, though there were no human participants other than those working with previously completed primary research, ethical approval was taken from the Ethics Committee at

the School of Healthcare Practice, University of Bedfordshire by submitting the Research Proposal Ethics Application Form. The dissertation reference number (SSCHREC Application Number) was STI011-6-2022-2-001.

2.8. Data analysis

As our review contained both qualitative and qualitative studies, the synthesized data, and findings, in other words, were coded, grouped and written in a qualitative approach, descriptive narrative style. Meta-analysis was not applied as a wide range of studies were included and they were different in terms of clinical, methodological and statistical areas.

3. RESULTS

3.1. Summary of Selection Process

A total of 6,282 papers (principal reviewer - 3,274 and co-reviewer - 3,008) were discovered using PubMed and Medline, Google Scholar, and HINARI. The duplicated 2,198 papers were removed and the remaining 4,084 papers were screened for title and abstract. After removing irrelevant papers from the pool of 4,084 papers, 153 were chosen for full-text screening. Out of them, 84 were removed again based on paper inclusion and exclusion criteria, leaving 69 papers for review analysis (Fig. 1).

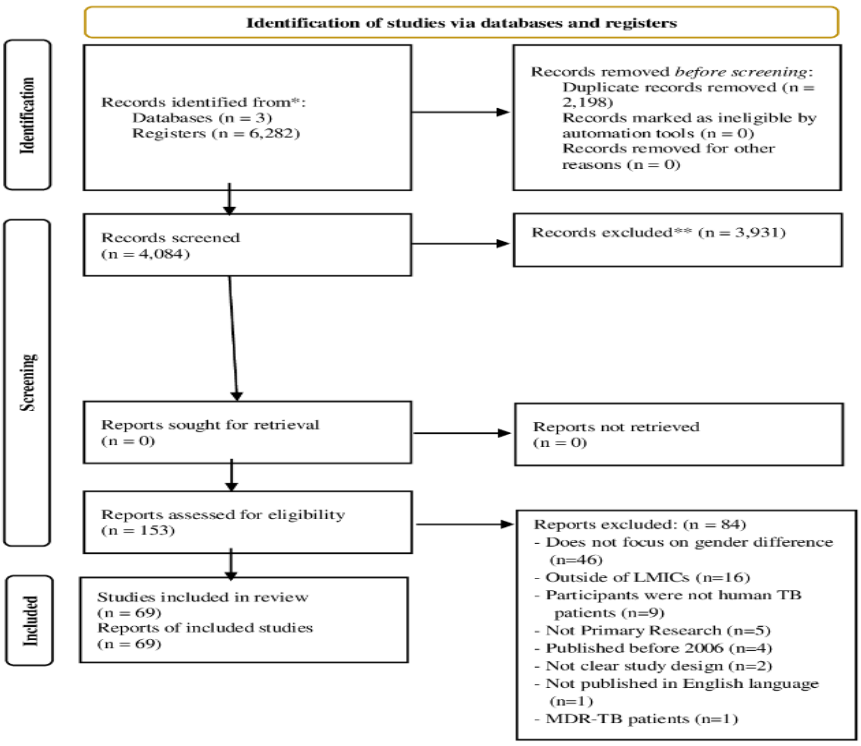

Figure.1. Flow Diagram of Paper Selection Process

3.2. Characteristics of Included Studies

The characteristics of the 69 selected studies in this review were described by frequencies and percentages in Table (4).

Table 4. Characteristics of the Included Studies

Characteristics of the Included Studies	Frequency	Percentage
Year of Publication		
2015	7	10.1%
2013	6	8.7%
2014	6	8.7%
2019	6	8.7%
2020	6	8.7%
2011	5	7.2%
2012	5	7.2%
2021	5	7.2%
2016	4	5.8%
2007	3	4.3%
2010	3	4.3%
2017	3	4.3%
2018	3	4.3%
2006	2	3.0%
2008	2	2.9%
2009	2	2.9%
2022	1	1.4%
Country of Study		
Lower Middle-Income Countries	36	52.2%
Upper Middle-Income Countries	27	39.1%
Low-Income Countries	6	8.7%
Focus of Study		
Identifying determinant factors	43	62.3%
Examining the gender difference in TB burden, diagnosis and treatment	19	27.3%
Examining TB burden and impacts	4	6.0%
Identifying differences between types of pulmonary and extra-pulmonary TB	3	4.3%
Study Population		
Tuberculosis patients	52	75.0%
HIV patients	5	7.0%
Community people	5	7.0%
Presumptive TB patients	4	6.0%
TB/HIV co-infected patients	1	1.0%
Injection drug users	1	1.0%
Standardized TB patients	1	1.0%
Study Design		
Cross-sectional quantitative study	35	50.7%
Cohort study	26	37.7%
A combined cross-sectional and retrospective study	5	7.2%
Cross-sectional qualitative study	2	2.9%
Case-cohort study	1	1,4%
Data Collection Tool		
Patients' registers and electronic medical records	44	63.8%
Combined interview and patients' records	13	18,8%
Interview alone	8	11,6%
Patients' records alone	2	2,9%
Focus Group Discussion	2	2.9%
Quality Appraisal		
Scored as 100%	33	47.8%
Scored as 80%	32	46.4%
Scored as 60%	4	5.8%

3.3. Determinant Factors for Tuberculosis Burden among Men and Women

3.3.1. Individual and Behavioural Factors

In revising the individual and behavioral predictors for gender disparities in tuberculosis burden, men were found more likely to develop pulmonary tuberculosis, defaulter, retreatment, poor treatment adherence and TB mortality than women [11, 13-15, 17, 30, 46, 55-57].As a controversy, women were reported more likely to have poor treatment outcomes, poor treatment adherence and defaulter than men [58, 29] whereas cure and completed outcome were higher among females [57].And women TB patients were associated with a higher risk of rifampicin resistance and faster culture conversion than men [56, 58].In the aspects of aging, older men were statistically more likely to suffer tuberculosis than older women [10, 16, 28-30, 59-61], but not in women at 18-24 years and over 64 years [55, 58].Moreover, older men were reported more likely for getting bad treatment outcomes than those women [58]. Additionally, men who used both smoking and drugs as well as women who were exposed to smoke had a greater risk of developing tuberculosis [29, 9].Current alcohol user men, however, were more likely to develop tuberculosis and poor TB outcomes than women [15, 44, 62].

Besides, the male prisoner was more chance of getting tuberculosis infection than those females [13, 28, 46]. In this review, diabetic men and diabetic women had a higher incidence of pulmonary tuberculosis [29] but only those men were significantly associated with poor TB treatment outcomes [18]. Furthermore, HIV-infected women were found more likely to develop tuberculosis than men [22, 24, 63, 64]. A paradoxical result, nevertheless, found that women with HIV were less likely to develop tuberculosis than men regardless of ART status [65]. With regards to treatment outcome, both TB-HIV co-infected women were more likely to develop a lower treatment success rate [16, 58, 63].

As the previously mentioned co-morbidity conditions, hepatitis C virus co-infected men and under-nourished men were more likely to develop tuberculosis and poor treatment outcomes than women [29, 58, 66]. Furthermore, men with significantly lower energy and protein intake were more likely to develop tuberculosis and seek formal TB health care than women [26, 67].
According to presenting clinical features, men were more likely to present with abnormal CXR and clinical symptoms such as cough, weight loss and hemoptysis than women [10, 30, 46, 57, 68]. In CXR findings, men were more likely to present with advanced radiographic findings [58, 69, 70]. and were associated with poor treatment outcomes than women [58]. Unlike men, women were presented with multiple constitutional symptoms and were less likely to get smear-positive results due to less advanced radiographic findings [26, 69,71].

In reviewing different types of TB, extra-pulmonary tuberculosis was more likely to occur in women whereas pulmonary tuberculosis was more likely to occur in men [16, 17, 72, 73]. Further, men were more likely to produce good quality sputum and receive sputum examination [13, 14 60]. Urban women had a higher treatment success rate [16] and rural women had longer delayed for tuberculosis diagnosis and treatment [74]. In addition, men had more likely to suffer from Disability Adjusted Life Years (DALYs) due to tuberculosis, than women [75](Table 5).

Table 5. The gender disparities in tuberculosis burden according to the individual and behavioural factors

Exposures and Studies	Outcomes	Strength of Difference
Gender		
Hoa et al., 2010 [30] Dangisso, et al., 2014 [11] Khan et al., 2016 [55] Nair et al., 2016 [56] Ben Jmaa et al., 2020 [13] Eddabra and Neffa, 2020 [17]	Men were more likely to develop pulmonary tuberculosis than women including bacteriologically positive TB cases and smear-positive TB case	*P* ***
Hermosilla et al., 2017 [14]		aOR - 1.97 (1.25, 3.11)**
Grandjean et al., 2011 [66]		HR - 2.8*
Sarpal et al., 2015 [57]	The risk of TB after default was significantly higher in men than in women	Z score - 4.13**
Jiménez et al.,2006 [46] Dangisso, et al., 2014 [11]		OR - 1.06, 3.3
Sarpal et al., 2015 [57]	Retreatment TB cases were more likely to occur in men than women	Z score - 5.93**
Jiménez et al., 2006 [46]		HR - 3.15**
Murphy et al., 2018 [58]	Women were more likely to have poor treatment outcome than men	aOR - 2.00 (1.03, 3.90)*
Safwat, et al., 2019 [29]	Women were more likely to be defaulters than men	*P* **
Herrero et al., 2015 [15]	Men were more likely to have poor treatment adherence than women	OR - 3.53 (1.2 - 10.1)*
Safwat, et al., 2019 [29]	Men were more likely to have better treatment adherence and cure outcome than women	*P* **
Ben Jmaa et al., 2020 [13]	Death from TB was more likely to occur in men than women	HR - 2.23** OR - 1.7*
Nair et al., 2016 [56]	Women TB patients were at higher risk of rifampicin resistance than men	
Murphy et al., 2018 [58]	Cultural conversion among women was faster than among men	HR - 1.14* MGIT - 1.19**
Age		
Karim et al., 2007 [59] Ramsay et al., 2009 [60] Hoa et al., 2010 [30] Shin et al., 2010 [28] Patra et al., 2013 [61] Yüceege, et al., 2014 [10] Oshi et al., 2015 [16] Safwat, et al., 2019 [29]	Older men were statistically more likely to suffer tuberculosis than older women	*P* **
Khan et al., 2016 [55] Murphy et al., 2018 [58]	Women who were at a younger age (18-24 years) and older age (over 64 years) were statistically strongly associated with tuberculosis compared to those men	*P* ***
Shirzad-Aski et al., 2020 [47]	Extra-pulmonary tuberculosis was higher in younger women than those younger men	
Sreeramareddy et al., 2008 [72]	Extra-pulmonary TB cases were higher than pulmonary TB until the age of 40 in men and 60 in women	
Purohit et al., 2009 [71]	Tuberculous lymphadenitis was	*P* *

Exposures and Studies	Outcomes	Strength of Difference
	more likely to suffer in older men than those women	
Murphy et al., 2018 [58]	Older men were more likely to be bad treatment outcome than those women	aOR - 1.48 (1.02, 2.14)
Smoking and tobacco		
Safwat, et al., 2019 [29]	Smoking and tobacco were strong determinants for higher tuberculosis incidence and prevalence including smear-positive TB in men compared to women	RR - 2.2***
Safwat, et al., 2019 [29]	Men who used both smoking and drugs had a greater risk of developing tuberculosis than women	*P* ***
Alcohol		
Jiménez et al., 2006 [46] Gajalakshmi. Et al, 2009 [76] Shin et al., 2010 [28] Suhadev e al., 2011 [77] Peltzer et al., 2012 [78] De Castro et al., 2018 [79] Ben Jmaa et al., 2020 [13] Martins-Melo et al., 2020 [75]	Alcohol was the strong determinant factor for higher TB incidence in men compared to women	RR - 1.5***
Peltzer et al., 2012 [78]		aOR -1.34 (0.99, 1.83) in men aOR – 0.71 (0.53, 0.95) in women
Peltzer et al., 2012 [78]	Among alcoholics with daily tobacco smoke, the risk of tuberculosis was significantly higher in women than in men	aOR – 6.06 (4.02, 9.14) in women aOR – 3.71 (3.00, 4.59) in men
Dhanaraj et al., 2015 [44]	Current alcohol user men were more likely to develop bacteriologically positive TB cases and culture-positive TB cases when compared to women	OR - 3.01, (1.85, 4.89)*** OR - 3.51 (2.02, 6.11)
Herrero et al., 2015 [15] Veerakumar et al., 2015 [62]	Alcohol use was a determinant of poor TB outcomes among men compared to women	*P* **
Veerakumar et al., 2015 [62]	Alcoholic men with low educational grades and unskilled workers were statistically associated with higher TB risk and bad TB treatment outcomes than women	*P* *
Imprisonment and Drug abuse		
Jiménez et al., 2006 [46] Shin et al., 2010 [28] Ben Jmaa et al., 2020 [13]	Having a history of imprisonment was an important determinant factor for higher TB in men compared to women	*P* ***
Jiménez et al., 2006 [46] Hermosilla et al., 2015 [14] Martins-Melo et al., 2020 [75]	Men who used both drugs and injections had a significantly higher risk of developing tuberculosis than	OR 5.53 (2.74, 11.16)

Exposures and Studies	Outcomes	Strength of Difference
	women	
Diabetes Mellitus		
Safwat, et al., 2019 [29]	Diabetes was associated with a higher incidence of pulmonary tuberculosis and smear-positive tuberculosis in men than in women	OR - 2.1, (1.3, 3.4) RR - 1.73 (1.25, 2.38)***
Rashak et al., 2019 [18]	Tuberculosis was statistically strongly associated with diabetes among women in comparing men Men with diabetes were significantly associated with poor TB treatment outcomes when comparing women	OR - 1.4 (1.2, 1.6)
HIV		
Hermans et al., 2019 [80]	In the HIV era, women aged 15-34 years were more likely to develop tuberculosis than those men	
Alvarez-Uria et al., 2014 [65]	Women with HIV were less likely to develop tuberculosis than men regardless of ART status.	
Gesesew et al., 2016 [63] Said et al., 2017 [22] Ahmed et al., 2018 [64] Seifert et al., 2021 [24]	HIV-infected women were more likely to develop tuberculosis than men	43% vs 22%**
Oni et al., 2012 [81]	Smoking was statistically associated with an increased risk of latent tuberculosis infection (LTBI) in HIV-infected men when compared to those women	OR 3.12*
Fenner et al., 2011 [82] do Prado et al., 2014 [83]	HIV itself was a risk for higher TB burden in men when compared to women	OR - 1.06 (0.32, 0.95)
Fenner et al., 2011 [82]	Women patients on ART who received Isoniazid preventive therapy (IPT) were at lower risk of tuberculosis than men	*P* ***
Oshi et al., 2015 [16] Murphy et al., 2018 [58]	Both TB-HIV co-infected men and women were independently associated with lower treatment success rates but women were more significantly strongly associated than men	aOR - 1.5 (1.3, 2.2)* in men aOR - 2·7 (1·8, 4·2)** in women
Gesesew et al., 2016 [63]	Having TB-HIV coinfection in women increased the risk of dying when compared to those men	58.2 % versus 41.8 %
Hepatitis		
Safwat, et al., 2019 [29]	Hepatitis C virus co-infected men were more likely to develop tuberculosis than women	*P* *
Undernutrition		
Grandjean et al., 2011 [66]	Undernutrition took into account for higher TB incidence among men compared to women	
Praygod et al., 2013 [84]	.Men with lower fat mass index,	r – (-2.2) (-2.9, -

Exposures and Studies	Outcomes	Strength of Difference
	higher fat-free mass index and lower BMI were statistically strongly associated with smear-positive tuberculosis compared to women.	1.6)*** r - (1.5) (0.9, 2.0)*** *P* *
Ren et al., 2019 [67]	Men with significant lower energy and protein intake than recommended amount were more likely to develop tuberculosis than women	
Shin et al., 2010 [28]	Women with lower BMI were more likely to develop tuberculosis than men	*P* ***
Dogar et al., 2012 [9]	Women were more likely to spend indoors with household chores which lead to vitamin D deficiency resulting in a higher risk of tuberculosis	
Murphy et al., 2018 [58]	Men with lower BMI was statistically associated with poorer treatment outcome than women	*P* *
Health Seeking Behavior		
Karim et al., 2008 [26] Said et al., 2017 [22]	Men were more likely to seek TB health care than women and they were more likely to seek formal health care than women	67 % vs 33 %
Karim et al., 2007 [26]	Women were less likely to seek health care and had delayed health-seekingbehaviour than men	Mean day - 51.9 days and 48.7 days*
Clinical features and CXR		
Jiménez et al. 2006 [46] Miller et al., 2013 [68] Yüceege et al.,2014) [10]	In men, cough more than 2 weeks, weight loss and hemoptysis were more significant compared to women	*P* **
Purohit et al., 2009 [71]	Men were more likely to present with constitutional symptoms than women	*P* *
Eromosele et al., 2014 [85] William et al., 2015 [70]	Men had a higher sputum positive rate and they had higher grading of sputum smear than women	17 % vs 10 %
Jiménez et al., 2006 [46] Shin et al., 2010 [28]	In CXR findings of men, infiltrates and cavities were more significant than in women	*P* ** *P* *
Thorson, et al., 2007 [69] William et al., 2015 [70] Murphy et al., 2018 [58]	Men were more likely to present with advanced radiographic findings of TB with higher CXR scores compared to women	
Hoa et al., 2010 [30] Sarpal et al., 2015 [57]	Men were more likely to present with abnormal CXR and clinical symptoms than women	*P* ***
Murphy et al., 2018 [58]	Men with cavities were statistically associated with poor treatment outcomes than women	(aOR - 2.78 (1.59, 4.84)**
Purohit et al., 2009 [71]	The duration of neck mass	*P* *

Exposures and Studies	Outcomes	Strength of Difference
	(tuberculous lymphadenitis) was longer in men than in women Women were presented with multiple constitutional symptoms compared to men	
Thorson, et al., 2007 [69] Karim et al., 2008 [26]	Women were less likely to get smear positive result due to less cavitation and less advanced radiographic findings	Women to Men Ratio - 0.38
Type of TB		
Sreeramareddy et al.,2008[72] Oshi et al., 2015 [16] Eddabra and Neffa, 2020 [17] Verônica et al., 2020 [73]	Extra-pulmonary tuberculosis was more likely to occur in women whereas pulmonary tuberculosis more likely to occur in men	*P* ***
Thorson, et al. 2007 [69] Ben Jmaa et al., 2020 [13] Shirzad-Aski et al., 2020 [47]	Men were more likely to be suffered from pleuritis, miliary TB, meningeal TB, pleural TB and bone and joint TB than women	*P* ** *P* * *P* *** *P* ** *P* ***
Purohit et al., 2009 [71] Ben Jmaa et al., 2020 [13] Shirzad-Aski et al., 2020 [47]	Women were statistically more associated with lymph node TB, breast TB, cutaneous TB and abdominal TB than men	OR=2.6*** *P* *** OR=2.3*** OR=2***
Oshi et al., 2015 [16]	In extra-pulmonary TB cases, outcomes were poor for both sexes but the treatment success rate was generally higher in women than in men	52% versus 39%
Health-related quality of life		
Martins-Melo et al., 2020 [75]	Men had more than more likely to suffer from Disability-adjusted life years (DALYs) due to tuberculosis in comparison to women	2.4 times (177.75 DALYs/100000 inhabitants and 74.19 DALYs/100000 inhabitants)
Babikako et al., 2010 [86]	The health-related quality of life (HRQoL) scores and visual analogue scale were lower in men than women as more men presented with advanced TB disease	Physical health summary score - 0.68 (0.49, 0.95) - 0.87 (0.75, 0.99)
Sputum quality and amount		
Ramsay et al., 2009 [60] Ben Jmaa et al., 2020 [13]	Men were more likely to produce good quality sputum compared to women	*P* *
Ramsay et al., 2009 [60] Miller et al., 2013 [68]	Women were more likely to produce poor quality and less amount of sputum	
Hermosilla et al., 2017 [14]	Men were more received sputum examinations than women	
Residence		
Oshi et al., 2015 [16]	Compared to men, urban residence women were associated higher	*P* *

Exposures and Studies	Outcomes	Strength of Difference
	treatment success rate	
Chen, et al., 2019 [74]	Rural women were associated with a longer delay for tuberculosis diagnosis and treatment than men for 30 days, 60 days and90 days	aOR - 1.11 (0.90, 1.10) aOR - 1.17 (1.02, 1.21) aOR - 1.23 (1.10, 1.38)

*P<0.05, ** P<0.01, *** P<0.001

3.3.2. Socio-economic and contextual factors

In terms of socioeconomic and contextual factors, it was found that women earning lower income were more likely to suffer from tuberculosis [87] and be a longer diagnostic delay [88].Men who were homeless lived in a shelter and lived in the old aged center had higher TB incidence than women [13, 21, 46]. Moreover, women had comparatively lower socioeconomic conditions which led to delays in TB diagnosis and treatment [29, 46,89]. And lower educational status determined the probability of anxiety disorders and suicidal tendencies among women TB-HIV patients rather than those men [90]. As per employment conditions, employed men and manual workers had a higher probability of developing tuberculosis than those women [10] but unemployed men were more likely to develop tuberculosis than those women [29]. Ben Jmaa et al., (2020) reported that women have a lower TB risk than men because they spend more time at home [13] but the contrary outcome occurred because women care for sick patients at home [9]. Household heads and working men resulted in poor treatment adherence and treatment completion compared to women due to difficult times in accessing health care services [13, 15]. It was also reported urban migrant women had a higher probability of developing tuberculosis than those men [91]. In addition, women were more affected by fear, stigma and belief which caused them to delay seeking to appropriate tuberculosis health care [59, 72] (Table 6).

Table 6. The gender disparities in tuberculosis burden according to socio-economic and contextual factors

Exposures and Studies	Outcomes	Strength of Difference
Lower-income		
Mauch et al., 2011 [87]	Women with lower incomes were more likely to hav e tuberculosis compared to men	
Deng et al., 2006 [88]	Women with lower incomes were more likely to hav e a longer diagnostic delay compared to men.	OR - 7.6 (3.2, 12.0)
Poverty		
Jiménez et al., 2006 [46] Ben Jmaa et al., 2020 [13] Ahmad et al., 2021 [21]	Men who were homeless and lived in a shelter, or old-aged center were statistically significantly more likely than women to have TB, including smear-positive TB.	P *** P *** aOR - 2.49 (1.28, 4.86)**
Education and TB knowledge		
Jiménez et al., 2006 [46] Kumar et al., 2013 [89] Safwat, et al., 2019 [29]	Women were more likely to have delayed TB diagnosis and treatment compared to men because they had a lower chance of receiving formal	P *** P * P ***

Exposures and Studies	Outcomes	Strength of Difference
	education: less TB knowledge, lower social-economic status: as well as high negligence for diseases	
Van Den Heuvel et al., 2013 [90]	Women TB-HIV patients with lower educational status were more likely to have anxiety disorders and suicidal thoughts than those men	*P* ***
Employment		
Yüceege, et al., 2014 [10] Safwat, et al., 2019 [29]	Both employed and unemployed men, as well as manual men workers, were more likely than those women to develop tuberculosis	90.0% vs 38.1%***
Migration		
Shen et al., 2012 [91]	Urban migrant women were more likely than men to develop tuberculosis	OR - 2.46 (1.86, 3.28)***
Socio-cultural factors		
Karim et al., 2007 [59] Sreeramareddy et al., 2008 [72]	Social-cultural factors such as fear, stigma, and belief caused women more likely to delay seeking appropriate tuberculosis health care compared to men	
Ben Jmaa et al., 2020 [13]	Women have a lower TB risk than men because they spend more time at home and engage in less outside social activity	
Dogar et al., 2012 [9]	Women have more chance of exposing infectious agents of mycobacterium tuberculosis than men because they were caretakers for sick patients at home	
Herrero et al., 2015 [15] Ben Jmaa et al., 2020 [13]	Household heads and working men were more likely to have poor treatment adherence and treatment completion compared to women because they had a difficult time accessing health care services due to limited time to visit health care and DOT	

*P<0.05, ** P<0.01, *** P<0.001

3.3.3. Program and health system-related factors

In reviewing the program and health system-related factors, women with cough were reported as less likely to refer for sputum smear tests than men resulting in provider and diagnostic delays [26, 68]. As a consequence, women were less likely to complete sputum AFB testing and less presented with smear-positive [68]. And women were also associated with longer diagnosis delay (from symptoms noticed by the patient to the first visit to health care service) than males [74]. On the other hand, men had significantly less consultation time and were less likely to receive correct management than women [92]. As per service availability, treatment taking at public health services was associated with a lower treatment success rate for women [16]. Moreover, women were more likely to receive home-based care DOT than men [93]. In terms of gender disparities in the diagnostic tool, women were reported less sensitive to standardized TB diagnostic methods and less sensitive to smear microscopy than men [68]. Smear-negative females, therefore, yielded more sputum culture testing as additional case detection. This was consistent that tuberculosis in women was more diagnosed with culture than microscopy [55]. Regardless of TB treatment

regimen, initially treated or retreated, women had a higher treatment success rate significantly higher than men in a shorter 6-month regimen [16](Table 7).

Table (7)The gender disparities in tuberculosis burden according to program and health system-related factors

Exposures and Studies	Outcomes	Strength of Difference
Under-diagnosis and delayed diagnosis		
Karim et al., 2008 [26] Miller et al., 2013 [68]	Women with coughs were less likely to refer for sputum smear tests than men by a physician which lead to significant provider and diagnostic delay	Women to Men Ratio - 0.52***
Miller et al., 2013 [68]	Women were less likely to complete sputum AFB testing and less presented with smear-positive	*P* * *P* ***
Thorson, et al., 2007 [69]	Women were late for physician's diagnosis for TB than men due to less advanced radiographic findings	
Karim et al., 2007 [26]	Women had more delays in receiving treatment from diagnosis than men	Mean - 2.0 day in women and 1.9 days in men
Daniels et al, 2019 [92]	Men had significantly less consultation time and were less likely to receive correct management than women attributed to lower quality of health care service	36% vs 40%***
Chen, et al., 2019 [74]	Women were associated with longer diagnosis delay (from symptoms noticed by the patient to the first visit to health care service) than men for 30-days, 60 days and 90 days	aOR - 1.09 (1.01, 1.18) aOR - 1.15 (1.05, 1.26) aOR - 1.18 (1.06, 1.31)
Habib et al., 2022 [95]	Lower utilization of community-wide screening services causes women to be more delayed diagnosis and treatment of TB and to worsen TB outcomes compared to men	
Availability of health care service		
Sreeramareddy et al., 2008 [72] Habib et al., 2021 [95]	Lack of available health care services, absence of women health care providers, transportation challenges, not enough independent money, and prohibiting women from moving outside independently contributed to the health care seeking delayed more in women than men	
Oshi et al., 2015 [16]	Women who received care at private health care centers had a higher treatment success rate than men. Treated at public health services was associated with a lower treatment success rate in both genders, but more significantly for women than men	83% vs 77.8%* aOR - 2·8 (1·7, 4·6) in women aOR - 2·0 (1·3, 3·1) in men
Mhimbira et al., 2016 [93]	Women were more likely to receive home-based care DOT than men	aOR - 1.55 (1.34, 1.80)***
Role of the diagnostic tool on gender difference		
Miller et al., 2013 [68]	Women were less sensitive to standardized TB diagnostic methods and less sensitive to smear microscopy than men	

Exposures and Studies	Outcomes	Strength of Difference
Ramsay et al., 2009 [60]	If diagnostic thresholds for sputum smear-positive grading were reduced, there wasasignificantly increased detection rate in women than in men	*P* **
Khan et al., 2016 [55]	Women yielded a significantly higher proportion of additional case detection than men in sputum culture testing in smear-negative. Tuberculosis in women was more likely to diagnose with culture than microscopy	134 % vs 200 % 37 % vs 28%*
Treatment regimen		
Oshi et al., 2015 [16]	Compared to men, women had a higher treatment success rate regardless of TB treatment regimen, but more significantly higher in shorter 6-month regimen	75·2% vs 81·1%*

*P<0.05, ** P<0.01, *** P<0.001

4. DISCUSSION

Knowing gender disparity in tuberculosis burden is crucial for designing interventions, including gender-specific interventions, in optimizing TB prevention and control services. The review summarized that individual and behavioural factors, socio-economic and contextual factors, and program and health system-related factors determined gender differences in tuberculosis burden in LMICs.Our study showed that the male sex was an unpreventable determinant to have a higher TB risk than the female sex. This finding was consistent with another systematic review in low-and-middle-income countries [96] and other studies in the US, UK and South Korea [97, 98]. Differences in immune response mechanisms between males and females play a vital role and estrogen enhances T-helper type-1 and macrophages' response mechanism whereas testosterone downregulates them [49]. Higher immune response in women plays a role in reducing TB risk [13, 23, 57] and male sex was an independent risk factor for TB [99].Increased TB risk in men when in contact with MDR-TB might be associated with immune response mechanisms and independent risk [101].

Our review revealed that treatment outcomes were different between genders. Many studies included showed that men were more likely to occur bad treatment outcomes than women while some studies showed women experienced poor treatment outcomes than men. This may be due to the faster response to anti-TB treatment by women even though there were the same bacillary load in pretreatment in both sexes [58]. Treatment outcomes might be associated with poor treatment adherence in men which was 3.5 times higher than in women. A review by Uplekar *et al.*, (2001)comparably reported that women had better adherence than men because some women felt that they can take care of children and family if they are in good health [100].

Although old age had a higher risk of tuberculosis in both sexes due to impaired immunity, the study found that older men were more significantly associated with tuberculous infection than women of the same age. A review by Yew *et al.*, 2018 also reported that the prevalence of TB in older men was more than 2 times that of women of the same age group, significantly in the 55-64 age group and 65 years and more age group [102].

The review identified that smoking increased the risk of tuberculosis in men more than in women. This might be associated with a higher prevalence of active smoking status among men

than women. An ecological study by(Watkins and Plant, 2006)in 22 TB high burden countries revealed that smoking status was about 6 times higher in men than in women and in consequence, TB notification in men was 1.7 times higher than that of women and the disease severity, delayed positive progress and bad treatment outcomes were more common among men [103]. Contrarily, the results of a review by (Yew *et al.*, 2018) and a study by (Leung *et al.*, 2010) demonstrated that increased TB risk and poor TB outcomes were more common in women's passive smoking [102, 104]. Whatever these findings were, it claimed that active or passive smoking is one major determinant of gender differences in TB risks and outcomes.

The review revealed that alcohol was the strong determinant factor for higher tuberculosis and poorer treatment outcome in men when compared to women because of more prevalence of heavy alcohol drinking among men. Likewise, a study in a developed country, Portugal, reported that alcohol abuse in men had a 6.27 times higher risk of tuberculosis than in women (<0.001) [50]. Using alcohol heavily cause an impaired immune system in individual resulting in an increased risk of active TB disease and reactivation of latent infection. Furthermore, alcohol hinders the positive progress of TB treatment and reduces the absorption of isoniazid and its metabolism leading to bad treatment outcomes in heavy drinkers [105]. The review also found that synergistic effects of heavy drinking and consequences of social-economic status including men-related jobs caused more than 3 times higher TB treatment interruption and poor treatment outcomes. Interestingly, if men and women had both smoking and alcohol, the odds of TB risk were slightly higher in women. It may be due to epidemiological factors of the research context and further research will be needed. In the revelation of this review, men were more likely to have a history of imprisonment and drug use linked with heavy drinking. A Portugal study similarly reported that having a history of imprisonment and drug abuse were about 15 times and 3 times respectively more likely to develop tuberculosis in men than women (p-value: < 0.001) [50]. A review by Deiss, Rodwell and Garfein, (2009) also discussed that drug users were associated with a set of socio-economic risk factors including imprisonment and opiate itself causing deterioration of cell-mediated response system leading to increased risk of tuberculosis and poor response to TB treatment [106].

Although diabetes was associated with tuberculosis risk in both sexes, men had a higher risk of tuberculosis and were highly associated with poor treatment outcomes than women according to our review. Men with diabetes had a higher risk of tuberculosis than women with diabetes and also increased risk of TB development subsequently presented with the severe clinical and radiographic presentation, delayed sputum conversion and unsuccessful treatment outcome [102].The HIV infection increased the risk of tuberculosis in both sexes, but numerous studies in the review reported that the risk of tuberculosis was increased in HIV women. The cell-mediated immune response mechanism by estrogen in women was reversed following HIV infection resulting in a higher risk of tuberculosis infection and lower anti-TB treatment response [16]. Importantly, tuberculosis risks among genders also depend on access and utilization of ART and HIV women who received ART and IPT had a lower risk of developing tuberculosis than those HIV men [82]. When HIV men smoked and HIV women were pregnant, the risk of LTBI was high [9, 107]. TB-HIV co-infection was associated with a lower treatment success rate in both sexes, but HIV-TB co-infected women had a higher risk of mortality than HIV-TB infected men[108].Considering tuberculosis risk in Hepatitis C viral (HCV) infection, more men were affected than women according to our review. A nationwide population-based survey in Taiwan supported this finding that HCV infection affected the immune response mechanism leading to a higher risk of tuberculosis [109].

Logically, undernutrition was associated with higher TB risk in both genders and the other way around, tuberculosis cause weight loss in an individual. Undernutrition increased the risk of tuberculosis and poor treatment outcomes by 14 %. A review by (Padmapriyadarsini *et al.*, 2016)

concluded that more women were notified of severe chronic malnutrition than men after diagnosis of TB [110]. A study by (Nhamoyebonde and Leslie, 2014) demonstrated that the risk of Vitamin-D deficiency-induced tuberculosis was higher in women than in men because Vitamin-D deficiency is common in women that reduced direct mycobacteria resistance effect [49].

Relating to clinical features of TB, men were presented with more severe clinical symptoms and radiographic features than womenbecause of the androgen downregulatory effect on T-helper cell-mediated immune response mechanism [49]. In another consideration, men were more likely to be linked with poorer health-related quality of life and lesser health-seeking behaviours [75].Regarding types of TB between genders, pulmonary TB was more common in males whereas extrapulmonary TB was higher in women, this was consistent with a study by (Yang *et al.*, 2004) [111]. Endocrine factors, production of inflammatory mediators and immune responses (tumor necrotic factors and interleution-10, lymphocytes) determine the development of EP-TB in women [13]. In our study, lymph node TB, breast TB, and cutaneous and abdominal TB occurred commonly in women whereas pleuritis, miliary TB, meningeal TB, pleural TB and bone and joint TB were common in men.

The treatment success rates of EP-TB were not different in both sexes and treatment outcome of extrapulmonary TB might be poor due to variable clinical presentation, disease site, its aggressive nature, late diagnosis and diagnostic difficulty [112].The review found that men were more likely to seek health care including TB-related health care whereas women were less likely to seek health care and reach more to traditional healers. This happening was due to lower income, lower levels of education and knowledge, and dependency nature were more likely to occur among women than men. Also, fear, shyness, traditional belief, cultural constraint, stigma and social isolation were more significant impacts on women. A review by (Yang *et al.*, 2014)consistently reported that women were facing greater barriers and much longer delay from symptom presentation to diagnosis [113]. Both genders had different barriers to seeking health care because household head men prioritized earning and livelihood whereas women prioritized household chores and caring for family and children. These findings were consistent with a review on the gender difference in TB health-seeking patterns [101, 114].

Differences in tuberculosis risk among gender were associated with their employment statuses. Employed men were more likely to be field workers who had higher contact with tuberculosis patients and an increased chance of getting the disease. Unemployed and homeless men were more likely to be in poverty and undernutrition which in turn increased the risk of tuberculosis. Regarding migration and TB risk, the review found that migrant women were more likely to develop tuberculosis than migrant men. A Taiwan study concluded that migrant female workers were 1.4 times higher risk of tuberculosis than migrant men [115]. The population-based study in the UK on the TB risk of migrants reported that women had a higher prevalence of tuberculosis than men [116].

According to our review, more women were likely to be underdiagnosis and delayed diagnosis than men. Underdiagnosis in women might be because physicians were less suspicious of TB in women and their compliance to national guidelines in symptom screening and referring sputum testing [55, 59].. The review by Hof *et al.*, (2010) reported that women with presumptive TB were reluctant to provide sputum samples as they need approval from the household head whereas men preferred to obtain a complete clinical and diagnostic assessment [101]. A review by Storla, Yimer and Bjune, (2008) claimed that a wide range of socio-economic and cultural factors was more likely to be responsible for diagnosis delay among women [117]. Fear of stigma, social isolation, willingness to seek health care from the only traditional healers, and cultural factors were mostly associated with delayed seeking care in women. Lack of information

and knowledge due to lower level of education, financial constraint, prioritization of household jobs and dependency on household members in women were also associated with diagnosis delay. Another review reported that women were less suspicious of TB themselves because of the community's attitude towards TB that it is a common disease in males [118].

Our study revealed that women were less sensitive to sputum microscopy than men. The finding was consistent with an Indian study reporting that women were more likely to present with lower grade smear-positive than, the odd ratio was even higher after adjusting for all possible confounding. Lower sputum positivity, and lower susceptivity to tuberculosis in other words, in women, might be associated with cell-mediated immune response mechanism of microphage and TNF increased by estrogen. Less sputum productive capacity considerably occurred among women [119].

5. CONCLUSION

Gender disparity in tuberculosis disease burden is a historical issue around the world. TB is linked with poverty and a large proportion of TB cases occurred in LMICs; hence TB issue is the main concern in LMICs. As there are a lot of studies evidencing the causes of gender disparities in TB outcomes, it is required to review and summarize. This review included the systematic identification of these possible causal factors classified as individual and behavioural factors, socio-economic and cultural factors, and program and health system factors. The finding of this review came to improve the present knowledge of policymakers and programme managers for considering strategies that reduce the uneven distribution of tuberculosis burden between men and women. From the points discussed above, the TB programmers and policy-makers should balance the different gaps of gender in the TB prevention and control activities and should consider more appropriate approaches to be gender-based equal access to every TB-associated healthcare.

6. LIMITATIONS

Out of a total of 137 LMICs, the relevant studies were found from 26 countries which account for 19 % of total LMICs causing weakness in drawing generalizations and conclusions. As only peer-reviewed primary studies were retrieved from formal academic journals, there may have a missing high number of pertinent studies from institutional websites. Although inclusion and exclusion criteria were set to screen relevant studies and piloting, it might not be enabled to avoid some degree of subjectivity and there might be variation in interpretation of inclusion criteria between two reviewers. Besides, more than half (55%) of selected studies in this review were cross-sectional studies, hence, the associations between risk factors and outcomes from those studies were difficult to make inferences. As studies published other than the English language were excluded, quite a few numbers of appropriate studies might be excluded from the selection process resulting in selection bias in methodology.

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