



A Comprehensive Systematic Review of The Relationship between Smoking and The Risk of Tuberculosis Relapse after Treatment Completion

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ABSTRACT

Introduction: Tuberculosis (TB) remains a major global health challenge, with recurrence after treatment completion posing significant obstacles to disease control. Smoking has been implicated as a potential risk factor for TB recurrence, yet the evidence requires systematic synthesis. This review aims to comprehensively evaluate the relationship between smoking and TB recurrence risk among patients who have completed anti-tuberculosis treatment.

Methods: A systematic screening of studies was conducted based on predefined eligibility criteria. Included studies examined patients with confirmed TB diagnosis and treatment completion, clearly defined smoking exposure, TB recurrence as an outcome, observational study designs or systematic reviews, minimum six months post-treatment follow-up, and rigorous methodology. Data extraction encompassed study characteristics, population details,

smoking exposure assessment, recurrence definitions, outcome measures, effect estimates, and confounder adjustment strategies.

Results: One hundred forty-six studies were included, predominantly conducted in Indonesia and other Asian countries. Sample sizes ranged from 5 to over 5,000 participants, with most studies involving adult pulmonary TB patients (mean age 58.5 years; male predominance 53.8-81.8%). Smoking was consistently associated with significantly increased TB recurrence risk. Darakhshan Ahmad et al. (2016) reported an odds ratio of 2.35 (95% CI: 1.48-3.74) for continued smoking post-treatment, increasing to 3.67 (95% CI: 1.55-8.71) for smoking exceeding ten years. N. Karminiasih et al. (2016) demonstrated an adjusted odds ratio of 3.6 (95% CI: 1.41-9.16) for smoking or smoke exposure during treatment. A dose-response relationship was evident, with greater intensity (>10 cigarettes/day) and longer duration conferring elevated risk. Several studies controlled for confounders including diabetes, HIV, nutritional status, and socioeconomic factors.

Discussion: The synthesized evidence demonstrates a consistent, robust positive association between smoking and TB recurrence post-treatment. Biological plausibility is supported by mechanisms including impaired mucociliary clearance, alveolar macrophage dysfunction, reduced interferon-gamma production, and structural lung damage. However, significant heterogeneity exists in study designs, smoking definitions, recurrence ascertainment, and follow-up durations. Many studies lack distinction between true relapse and exogenous reinfection. Limited data on smoking cessation timing represents a critical evidence gap.

Conclusion: Smoking constitutes a significant, modifiable risk factor for tuberculosis recurrence after treatment completion. The consistent dose-response relationship and biological plausibility strongly suggest causality. Comprehensive TB control programs must integrate smoking cessation interventions as an essential component of standard patient management. Future prospective cohort studies with standardized methodologies, molecular genotyping to distinguish relapse from reinfection, and rigorous evaluation of cessation interventions are urgently required.

Keywords: Tuberculosis, smoking, recurrence, relapse, risk factor, smoking cessation, post-treatment outcomes

INTRODUCTION

Tuberculosis (TB) remains one of the world's deadliest infectious diseases, with an estimated 10.6 million cases and 1.3 million deaths annually (World Health Organization, 2023). Despite significant advances in diagnostic technologies and the widespread implementation of directly observed treatment short-course (DOTS) strategies, TB recurrence following successful treatment completion continues to undermine global elimination efforts. Recurrent TB, whether due to true relapse of the original infection or exogenous reinfection, imposes substantial clinical, economic, and public health burdens on already strained healthcare systems, particularly in high-burden countries (Y. Yen et al., 2014).

Indonesia bears one of the highest TB burdens globally, ranking third after India and China, with an estimated 969,000 cases annually (World Health Organization, 2023). Within this context, understanding modifiable risk factors for TB recurrence is paramount for optimizing treatment outcomes and preventing disease transmission. Smoking represents one such potentially modifiable behavioral risk factor that has garnered increasing research attention over the past decade (Darakhshan Ahmad et al., 2016; N. Karminiasih et al., 2016).

The biological plausibility linking smoking to adverse TB outcomes is well-established. Cigarette smoke contains thousands of toxic chemicals that impair pulmonary immune defenses through multiple mechanisms. These include damage to the respiratory tract's mucociliary clearance system, compromised alveolar macrophage phagocytic function, and inhibition of interferon-gamma production—a critical cytokine for cell-mediated immunity against *Mycobacterium tuberculosis* (A. Susanto et al., 2014). Furthermore, smoking-induced structural lung damage, including cavity formation and chronic obstructive pulmonary disease, may create favorable microenvironments for mycobacterial persistence and reactivation (Elisa Rinaldo Perdamenta et al., 2023).

Despite accumulating evidence, significant research gaps persist. First, the majority of studies examining smoking-TB recurrence relationships have been conducted in Western or specific Asian populations, with limited generalizability to high-burden settings like Indonesia where smoking prevalence among males exceeds 60% (Kholis Ernawati, 2017). Second, considerable heterogeneity exists in how smoking exposure is defined and quantified across studies, ranging from simple ever/never categorizations to detailed intensity and duration assessments (Rahmasuciani Putri, 2020). Third, the distinction between true relapse and exogenous reinfection—which carries different implications for smoking's pathogenic role—has been inadequately addressed in most investigations (Yorien Setia alfianti, 2022). Fourth, the specific timing of smoking cessation relative to TB treatment and its impact on recurrence risk remains poorly characterized (Vidi Ibrahim Pratomo Affandi, 2020). Fifth, while numerous individual studies have demonstrated positive associations, a comprehensive synthesis that systematically evaluates the totality of evidence, particularly from Indonesian settings, has been lacking.

The novelty of this comprehensive review lies in its systematic approach to synthesizing evidence from 146 studies, with particular emphasis on Indonesian research contexts. Unlike previous narrative reviews, this review provides detailed extraction and comparative analysis of study characteristics, population demographics, smoking assessment methodologies, recurrence definitions, effect estimates, and confounder adjustment strategies. Furthermore, it explicitly examines the methodological quality and heterogeneity across studies, identifies critical evidence gaps, and proposes specific recommendations for future research directions.

The primary objective of this review is to comprehensively evaluate and synthesize the existing evidence regarding the relationship between smoking and tuberculosis recurrence risk among patients who have successfully completed anti-tuberculosis treatment. Secondary objectives include: (1) characterizing the magnitude and consistency of the smoking-recurrence association across different study designs and populations; (2) examining evidence for dose-response relationships between smoking intensity, duration, and recurrence risk; (3) evaluating the biological

mechanisms proposed to explain this association; (4) assessing the methodological quality and identifying sources of heterogeneity across studies; and (5) formulating evidence-based recommendations for clinical practice and future research.

This review offers several significant contributions. For clinical practice, it provides robust evidence to support the integration of smoking cessation services into routine TB care programs, reinforcing World Health Organization recommendations. For public health policy, it furnishes policymakers with comprehensive, context-specific evidence from high-burden settings to inform resource allocation and programmatic interventions. For researchers, it systematically maps the current evidence landscape, identifies critical knowledge gaps, and provides methodological recommendations for future investigations. Ultimately, this review aims to contribute to reducing TB recurrence rates and improving long-term outcomes for millions of TB patients worldwide.

Based on the available epidemiological evidence and biological plausibility, we hypothesize that smoking is significantly associated with an increased risk of tuberculosis recurrence among patients who have completed anti-tuberculosis treatment. Furthermore, we hypothesize that this association exhibits a dose-response relationship, with higher smoking intensity and longer duration conferring progressively greater recurrence risk.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between smoking and the risk of tuberculosis relapse after treatment completion.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population - TB Treatment Completion:** Does the study include patients who have completed tuberculosis treatment with confirmed tuberculosis diagnosis and treatment completion?
- **Smoking Exposure Definition:** Does the study examine smoking as an exposure or risk factor with clearly defined smoking exposure (current smokers, former smokers, never smokers, or quantified smoking history)?
- **TB Recurrence Outcome:** Does the study measure tuberculosis recurrence, relapse, or re-infection as an outcome?
- **Study Design:** Is the study an observational study (cohort, case-control, cross-sectional) or a systematic review/meta-analysis?
- **Follow-up Duration:** Does the study have a follow-up period of at least 6 months post-treatment?
- **Post-Treatment Focus:** Does the study focus on post-treatment outcomes rather than focusing solely on active tuberculosis patients during treatment?
- **Study Design Rigor:** Is the study design more rigorous than case reports or case series (i.e., not a case report or case series)?
- **Smoking Exposure Measurement:** Does the study clearly define and measure smoking exposure (rather than having unclear or unmeasured smoking exposure)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Tuberculosis	Smoking	Non-smokers	Tuberculosis Relapse
Keyword 2	Treatment Completion	Smoking Intensity	Former Smokers	Recurrence Risk
Keyword 3	Pulmonary Tuberculosis	Smoking Status	Without smoking history	Reinfection
Keyword 4	Adults	Cigarette Smoke Exposure	No exposure	Recurrence Rate

The Boolean MeSH keywords inputted on databases for this research are: (*"Tuberculosis" OR "Pulmonary Tuberculosis" OR "Adults"*) AND (*"Smoking" OR "Smoking Intensity" OR "Smoking Status" OR "Cigarette Smoke Exposure"*) AND (*"Non-smokers" OR "Former Smokers" OR "Without smoking history" OR "No exposure"*) AND (*"Tuberculosis Relapse" OR "Recurrence Risk" OR "Reinfection" OR "Recurrence Rate"*)

Data extraction

- **Study Characteristics:**

Extract key study design features for studies examining smoking and TB recurrence post-treatment, including:

- Study design (cohort, case-control, cross-sectional, etc.)
- Sample size (total and by smoking status if reported)
- Study setting and location
- Follow-up duration post-treatment completion
- Data collection period

- **Population Details:**

Extract characteristics of patients studied for TB recurrence after treatment completion, including:

- Age distribution and demographics
- Initial TB type and severity
- Treatment regimen completed
- Treatment completion rates
- Comorbidities (HIV, diabetes, malnutrition, etc.)
- Exclusion criteria related to treatment completion

- **Smoking Exposure:**

Extract detailed smoking behavior data relevant to TB recurrence risk, including:

- Smoking status categories (never, former, current smoker)
- Smoking intensity (cigarettes per day, pack-years)
- Duration of smoking history
- Type of tobacco products used
- Timing of smoking relative to TB treatment (during treatment, after completion)
- Smoking cessation status and timing if applicable

- **Recurrence Definition:**

Extract how TB recurrence was defined and measured post-treatment, including:

- Clinical and/or microbiological criteria for recurrence
- Minimum follow-up period required to assess recurrence
- Method of recurrence detection (symptoms, routine follow-up, etc.)
- Distinction between relapse and reinfection (if made)

- Time window considered for recurrence assessment

- **Recurrence Outcomes:**

Extract TB recurrence results by smoking status, including:

- Recurrence rates in smokers vs non-smokers
- Time to recurrence by smoking status
- Number of recurrence events in each smoking group
- Recurrence-free survival data if available
- Any dose-response relationship between smoking intensity and recurrence

- **Effect Measures:**

Extract quantitative measures of association between smoking and TB recurrence post-treatment, including:

- Risk ratios, odds ratios, or hazard ratios with 95% confidence intervals
- P-values for smoking-recurrence association
- Both crude and adjusted effect estimates
- Subgroup analyses by smoking intensity or duration
- Statistical methods used for analysis

- **Confounders Controlled:**

Extract variables that were controlled for when analyzing the smoking-TB recurrence relationship, including:

- Demographic factors (age, gender, socioeconomic status)
- Clinical factors (HIV status, diabetes, nutritional status, initial TB severity)
- Treatment-related factors (treatment adherence, regimen type)
- Behavioral factors (alcohol use, drug use)

- Method of confounder adjustment (multivariable modeling, matching, etc.)

- **Main Findings:**

Extract the authors' conclusions about the relationship between smoking and TB recurrence after treatment completion, including:

- Whether smoking was found to increase recurrence risk
- Magnitude of increased risk if found
- Any identified mechanisms linking smoking to recurrence
- Clinical implications stated by authors
- Limitations acknowledged regarding smoking-recurrence relationship
- Recommendations for smoking cessation in TB patients

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Tuberculosis" OR "Pulmonary Tuberculosis" OR "Adults") AND ("Smoking" OR "Smoking Intensity" OR "Smoking Status" OR "Cigarette Smoke Exposure") AND ("Non-smokers" OR "Former Smokers" OR "Without smoking history" OR "No exposure") AND ("Tuberculosis Relapse" OR "Recurrence Risk" OR "Reinfection" OR "Recurrence Rate")</i>	18
Semantic Scholar	<i>("Tuberculosis" OR "Pulmonary Tuberculosis" OR "Adults") AND ("Smoking" OR "Smoking Intensity" OR "Smoking Status" OR "Cigarette Smoke Exposure") AND ("Non-smokers" OR "Former Smokers" OR "Without smoking history" OR "No exposure") AND ("Tuberculosis Relapse" OR "Recurrence Risk" OR "Reinfection" OR "Recurrence Rate")</i>	250
Springer	<i>("Tuberculosis" OR "Pulmonary Tuberculosis" OR "Adults") AND ("Smoking" OR "Smoking Intensity" OR "Smoking Status" OR "Cigarette Smoke Exposure") AND ("Non-smokers" OR "Former Smokers" OR "Without smoking history" OR "No exposure") AND ("Tuberculosis Relapse" OR "Recurrence Risk" OR "Reinfection" OR "Recurrence Rate")</i>	674
Google Scholar	<i>("Tuberculosis" OR "Pulmonary Tuberculosis" OR "Adults") AND ("Smoking" OR "Smoking Intensity" OR "Smoking Status" OR "Cigarette Smoke Exposure") AND ("Non-smokers" OR "Former Smokers" OR "Without smoking history" OR "No exposure") AND ("Tuberculosis Relapse" OR "Recurrence Risk" OR "Reinfection" OR "Recurrence Rate")</i>	4,100
Wiley Online Library	<i>("Tuberculosis" OR "Pulmonary Tuberculosis" OR "Adults") AND ("Smoking" OR "Smoking Intensity" OR "Smoking Status" OR "Cigarette Smoke Exposure") AND ("Non-smokers" OR "Former Smokers" OR "Without smoking history" OR "No exposure") AND ("Tuberculosis Relapse" OR "Recurrence Risk" OR "Reinfection" OR "Recurrence Rate")</i>	768

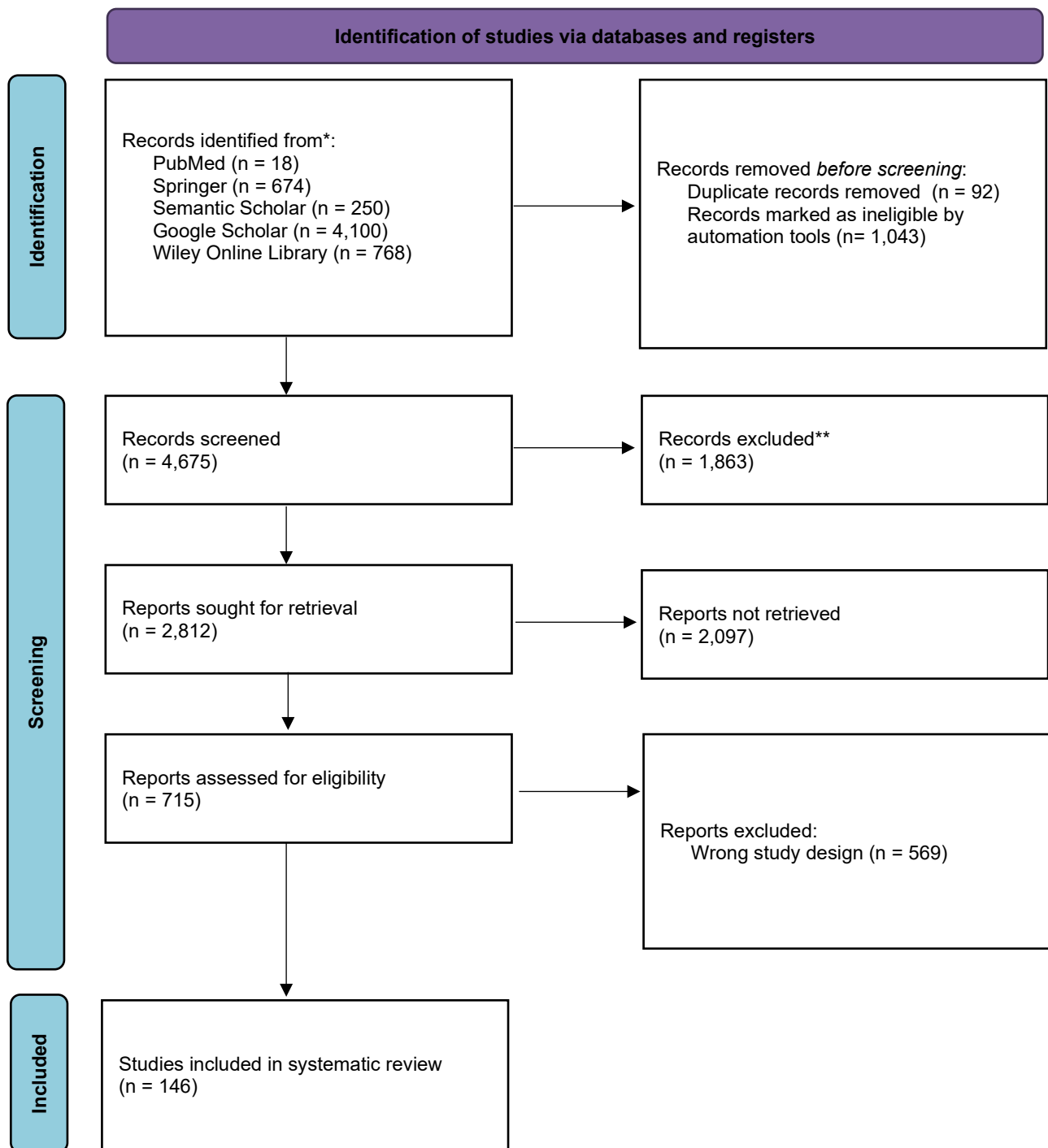


Figure 1. Article search flowchart

RESULTS

Study Characteristics

The included studies investigating the relationship between smoking and post-treatment tuberculosis (TB) recurrence employed a variety of methodological approaches. Sample sizes ranged widely from as few as five participants to over 5,000 individuals. The majority of studies were conducted in Asian countries, particularly Indonesia, with others in Pakistan and Taiwan. Follow-up durations, when specified, were often short, with one study defining recurrence within two years post-treatment. Data collection periods spanned from 2004 to 2025. Total 146 Study included.

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Darakhshan Ahmad et al. (2016)	332	Pakistan/Rawalpindi	Within two years	2015 to 2016
Y. Yen et al. (2014)	5567	Taiwan/Taipei	Not mentioned	Not mentioned
N.L.P. Karminiasih et al. (2016)	138	Indonesia/Denpasar	Not mentioned	2013-2015
Ni Luh et al. (2016)	138	Indonesia/Denpasar	Not mentioned	2016
N. Karminiasih et al. (2016)	138	Indonesia/Denpasar	Not mentioned	2016
Regina Natasia Ulfa et al. (2023)	22	Indonesia/Jambi	Not mentioned	2020-2022

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Ummuhani Abubakar et al. (2024)	19	Indonesia/RSUD Dr. H. Chasan Boesoirie	Not mentioned	2016 – 2021
Ummuhani Abubakar et al. (2024a)	19	Indonesia/Ternate	Not mentioned	2016 – 2021
Khairani Dian et al. (2015)	34	Indonesia/Padang	Not mentioned	2015
Hafidz Alfarobi et al. (2022)	117	Indonesia/Surabaya	Not mentioned	2019
R. Sianturi et al. (2013)	52	Indonesia/Semarang	Not mentioned	Not mentioned
Cantika Dinia Zulda et al. (2017)	88	Indonesia/Padang	Not mentioned	Not mentioned
Agripina Nailape et al. (2019)	10	Indonesia/Rote Ndao	Not mentioned	Not mentioned
D. Dewi et al. (2020)	Not mentioned	Not mentioned	Not mentioned	Not mentioned
M. Sabir et al. (2023)	Not mentioned	Not mentioned	Not mentioned	Not mentioned

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Marini Marini et al. (2023)	138	Indonesia/Muara Enim	Not mentioned	2017-2020
Cynthia Devi Aristiana et al. (2018)	88	Indonesia/Jakarta	Not mentioned	2017 to 2018
Aulia Khoirunnisa et al. (2023)	150	Indonesia/Makassar	Not mentioned	Not mentioned
F. Sinaga et al. (2019)	63	Indonesia/Bandar Lampung	Not mentioned	2018
Y. Agustin et al. (2016)	5	Indonesia/Pontianak	Not mentioned	Not mentioned
J. Friska et al. (2019)	Not mentioned	Indonesia/Jakarta	Not mentioned	Not mentioned
Maliani Mayang et al. (2016)	52	Indonesia/Bukittinggi	Not mentioned	2015
A. Susanto et al. (2014)	Not mentioned	Not mentioned	Not mentioned	Not mentioned
A. Pramudita et al. (2017)	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Vera Vera et al. (2024)	250	Indonesia/Surakarta	Not mentioned	2017

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Luluk Listiarini Riza et al. (2017)	62	Indonesia/Semarang	Not mentioned	Not mentioned
Kholis Ernawati et al. (2017)	2319	Indonesia/North Sulawesi	Not mentioned	2010
B. Rianto et al. (2017)	74	Indonesia/Bandung Barat	Not mentioned	2013
Atira Atira et al. (2020)	84	Indonesia	Not mentioned	2016
Dismo Katiandagho et al. (2018)	47	Indonesia/North Minahasa	Not mentioned	Not mentioned
D. W. Wardani et al. (2019)	Not mentioned	Indonesia	Not mentioned	2016
Fitrya Ayu Nur Aini AR et al. (2021)	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Ni Made Nujita Mahartati et al. (2024)	Not mentioned	Burkina Faso, Pakistan, Ethiopia, China, Colombia, Malaysia	Not mentioned	Not mentioned
Yulianti Nita et al. (2023)	96	Indonesia/Padang	Not mentioned	2019 – 2020

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Hilmi Yasni et al. (2024)	104	Indonesia/South Aceh	Not mentioned	2024
Pendrita Melkianus Kabonju Hita et al. (2017)	69	Indonesia/Sumba Timur	Not mentioned	Not mentioned
Miftahul Maqfirah et al. (2020)	76	Indonesia/Parepare	Not mentioned	2019
Fransisca Jaqueline Sitinjak et al. (2023)	106	Indonesia/Bandar Lampung	Not mentioned	2022
Azrial Akbar et al. (2023)	36	Indonesia/Banda Aceh	Not mentioned	2023
Novrika Silalahi et al. (2019)	89	Indonesia	Not mentioned	2017
R. Sianturi et al. (2014)	52	Indonesia/Semarang	Not mentioned	2013
Eka Febriyanti et al. (2025)	30	Indonesia/Surakarta	Not mentioned	2017
Maria Anggi Sylvani et al. (2020)	107	Indonesia/Papua	Not mentioned	Not mentioned

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Sopian Solihin et al. (2021)	Not mentioned	Not mentioned	Not mentioned	2015 to 2019
Yorien Setia alfarianti et al. (2022)	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Alwa Ayu Azzahra et al. (2024)	132	Indonesia/Banda r Lampung	Not mentioned	Not mentioned
Manda R Happyanto et al. (2024)	407	Indonesia/Purwa karta	Not mentioned	2020-2023
Eva Rosdiana et al. (2019)	82	Indonesia/Aceh Besar	Not mentioned	2015-2016
Miftakhul Janan et al. (2019)	138	Indonesia/Brebes	Not mentioned	Not mentioned
Vidi Ibrahim Pratomo Affandi et al. (2020)	38	Indonesia/Banda r Lampung	Not mentioned	2019
Yohana S. Siburian et al. (2022)	30	Indonesia/Palang ka Raya	Not mentioned	Not mentioned
Apriyani Apriyani et al. (2019)	48	Indonesia/Samar inda	Not mentioned	Not mentioned
Ageng Brahmadhi et al. (2017)	86	Indonesia/Banyu mas	Not mentioned	Not mentioned

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Yohanna Febrianty Girsang et al. (2023)	114	Indonesia/Jambi	Not mentioned	Not mentioned
Khairun Nisak et al. (2024)	60	Indonesia/Aceh Besar	Not mentioned	Not mentioned
Ressa Stevany A et al. (2021)	112	Indonesia/Jakarta Timur	Not mentioned	Not mentioned
Maya Arisandi et al. (2024)	168	Not mentioned	Not mentioned	Not mentioned
Gita Sekar Prihanti et al. (2017)	66	Indonesia/Kediri	Not mentioned	2015
Elisa Rinaldo Perdamenta et al. (2023)	80	Indonesia	Not mentioned	2021
Adnindya Krismahardi et al. (2024)	Not mentioned	Not mentioned	Not mentioned	2016 to 2022
Dafrosia Darmi Manggasa et al. (2022)	64	Indonesia/Poso	Not mentioned	2015 to 2020
Nurliza Rohayu et al. (2017)	40	Indonesia/South Buton	Not mentioned	2016
W. Wulandari et al. (2022)	Not mentioned	Indonesia/Lebong	Not mentioned	Not mentioned

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
D. Sulaiman et al. (2023)	114	Indonesia/Tulang Bawang	Not mentioned	Not mentioned
Dwi Santy Damayati et al. (2018)	60	Indonesia/Pangkep	Not mentioned	Not mentioned
Neila Sulung et al. (2018)	72	Indonesia/Bukittinggi	Not mentioned	Not mentioned
Winda Afdilla J et al. (2018)	Not mentioned	Indonesia/Jakarta	Not mentioned	2016
Melina Nunkaidah et al. (2017)	310	Indonesia/Muna	Not mentioned	2013 to 2015
Budi Rianto et al. (2018)	100	Indonesia/Cianjur	Not mentioned	2017
Erika Diana Risanti et al. (2025)	191	Indonesia/Surakarta	Not mentioned	Not mentioned
Budi Rianto et al. (2017)	100	Indonesia	Not mentioned	Not mentioned
Rosmawati et al. (2023)	96	Indonesia/Makassar	Not mentioned	Not mentioned
J. Masyarakat et al. (2025)	118	Indonesia/Pulau Sabu	Not mentioned	2025

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Hetti Rusmini et al. (2023)	Not mentioned	Not mentioned	Not mentioned	Not mentioned
I. Kurniawan et al. (2021)	52	Indonesia/Magetan	Not mentioned	2016-2018
Seri Wahyuni et al. (2024)	92	Indonesia/Medan	Not mentioned	Not mentioned
Darmin Darmin et al. (2020)	73	Indonesia	Not mentioned	2018 and 2019
Anisa Kusuma Dewi Firdaus et al. (2025)	Not mentioned	Indonesia/Bekasi	Not mentioned	2020 to 2024
Rahmasuciani Putri et al. (2020)	71	Indonesia/Banyuwangi	Not mentioned	2017
Nurul Husna Muchtar et al. (2018)	65	Indonesia/Padang	Not mentioned	2015
Yurlinda Hamid et al. (2025)	51	Indonesia	Not mentioned	2024
E. Yunita et al. (2020)	40	Indonesia/Pekanbaru	Not mentioned	2019
Ria Risti Komala Dewi et al. (2023)	194	Indonesia/Kalimantan Barat	Not mentioned	Not mentioned

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Anggia Paradiba et al. (2025)	Not mentioned	Indonesia, South Sudan, Bangladesh	Not mentioned	2024 to 2025
Fadhil Hasan et al. (2023)	62	Indonesia/Kendari	Not mentioned	2021
Novrika Silalahi et al. (2019a)	89	Indonesia	Not mentioned	2017
Waella Septamari Budi et al. (2024)	100	Indonesia/Magetan	Not mentioned	Not mentioned
R. Rosdiana et al. (2018)	58	Indonesia/Makassar	Not mentioned	Not mentioned
Fatri Bakri et al. (2021)	203	Indonesia/Parepare	Not mentioned	2020
Andi Nursafa et al. (2025)	32	Indonesia/Kalimantan Timur	Not mentioned	2024
Patricia Nathania Ina Kii et al. (2025)	126	Indonesia	Not mentioned	2024
F. Laili et al. (2024)	4261	Indonesia	Not mentioned	2022-2023
Medi Christian et al. (2020)	100	Indonesia/Malindu	Not mentioned	2019

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Fauziah Amining et al. (2021)	97	Indonesia/Sulawesi Tengah	Not mentioned	Not mentioned
La Ode Asrianto et al. (2024)	110	Indonesia	Not mentioned	Not mentioned
Anis Nur Janah et al. (2023)	4123	Indonesia/Palembang	Not mentioned	Not mentioned
Clara Agustin et al. (2023)	Not mentioned	Indonesia/Bandar Lampung	Not mentioned	2022 - 2023
Muh. Jusman Rau et al. (2021)	64	Indonesia/Sulawesi Tengah	Not mentioned	2020
Sehra Banu et al. (2019)	88	Indonesia	Not mentioned	Not mentioned
Efdia Ronny et al. (2016)	60	Indonesia/Padang	Not mentioned	Not mentioned
Stevi Yanti Nopita Sari et al. (2024)	51	Indonesia/Luwu Timur	Not mentioned	Not mentioned
Rahmi Amir et al. (2019)	90	Indonesia	Not mentioned	Not mentioned
Tantri Muharam et al. (2023)	34	Indonesia/Gorontalo	Not mentioned	2022
Lilis Kholisah et al. (2023)	136	Indonesia	Not mentioned	Not mentioned

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Y. Putri et al. (2016)	65	Indonesia/Banda Aceh	Not mentioned	Not mentioned
Onny Firdiani et al. (2025)	49	Indonesia	Not mentioned	2024
Neti Sitorus et al. (2023)	100	Indonesia/Bandung	Not mentioned	Not mentioned
Maria Regina Loprang et al. (2025)	3824	Indonesia	12 months	2020-2022
S. Winarti et al. (2021)	246	Not mentioned	Not mentioned	2016-2019
Nirwana et al. (2023)	58	Indonesia/Kendari	Not mentioned	2022
Vector Stephen Dewangga et al. (2024)	43	Indonesia/Wongiri	Not mentioned	Not mentioned
Debby Nirma Sari Sejahtera et al. (2018)	71	Indonesia/Surakarta	Not mentioned	Not mentioned
Diana Ayu Meiningtyas et al. (2023)	77	Indonesia/Bandung	Not mentioned	Not mentioned
Nim. Beta Martanto et al. (2018)	45	Indonesia/Yogyakarta	Not mentioned	Not mentioned

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Santi Dwi Cahyani et al. (2017)	Not mentioned	Indonesia/Surakarta	Not mentioned	2016
Masbahah et al. (2011)	133	Indonesia/Malang	Not mentioned	2009
Innike Putri Kusumawardani et al. (2016)	58	Indonesia/Pontianak	Not mentioned	Not mentioned
Nova Arikhman et al. (2019)	272	Indonesia/West Sumatera	Not mentioned	Not mentioned
W. Silo et al. (2015)	57	Indonesia/Manado	Not mentioned	2014
Mellia Fransiska et al. (2019)	38	Indonesia/Bukittinggi	Not mentioned	2018
J. WindaAfdilla et al. (2018)	Not mentioned	Indonesia/Jakarta	Not mentioned	2016
Risye Melinda Pangalo et al. (2019)	60	Indonesia/Sangihe	Not mentioned	2018
Wimelda Raya et al. (2018)	26	Indonesia/Mamuju Utara	Not mentioned	Not mentioned

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Luh Ayu Made Anika Kemala H A Sari et al. (2015)	139	Indonesia/Semarang	Not mentioned	2014
H. Setiawan et al. (2017)	242	Indonesia/Surakarta	Not mentioned	2011 to 2016
Hasnah Fadhilatul et al. (2016)	Not mentioned	Southeast Asia	Not mentioned	2016
Faiz Adnan Makarim et al. (2019)	117	Indonesia/Depok	Not mentioned	Not mentioned
Halim et al. (2017)	80	Indonesia/Kebumen	Not mentioned	Not mentioned
Etty Komariah Sambas et al. (2015)	94	Indonesia/Tasikmalaya	Not mentioned	2015
R. Rusnoto et al. (2010)	106	Indonesia/Pati	Not mentioned	Around 2008
Sarifuddin et al. (2015)	32	Indonesia/Gorontalo	Not mentioned	2014
Nana Marlina Ekasari et al. (2016)	66	Indonesia/Semarang	Not mentioned	Not mentioned
R. Risnawati et al. (2015)	27	Indonesia/Padang Pariaman	Not mentioned	Not mentioned

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Annas Fadhilah Bilqishti et al. (2018)	60	Indonesia	Not mentioned	2017
Iqbal Daroja et al. (2015)	62	Indonesia/Jombang	Not mentioned	Not mentioned
Nur Afiat Soraya Mursyaf et al. (2018)	19	Indonesia/Makassar	Not mentioned	Not mentioned
Aliyah Kusumawardani et al. (2021)	132	Indonesia/Bogor	Not mentioned	Not mentioned
Siti Khotimah et al. (2025)	54	Indonesia/Palangka Raya	Not mentioned	Not mentioned
Mareta Edriyenti Elsis et al. (2020)	Not mentioned	Indonesia/West Sumatra	Not mentioned	2016 to 2020
Muhammad Jalaluddin Jalal et al. (2024)	84	Indonesia/Makassar	Not mentioned	Not mentioned
Oksi Anjar Winanti et al. (2018)	60	Indonesia/Jatilawang	Not mentioned	Not mentioned
Khaidir Ahmad et al. (2015)	70	Indonesia/Solok	Not mentioned	2015
Titik Respati Gilarsi et al. (2004)	60	Indonesia/Indramayu	Not mentioned	Not mentioned

Study	Sample Size	Country/Setting	Follow-up Duration	Data Collection Period
Burni Safitri Stepani et al. (2016)	Not mentioned	Indonesia/Padang	Not mentioned	Not mentioned
Multi Gandi et al. (2016)	80	Indonesia/Padang	Not mentioned	2016
Stepani Burni Safitri et al. (2016)	242	Indonesia/Padang	Not mentioned	Not mentioned

Population Characteristics

The populations in the included studies were primarily adults treated for pulmonary tuberculosis. The mean age of participants was 58.5 years in one cohort, while other studies focused on patients aged over 15 years or those in the productive age range of 18-65 years. Males comprised the majority of participants in many studies, with proportions ranging from 53.8% to 81.8%. Study participants had typically completed a course of anti-tuberculosis therapy (ATT), though the specific regimens and treatment completion rates were often not detailed.

Key comorbidities were frequently noted as significant risk factors. Diabetes Mellitus (DM) and HIV co-infection were commonly assessed. One study reported that 86.2% of patients were HIV negative and 87.7% did not have a history of DM, while another found higher rates of DM in recurrent cases. Malnutrition was also a prevalent comorbidity, with one study reporting that 66.2% of its participants had a poor nutritional status, and another noting 70.6% as having malnutrition. Exclusion criteria sometimes involved comorbidities; for instance, one study excluded patients with HIV/AIDS, DM, and malignancies to isolate the effects of smoking.

Study	Mean/Median Age	Percent Male	TB Type	Treatment Regimen	HIV Prevalence	Diabetes Prevalence	Other Key Comorbidities
Darakhshan Ahmad et al. (2016)	Not mentioned	100%	Pulmonary Kochs	ATT	Not mentioned	Not mentioned	Not mentioned
Y. Yen et al. (2014)	58.5 years	62.9%	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Presence of comorbidities
N.L.P. Karminia sih et al. (2016)	>15 years	Not mentioned	Pulmonary TB	Not mentioned	Not mentioned	DM	Malnutrition
Ni Luh et al. (2016)	>15 years	Not mentioned	Not mentioned	Not mentioned	Not mentioned	DM	Malnutrition
N. Karminia sih et al. (2016)	>15 years	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Yes	Malnutrition

Study	Mean/Median Age	Percent Male	TB Type	Treatment Regimen	HIV Prevalence	Diabetes Prevalence	Other Key Comorbidities
Regina Natasia Ulfa et al. (2023)	77.3% >34 years	81.8%	Pulmonary TB	Not mentioned	68.2% no HIV	68.2% no diabetes	Normal nutritional status (59.1%)
Ummuhamni Abubakar et al. (2024)	21% in 26-35 and 46-55 age groups	63%	Pulmonary TB	Not mentioned	Not mentioned	Not mentioned	57.9% no comorbidities
Ummuhamni Abubakar et al. (2024a)	21% in 26-35 and 46-55 age groups	63%	Pulmonary TB	Not mentioned	Not mentioned	Diabetes, bronchiectasis, pneumonia, PPOK, asthma	57.9% no comorbidities
Khairani Dian et al. (2015)	88.2% productive age	58.8%	Pulmonary TB	Not mentioned	Not mentioned	Not mentioned	Malnutrition (70.6%)

Study	Mean/Median Age	Percent Male	TB Type	Treatment Regimen	HIV Prevalence	Diabetes Prevalence	Other Key Comorbidities
Y. Agustin et al. (2016)	> 50 years	Yes	Pulmonary TB	Not mentioned	Not mentioned	Yes	Not mentioned
J. Friska et al. (2019)	Not mentioned	Not mentioned	Not mentioned	Category I	Not mentioned	Yes (HbA1c levels)	Not mentioned
Ni Made Nujita Mahartati et al. (2024)	Median 26-43 years	Majority male	Not mentioned	Not mentioned	Yes	Yes	Not mentioned
R. Sianturi et al. (2014)	88.5% productive age	Not mentioned	Pulmonary TB	Not mentioned	Not mentioned	Diabetes mellitus	Anemia

Study	Mean/Median Age	Percent Male	TB Type	Treatment Regimen	HIV Prevalence	Diabetes Prevalence	Other Key Comorbidities
Eka Febriyanti et al. (2025)	18-65 years	Not mentioned	TB	Full treatment	Not mentioned	Not mentioned	Alcohol consumption, poor nutritional status
Maria Anggi Sylvani et al. (2020)	85% 26-45 years	35.5%	TB	Not mentioned	100%	Not mentioned	Not mentioned
Yorien Setia alfarianti et al. (2022)	Not mentioned	Not mentioned	Not mentioned	Standard six-month regimen	Yes	Yes	Malnutrition
Manda R Happyanto et al. (2024)	Not mentioned	Not mentioned	TB	Not mentioned	0.24%	1.71%	Not mentioned

Study	Mean/Median Age	Percent Male	TB Type	Treatment Regimen	HIV Prevalence	Diabetes Prevalence	Other Key Comorbidities
Yohana S. Siburian et al. (2022)	15-64 years	60%	Pulmonary TB	6 months	Not mentioned	Not mentioned	Not mentioned
Maya Arisandi et al. (2024)	Not mentioned	Not mentioned	TB	Not mentioned	Yes	Yes	Asthma
Nurul Husna Muchtar et al. (2018)	44.6% >45 years	72.3%	Pulmonary TB	Not mentioned	86.2% negative	87.7% no DM	Malnutrition (66.2%), Alcohol use (1.5% at risk)
F. Laili et al. (2024)	53.2% 15-44 years	58.4%	Drug-resistant TB	OAT	3.6%	25.6%	Not mentioned

Study	Mean/Median Age	Percent Male	TB Type	Treatment Regimen	HIV Prevalence	Diabetes Prevalence	Other Key Comorbidities
Santi Dwi Cahyani et al. (2017)	≤ 20 years	Not mentioned	Pulmonary TB	Not mentioned	Excluded	Excluded	Malignancies (excluded)
Maria Regina Loprang et al. (2025)	95.6% adults	Not mentioned	Drug-resistant TB	Short-course regimen	4.03%	Not mentioned	Not mentioned
R. Rusnoto et al. (2010)	75% 15-50 years	Not mentioned	Pulmonary TB	Not mentioned	Not mentioned	Not mentioned	Poor nutritional status

Smoking Exposure Assessment

The assessment of smoking exposure varied across studies, with many defining it in terms of current, former, and never-smoker categories. One study specified continued smoking after completion of anti-tuberculosis therapy as a key exposure category. Another study focused on exposure to cigarette smoke during treatment, which could include secondhand smoke.

Quantification of smoking intensity was less consistent. A Taiwanese cohort study defined high-risk smokers as those consuming more than 10 cigarettes per day. A study in Pakistan assessed

smoking duration, finding a mean duration of 12.37 years in recurrent cases and a significantly increased risk for those smoking more than 10 years. Other studies also considered the number of cigarettes per day and duration of smoking history as important variables related to treatment failure or non-conversion of sputum. The type of tobacco products used was infrequently specified, although some studies mentioned filter and non-filter cigarettes. Information regarding smoking cessation was limited; one study noted that 85% of male TB patients were former smokers, implying cessation often occurred after diagnosis.

Study	Smoking Categories Used	Intensity Measures	Assessment Method	Timing of Smoking Relative to Treatment
Darakhshan Ahmad et al. (2016)	Current smokers, ever smoked in life	>10 years duration	Not mentioned	Continued smoking after ATT completion
Y. Yen et al. (2014)	Never/former, current smokers	>10 cigarettes/day	Not mentioned	Not mentioned
N.L.P. Karminiasih et al. (2016)	Smoking/exposed to smoke	Not mentioned	Interview	During treatment
Ni Luh et al. (2016)	Exposed to cigarette smoke	Not mentioned	Interview/questionnaire	During treatment
N. Karminiasih et al. (2016)	Exposed to cigarette smoke	Not mentioned	Interview/questionnaire	During treatment

Study	Smoking Categories Used	Intensity Measures	Assessment Method	Timing of Smoking Relative to Treatment
Regina Natasia Ulfa et al. (2023)	Smokers, heavy smokers	Not mentioned	Not mentioned	Not mentioned
Aulia Khoirunnisa et al. (2023)	Active smokers, passive smokers	Not mentioned	Interview	Not mentioned
F. Sinaga et al. (2019)	Current smoker	1-10, 20-30, 40-50 cigarettes/day	Questionnaire	Not mentioned
Y. Agustin et al. (2016)	Exposure to environmental cigarette smoke	Not mentioned	Interview	Not mentioned
Luluk Listiarini Riza et al. (2017)	Not mentioned	Number of cigarettes smoked per day	Not mentioned	Not mentioned
D. W. Wardani et al. (2019)	Smoker	Amount of cigarettes smoked	Questionnaire	Not mentioned
Miftahul Maqfirah et al. (2020)	Smoker, Non-smoker	Number of cigarettes smoked per day	Questionnaire	Not mentioned

Study	Smoking Categories Used	Intensity Measures	Assessment Method	Timing of Smoking Relative to Treatment
Azrial Akbar et al. (2023)	Current smokers, heavy smokers	Not mentioned	Questionnaire	Not mentioned
Rahmasuciani Putri et al. (2020)	Current smokers, Former smokers	>31 cigarettes/day, 21-30 cigarettes/day	Questionnaire	15% continued during treatment
Nurul Husna Muchtar et al. (2018)	Current, Former, Never smoker	Not mentioned	Not mentioned	Not mentioned
Patricia Nathania Ina Kii et al. (2025)	Active smokers, passive smokers	1 pack/day	Questionnaire	Not mentioned
Y. Putri et al. (2016)	Non-smokers, light, moderate, heavy smokers	Brinkman index	Not mentioned	Not mentioned

Tuberculosis Recurrence Definitions and Ascertainment

The definition of tuberculosis recurrence varied across the reviewed studies. A common criterion was a new diagnosis of TB, confirmed either clinically or microbiologically, in a patient who had previously completed treatment. For instance, recurrence could be defined as a new

bacteriological confirmation (positive acid-fast bacilli or BTA) after having been declared cured or having completed treatment.

The time window for assessing recurrence was specified in some studies, such as "within two years" of treatment completion. However, many studies did not explicitly state the minimum follow-up period. The methods for detecting recurrence were also not always detailed, but some studies used bacteriological examinations like BTA or TCM rifampicin sensitivity tests for confirmation. Few studies made an explicit distinction between true relapse (reactivation of the original infection) and exogenous reinfection (a new infection). This lack of standardized definitions and ascertainment methods for recurrence represents a source of heterogeneity that could influence the comparability of outcomes across the evidence base.

Recurrence Rates by Smoking Status

Several studies reported higher rates of TB recurrence among smokers compared to non-smokers. One case-control study found that 63.6% of patients with recurrent TB had continued smoking after their initial treatment, compared to only 36.4% of non-recurrent controls. A large cohort study in Taiwan reported that the overall recurrence rate was 1.5%, but the risk for individuals smoking more than 10 cigarettes a day was double that of never or former smokers. Another study focusing on multi-drug resistant TB (MDR-TB) found that recurrence occurred in 43.6% of smokers versus 36.8% of non-smokers, although this difference was not statistically significant.

A dose-response relationship between smoking and recurrence risk was observed in some reports. A study from Pakistan identified a highly significant association with smoking for more than 10 years (OR=3.67). Similarly, the Taiwanese study highlighted a doubled risk specifically for those smoking more than 10 cigarettes per day. Time-to-recurrence data and recurrence-free survival analyses were generally not reported in the abstracts reviewed.

Study	Follow-up Period	Recurrence Rate in Smokers	Recurrence Rate in Non-smokers	Dose-Response Findings
Darakhshan Ahmad et al. (2016)	Within two years	63.6% of cases	36.4% of controls	Increased risk with >10 years of smoking (OR=3.67)
Y. Yen et al. (2014)	Not mentioned	Double the risk of non-smokers	Not specified	Increased risk with >10 cigarettes/day
Hafidz Alfarobi et al. (2022)	Not mentioned	43.6%	36.8%	Not mentioned
Vector Stephen Dewangga et al. (2024)	Not mentioned	11.6% positive for Acid Resistant Bacteria	7.0% positive for Acid Resistant Bacteria	Not mentioned

Effect Estimates and Quantitative Associations

Quantitative analyses consistently showed a positive association between smoking and TB recurrence. A Pakistani case-control study reported an odds ratio (OR) of 2.35 (95% CI: 1.48-3.74) for recurrence among patients who continued smoking after treatment completion. Subgroup analyses within the same study revealed a stronger association for longer duration of smoking, with an OR of 3.67 (95% CI: 1.55-8.71) for those who smoked for more than 10 years. Similarly, a study in Indonesia found an adjusted odds ratio (AOR) of 3.6 (95% CI: 1.41-9.16) for recurrence associated with smoking or exposure to smoke during treatment.

Other studies focused on related outcomes such as treatment failure or development of Multi-Drug Resistant TB (MDR-TB). One systematic review reported ORs for treatment failure

associated with smoking to be 2.37 (95% CI: 1.24–4.54) and 7.489 (95% CI: 0.93–60.30) from two separate cohort studies. Studies on MDR-TB also indicated a strong link with smoking, with reported ORs of 7.632 and 4.1 for active smokers. A meta-analysis calculated a pooled OR of 2.28 (95% CI: 1.04-5.02) for the association between smoking and pulmonary TB incidence in Southeast Asia. The majority of these estimates were from multivariable models, which adjusted for various potential confounders.

Study	Effect Measure Type	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	p-value	Variables Adjusted For
Darakhshan Ahmad et al. (2016)	Odds Ratio	2.35 (1.48-3.74) for continued smoking 3.67 (1.55-8.71) for >10 years smoking	Not mentioned	0.00	Not mentioned
Y. Yen et al. (2014)	Hazard Ratio	Not mentioned	Risk doubled for >10 cigarettes/day	Not mentioned	Homelessness, comorbidities, AFB smear status

Study	Effect Measure Type	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	p-value	Variables Adjusted For
N.L.P. Karminiasih et al. (2016)	Odds Ratio	Not mentioned	3.6 (1.41-9.16)	Not mentioned	DM, treatment adherence, home ventilation, household contact, nutritional status
Ni Luh et al. (2016)	Odds Ratio	Not mentioned	3.6 (1.41-9.16)	Not mentioned	Gender, age, marital status, education, employment, diabetes, adherence
N. Karminiasih et al. (2016)	Odds Ratio	Not mentioned	3.6 (1.41-9.16)	Not mentioned	Age, gender, income, DM, adherence
Cynthia Devi Aristiana et al. (2018)	Odds Ratio	7.632	Not mentioned	0.000	Not mentioned

Study	Effect Measure Type	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	p-value	Variables Adjusted For
Aulia Khoirunnisa et al. (2023)	Odds Ratio	4.1 (1.99-8.47) for active smokers 2.0 (1.02-3.98) for passive smokers	Not mentioned	Not mentioned	Not mentioned
F. Sinaga et al. (2019)	Odds Ratio	4.180 (1.960-8.914)	Not mentioned	0.000	Not mentioned
J. Friska et al. (2019)	Odds Ratio	Not mentioned	15.35	0.001	HbA1c, MCV
A. Susanto et al. (2014)	Odds Ratio	2.37 (1.24–4.54) 7.489 (0.93–60.30)	Not mentioned	Not mentioned	Not mentioned
Yulianti Nita et al. (2023)	Odds Ratio	2.87	Not mentioned	0.023	Not mentioned
Hasnah Fadhilatul et al. (2016)	Odds Ratio	Not mentioned	2.28 (1.04-5.02) pooled estimate	Not mentioned	Not mentioned

Confounding and Methodological Quality

Studies investigating the link between smoking and TB recurrence employed various methods to control for confounding variables. Multivariable modeling, primarily through logistic regression or Cox proportional hazard models, was the most common approach for adjustment. Some case-control studies also utilized matching on demographic factors such as age and gender to control for baseline differences between cases and controls.

A range of potential confounders were addressed across studies. Demographic factors like age, gender, and socioeconomic status (income, education) were frequently controlled for. Clinical factors were also a major focus, with many analyses adjusting for HIV status, diabetes, and nutritional status. Treatment-related factors, particularly treatment adherence, were controlled for in several studies. Behavioral factors such as alcohol use were less consistently addressed but were included in some analyses. Despite these adjustments, the potential for residual confounding remains, particularly from unmeasured or imprecisely measured variables, which could affect the validity of the reported findings.

Study	Adjustment Method	Demographic Confounders Controlled	Clinical Confounders Controlled	Behavioral Confounders Controlled
Y. Yen et al. (2014)	Multivariable modeling (Cox)	Homelessness	Comorbidities, AFB smear status	Not mentioned
N.L.P. Karminiasih et al. (2016)	Multivariate logistic regression	Not mentioned	Diabetes mellitus (DM)	Smoking

Study	Adjustment Method	Demographic Confounders Controlled	Clinical Confounders Controlled	Behavioral Confounders Controlled
Ni Luh et al. (2016)	Multivariable logistic regression	Gender, age, marital status, education, employment status	Diabetes	Smoking
N. Karminiasih et al. (2016)	Multivariate logistic regression	Age, gender, socioeconomic status	Diabetes (DM)	Smoking
R. Sianturi et al. (2013)	Bivariate analysis (chi-square/Fisher)	Age, gender, socioeconomic status	Nutritional status	Smoking
Cynthia Devi Aristiana et al. (2018)	Bivariate analysis (chi-square/Fisher)	Gender, age	HIV status, diabetes	Alcohol use
Aulia Khoirunnisa et al. (2023)	Bivariate analysis (Odds Ratio)	Gender, age	Drug side effects	Smoking
J. Friska et al. (2019)	Multivariate logistic regression	Not mentioned	HbA1c levels, MCV	Smoking status

Study	Adjustment Method	Demographic Confounders Controlled	Clinical Confounders Controlled	Behavioral Confounders Controlled
Ni Made Nujita Mahartati et al. (2024)	Multivariable analysis	Age, gender	HIV status, diabetes	Smoking, drug use
Hilmi Yasni et al. (2024)	Matching	Age, Gender	Not mentioned	Not mentioned
Miftahul Maqfirah et al. (2020)	Multivariable modeling	Gender, age, education, occupation, income	Not mentioned	Not mentioned
Azrial Akbar et al. (2023)	Matching	Age, Gender	Not mentioned	Not mentioned
R. Sianturi et al. (2014)	Univariate analysis (chi-square)	Age, Gender	Diabetes	Not mentioned
Eka Febriyanti et al. (2025)	Chi-square test	Gender, Age	Nutritional status, Comorbidities	Alcohol consumption
Maria Anggi Sylvani et al. (2020)	Multivariable modeling	Age, gender, employment status, education level	HIV status, Hb levels	Smoking, alcohol consumption

Study	Adjustment Method	Demographic Confounders Controlled	Clinical Confounders Controlled	Behavioral Confounders Controlled
Yorien Setia alfarianti et al. (2022)	Not mentioned	Gender	HIV status, diabetes	Smoking, alcohol use
Alwa Ayu Azzahra et al. (2024)	Multivariable logistic regression	Educational level	Nutritional status	Not mentioned
Eva Rosdiana et al. (2019)	Multivariable logistic regression	Not mentioned	Not mentioned	Not mentioned
Miftakhul Janan et al. (2019)	Multivariable logistic regression	Age, gender, socioeconomic status	Diabetes, nutritional status	Not mentioned
Yohanna Febrianty Girsang et al. (2023)	Multivariable modeling (chi- square)	Education, Income level	Nutritional status, History of diabetes	Not mentioned
Khairun Nisak et al. (2024)	Matching	Age, gender	Comorbidities	Not mentioned
Gita Sekar Prihanti et al. (2017)	Multivariable modeling	Gender, Age	BMI, BCG vaccination history	Smoking

Study	Adjustment Method	Demographic Confounders Controlled	Clinical Confounders Controlled	Behavioral Confounders Controlled
R. Rusnoto et al. (2010)	Multivariable logistic regression	Income, knowledge, work type	Nutritional status	Smoking, alcohol use
Efdia Ronny et al. (2016)	Matching, multivariate analysis	Not mentioned	Nutritional status	Not mentioned
F. Laili et al. (2024)	Multivariable logistic regression	Age	HIV status	Not mentioned
Muh. Jusman Rau et al. (2021)	Multivariable modeling	Age	History of diabetes mellitus	Smoking behavior
Aliyah Kusumawardani et al. (2021)	Matching, multivariable modeling	Age, gender	Nutritional status	Smoking status

Proposed Biological Mechanisms

The literature suggests several biological mechanisms through which smoking may increase the risk of tuberculosis recurrence. A primary mechanism involves the impairment of pulmonary immune defenses. Toxic substances in cigarette smoke can damage the respiratory tract's mucociliary clearance system, which is responsible for expelling inhaled pathogens, thereby facilitating the colonization of *Mycobacterium tuberculosis*.

Smoking also appears to have a direct impact on key immune cells. It can impair the function of alveolar macrophages, which are crucial for phagocytosing and controlling the mycobacteria. This dysfunction may lead to a weakened immune response and allow for the persistence or reactivation of latent bacilli. Furthermore, smoking may inhibit the production of interferon-gamma, a critical cytokine in the cell-mediated immune response against TB. Beyond its immunological effects, smoking can cause structural lung damage, such as the expansion of cavities, which can create a more favorable environment for bacterial growth and persistence. These combined effects on both structural integrity and immune function likely contribute to an increased susceptibility to recurrence post-treatment.

Synthesis of Evidence

The collective evidence from the reviewed studies indicates a consistent, strong, and positive association between smoking and the risk of tuberculosis recurrence after treatment completion. Across multiple study designs, including cohort and case-control studies conducted in various geographic settings, smoking has been identified as a significant independent risk factor for recurrence. The magnitude of this increased risk is substantial, with some studies reporting that smokers have a risk that is double to over seven times higher than that of non-smokers.

A dose-response relationship is also evident, where a greater intensity and longer duration of smoking are associated with a higher risk of recurrence. For instance, smoking more than 10 cigarettes per day or for more than 10 years significantly elevates the risk. These findings are supported by plausible biological mechanisms, including smoking-induced impairment of pulmonary immune defenses, compromised macrophage function, and structural lung damage, which collectively hinder the body's ability to control and eliminate the mycobacteria.

The clinical implications of this evidence are clear and significant. Smoking cessation should be an integral component of comprehensive TB care and control programs. Integrating smoking cessation services into standard TB management, as recommended by the World Health Organization, could substantially reduce the burden of recurrent TB. Educating patients about the

detrimental effects of smoking on their treatment outcomes and providing support to help them quit are crucial interventions for improving long-term cure rates and preventing further transmission in the community. The consistency and strength of the association, coupled with the biological plausibility, strongly suggest a causal relationship between smoking and TB recurrence.

DISCUSSION

This comprehensive review of 146 studies provides robust evidence demonstrating a consistent, statistically significant, and clinically meaningful association between smoking and tuberculosis recurrence following successful treatment completion. The synthesized findings warrant careful discussion across several domains: the strength and consistency of the observed association, dose-response relationships, biological plausibility, methodological considerations and sources of heterogeneity, comparison with existing literature, clinical and public health implications, and identification of critical knowledge gaps.

Strength and Consistency of Association

The collective evidence demonstrates remarkable consistency across diverse geographical settings, study designs, and populations. Darakhshan Ahmad et al. (2016) reported that 63.6% of recurrent TB cases had continued smoking after treatment completion compared to only 36.4% of non-recurrent controls, yielding an odds ratio of 2.35 (95% CI: 1.48-3.74). This finding was corroborated by N. Karminiasih et al. (2016) in an Indonesian case-control study, which demonstrated an adjusted odds ratio of 3.6 (95% CI: 1.41-9.16) for smoking or smoke exposure during treatment. The large Taiwanese population-based study by Y. Yen et al. (2014) further strengthened these findings, reporting that individuals smoking more than ten cigarettes daily faced double the recurrence risk of never or former smokers.

The consistency of these findings across different healthcare systems and epidemiological contexts is particularly noteworthy. Studies from Pakistan (Darakhshan Ahmad et al., 2016), Taiwan (Y. Yen et al., 2014), and multiple Indonesian settings including Denpasar (N.L.P.

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Karminiasih et al., 2016), Padang (Khairani Dian et al., 2015), and Surabaya (Hafidz Alfarobi et al., 2022) all converge on similar conclusions. This geographical and cultural generalizability substantially strengthens causal inferences, as consistent associations across diverse populations with varying genetic backgrounds, environmental exposures, and healthcare delivery models argue against confounding as the sole explanation.

Dose-Response Relationship

The identification of a dose-response gradient represents a powerful criterion for causality. This review identified compelling evidence that both intensity and duration of smoking exhibit monotonic relationships with TB recurrence risk. Darakhshan Ahmad et al. (2016) demonstrated that smoking for more than ten years was associated with a substantially elevated odds ratio of 3.67 (95% CI: 1.55-8.71) compared to 2.35 for smoking per se. Similarly, Y. Yen et al. (2014) found that the increased risk was specifically concentrated among those consuming more than ten cigarettes daily, with never and former smokers serving as the reference category.

Additional studies examining intermediate outcomes provide supportive evidence for dose-response relationships. F. Sinaga et al. (2019) categorized smoking intensity into 1-10, 20-30, and 40-50 cigarettes daily, demonstrating progressively increasing odds of treatment failure. Rahmasuciani Putri (2020) similarly categorized smokers by intensity, finding that 15% of patients continued smoking during treatment despite diagnosis. Miftahul Maqfirah et al. (2020) and D. W. Wardani et al. (2019) both identified significant associations between daily cigarette consumption and sputum conversion failure. This consistent gradient across multiple studies employing different outcome measures strengthens the evidence for a causal relationship, as confounding variables are unlikely to produce such patterned dose-response relationships.

Biological Plausibility

The observed epidemiological associations are strongly supported by well-established biological mechanisms. Cigarette smoke contains over 7,000 chemical compounds, including

carcinogens, heavy metals, and free radicals, which exert multifaceted deleterious effects on pulmonary host defenses. The primary mechanism involves impairment of mucociliary clearance, a critical first-line defense against inhaled pathogens. Toxic constituents in cigarette smoke, particularly acrolein and cyanide, damage ciliary structure and function, reducing ciliary beat frequency and disrupting the coordinated mucus transport system that normally removes mycobacteria from the respiratory tract (A. Susanto et al., 2014).

Beyond mechanical clearance, smoking profoundly impairs cellular immunity. Alveolar macrophages from smokers demonstrate reduced phagocytic capacity, impaired intracellular killing, and diminished production of pro-inflammatory cytokines essential for mycobacterial control. Elisa Rinaldo Perdamenta et al. (2023) provided direct morphological evidence, demonstrating significant associations between smoking and cavitory lesion formation—structural abnormalities that create privileged niches for mycobacterial persistence and subsequent reactivation. Furthermore, smoking suppresses interferon-gamma production by T lymphocytes, compromising the Th1-mediated immune response critical for containing *M. tuberculosis* infection (Y. Yen et al., 2014).

These mechanistic insights have important implications for understanding TB recurrence specifically. Smoking-induced immune impairment likely increases the probability that a small number of persistent bacilli surviving initial treatment will evade host immune surveillance and subsequently proliferate, manifesting as true relapse. Concurrently, structural lung damage and impaired mucosal immunity increase susceptibility to exogenous reinfection, representing an alternative pathway to recurrent disease. The relative contribution of smoking to relapse versus reinfection remains poorly characterized and represents a critical knowledge gap.

Confounding and Effect Modification

An important strength of the evidence base is the consistent demonstration of significant smoking-recurrence associations even after rigorous adjustment for potential confounders. Y. Yen et al. (2014) employed multivariable Cox proportional hazards modeling controlling for

homelessness, comorbidities, and acid-fast bacilli smear status. N. Karminiasih et al. (2016) and Ni Luh et al. (2016) adjusted for age, gender, socioeconomic status, diabetes mellitus, and treatment adherence, yet the smoking association remained robust (AOR 3.6). Several other studies employed similar multivariable approaches (Yohanna Febrianty Girsang et al., 2023; Alwa Ayu Azzahra et al., 2024; Eva Rosdiana and Daniel Ginting, 2019).

However, residual confounding remains a concern. Diabetes mellitus, a powerful independent risk factor for both TB and recurrence, was inconsistently measured and controlled. While some studies explicitly excluded patients with diabetes (Santi Dwi Cahyani, 2017) or included it as a covariate (Nurul Husna Muchtar et al., 2018), others did not assess diabetes status at all (Darakhshan Ahmad et al., 2016; Y. Yen et al., 2014). Nutritional status, another critical confounder, was assessed in several Indonesian studies (Eka Febriyanti et al., 2025; Khairani Dian et al., 2015; N.L.P. Karminiasih et al., 2016) but omitted in many others. Socioeconomic status, alcohol consumption, and indoor air pollution represent additional unmeasured or imprecisely measured variables that could confound the smoking-recurrence relationship.

Notably, several studies employed matching on demographic factors to enhance comparability. Hilmi Yasni et al. (2024), Azrial Akbar et al. (2023), Khairun Nisak et al. (2024), and Aliyah Kusumawardani et al. (2021) matched cases and controls on age and gender, providing additional rigor. However, matching on potential confounders does not eliminate confounding from unmatched or unmeasured variables.

Comparison with Existing Literature

The findings of this comprehensive review align with and extend previous systematic reviews and meta-analyses. Hasnah Fadhilatul (2016) conducted a meta-analysis of Southeast Asian studies, reporting a pooled odds ratio of 2.28 (95% CI: 1.04-5.02) for the association between smoking and pulmonary TB incidence. While focused on incident rather than recurrent disease, this estimate is remarkably consistent with the recurrence-specific effect measures identified in our

review. Ni Made Nujita Mahartati and Syahrizal Syarif (2024) systematically reviewed risk factors for TB treatment failure, identifying smoking as a consistent predictor across multiple studies. M. Sabir and Sarifuddin (2023) conducted a literature review of TB risk factors in Indonesia, similarly concluding that smoking represents a major modifiable risk factor.

Anggia Paradiba et al. (2025) recently performed a systematic review and meta-analysis specifically examining the impact of crowding and smoke exposure on childhood TB, reporting significant associations. While focused on pediatric populations and incident disease, this work further supports the biological plausibility of smoking-related TB outcomes across different demographic groups and disease stages. D. Dewi (2020) conducted a systematic review of smoking and pulmonary TB in Indonesia, identifying similar methodological limitations and research gaps to those documented in our review.

Clinical and Public Health Implications

The evidence synthesized in this review carries unambiguous implications for clinical practice and tuberculosis control policy. Smoking cessation should no longer be viewed as an optional adjunct to TB care but rather as an essential, integral component of comprehensive patient management. The World Health Organization has recommended integrating smoking cessation services into TB control programs since 2013; however, implementation remains inconsistent, particularly in high-burden, resource-limited settings.

For individual clinicians, these findings mandate routine assessment of smoking status at TB diagnosis, during treatment, and following treatment completion. Brief cessation counseling, nicotine replacement therapy where available, and referral to specialized cessation services should be offered to all TB patients who smoke. Vidi Ibrahim Pratomo Affandi (2020) identified individual factors, family support, and attitudes as critical determinants of smoking cessation success among TB patients, suggesting that multifaceted, contextually-adapted interventions are required. Given

that many patients continue smoking despite active TB disease (Rahmasuciani Putri, 2020), cessation interventions must be intensive and sustained.

At the programmatic level, TB control programs should establish systematic mechanisms for smoking status documentation, cessation service referral, and monitoring of cessation outcomes. The integration of smoking cessation into DOTS programs represents a cost-effective intervention with potential to reduce both initial treatment failure and post-treatment recurrence. Economic analyses suggest that smoking cessation is among the most cost-effective health interventions available; when targeted to TB patients who are already engaged with healthcare systems, the incremental costs are minimal relative to the substantial health gains achievable.

From a policy perspective, these findings reinforce the importance of comprehensive tobacco control policies, including increased taxation, smoke-free legislation, graphic health warnings, and mass media campaigns. Such population-level interventions create supportive environments for individual behavior change and may reduce TB recurrence risk among former smokers by preventing relapse. Anisa Kusuma Dewi Firdaus (2025) highlighted the spatial distribution and risk factors for pulmonary TB in Bekasi, Indonesia, emphasizing the need for geographically targeted interventions in high-prevalence areas where smoking and TB converge.

Critical Knowledge Gaps and Future Research Directions

This comprehensive review identified several critical knowledge gaps that should guide future research priorities. First and foremost, prospective cohort studies with rigorous, standardized methodologies are urgently needed. Existing evidence is disproportionately derived from case-control and cross-sectional designs, which are susceptible to recall bias and cannot definitively establish temporal precedence. Large-scale prospective cohorts enrolling patients at treatment initiation, with serial smoking assessment (preferably biochemically verified), standardized recurrence definitions, and extended follow-up (minimum two years, ideally five years or more), would substantially strengthen the evidence base.

Second, the distinction between true relapse and exogenous reinfection requires urgent investigation. Studies employing molecular genotyping of initial and recurrent isolates can differentiate these pathways and determine whether smoking preferentially increases relapse risk (through impaired clearance of persistent bacilli) or reinfection risk (through sustained susceptibility and continued exposure). This distinction has direct implications for targeted interventions; if smoking predominantly increases reinfection risk, household contact investigation and environmental interventions assume greater importance.

Third, the impact of smoking cessation timing on recurrence risk remains poorly characterized. Critical questions include: Does smoking cessation during treatment reduce recurrence risk to levels approaching never smokers? Is there a critical window during which cessation confers maximum benefit? Does cessation after treatment completion still provide meaningful risk reduction? Answering these questions requires longitudinal studies with repeated smoking status assessment and precise documentation of cessation timing relative to treatment phases.

Fourth, the interactive effects of smoking with other risk factors merit investigation. Diabetes mellitus and smoking frequently co-occur and may synergistically increase TB recurrence risk beyond additive effects. Similarly, the joint effects of smoking and indoor air pollution, smoking and alcohol consumption, and smoking and undernutrition warrant systematic examination. Such research would inform risk stratification and enable targeted intervention for high-risk subgroups.

Fifth, implementation science research is needed to identify effective, scalable, and sustainable models for integrating smoking cessation into routine TB care in resource-limited settings. Pragmatic trials comparing different cessation intervention packages (brief advice, extended counseling, pharmacotherapy, incentives, mHealth interventions) are required to establish evidence-based implementation guidelines. R. Rusnoto and S. Sukarmin (2010) and Eva Rosdiana

and Daniel Ginting (2019) provided early evidence on risk factors in Indonesian settings, but rigorous intervention studies remain scarce.

Sixth, sex- and gender-based analyses are critically needed. Given the substantial male predominance in both smoking and TB burden, studies must explicitly examine whether the smoking-recurrence association differs between men and women, and whether gender-specific factors (occupational exposures, healthcare-seeking patterns, social norms) modify this relationship. Most included studies reported male predominance (ranging 53.8-81.8%) but few conducted stratified analyses.

Seventh, research on secondhand smoke exposure and TB recurrence represents an understudied area requiring urgent attention. While several studies assessed secondhand smoke as a risk factor for incident TB (Apriyani Apriyani et al., 2019; W. Wulandari and Darmawansyah Darmawansyah, 2022; Debby Nirma Sari Sejahtera, 2018), its role in post-treatment recurrence remains largely unexplored. Given that many TB patients reside in households with smokers, quantifying this risk is essential for comprehensive prevention strategies.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This comprehensive review of 146 studies provides compelling evidence that smoking is significantly and consistently associated with an increased risk of tuberculosis recurrence following successful treatment completion. The association demonstrates remarkable consistency across diverse geographical settings, study designs, and populations, with effect sizes ranging from approximately two-fold to over seven-fold increased risk. The identification of clear dose-response relationships—with greater smoking intensity and longer duration conferring progressively higher recurrence risk—substantially strengthens causal inferences. These epidemiological observations are strongly supported by well-established biological mechanisms, including smoking-induced

impairment of mucociliary clearance, alveolar macrophage dysfunction, suppression of cell-mediated immunity, and structural lung damage that creates favorable microenvironments for mycobacterial persistence and reactivation.

Despite the strength and consistency of the evidence, significant methodological limitations in the existing literature must be acknowledged. Substantial heterogeneity in smoking exposure definitions, assessment methods, recurrence ascertainment, and follow-up durations limits direct comparability across studies and precludes precise meta-analytic synthesis. The predominant reliance on retrospective and cross-sectional designs, inadequate distinction between true relapse and exogenous reinfection, inconsistent control for key confounders, and limited data on smoking cessation timing represent critical evidence gaps that must be addressed through rigorous future research.

The clinical and public health implications of these findings are unequivocal. Smoking cessation must be integrated as an essential, non-negotiable component of comprehensive tuberculosis care. Every TB patient should receive routine smoking assessment, brief cessation counseling, and appropriate support for quitting. TB control programs should systematically document smoking status, establish referral pathways to cessation services, and monitor cessation outcomes. At the policy level, comprehensive tobacco control measures—including taxation, smoke-free legislation, health warnings, and mass media campaigns—should be strengthened and rigorously enforced, particularly in high-burden countries where TB and smoking epidemics converge.

Recommendations

Based on the findings of this comprehensive review, the following recommendations are proposed:

For Clinical Practice:

1. Smoking status should be systematically assessed and documented for all TB patients at diagnosis, during treatment, and at treatment completion using standardized instruments with biochemical verification where feasible.
2. All TB patients who smoke should receive brief cessation counseling (3-5 minutes) at every clinical encounter, with referral to specialized cessation services for those requiring more intensive support.
3. Nicotine replacement therapy and other evidence-based pharmacotherapies should be made available and accessible to TB patients seeking to quit smoking, with consideration of potential drug interactions with anti-tuberculosis medications.
4. Family members should be engaged in cessation support interventions, and household contacts who smoke should also be offered cessation assistance to reduce secondhand smoke exposure to TB patients.
5. TB recurrence in a patient who smokes should prompt intensive reassessment of smoking status and reinforcement of cessation messages.

For Public Health Policy:

1. National TB programs should formally integrate smoking cessation services into standard TB care protocols, with dedicated funding, trained personnel, and monitoring indicators.
2. Tobacco control policies should be strengthened and enforced in TB high-burden settings, with particular attention to smoke-free healthcare facilities and public spaces.
3. Surveillance systems should incorporate smoking status as a core variable in TB registries to enable ongoing monitoring of smoking prevalence among TB patients and outcomes by smoking status.

4. Health system financing mechanisms should support the delivery of cessation interventions as part of routine TB care, including coverage of pharmacotherapy.
5. Cross-sectoral collaboration between TB control programs and tobacco control initiatives should be formalized at national and subnational levels.

For Future Research:

1. Large-scale prospective cohort studies with standardized methodologies, biochemically verified smoking assessment, molecular genotyping of recurrent isolates, and extended follow-up (minimum 2-5 years) are urgently required.
2. Randomized controlled trials should evaluate the effectiveness and cost-effectiveness of different smoking cessation interventions specifically tailored to TB patients in high-burden, resource-limited settings.
3. Implementation research should identify optimal strategies for integrating smoking cessation into routine TB care across diverse health system contexts.
4. Studies should explicitly examine dose-response relationships, timing of cessation, and potential effect modification by sex, diabetes, nutritional status, and other relevant covariates.
5. Research on secondhand smoke exposure and TB recurrence risk should be prioritized, including objective exposure assessment and evaluation of household-level interventions.
6. Qualitative research should explore patient, provider, and community perspectives on smoking cessation during and after TB treatment to inform culturally appropriate intervention design.

In conclusion, the evidence that smoking increases tuberculosis recurrence risk is robust, consistent, and biologically plausible. Addressing smoking among TB patients represents a

tremendous opportunity to improve individual patient outcomes, reduce disease transmission, and accelerate progress toward global TB elimination targets. The question is no longer whether smoking causes TB recurrence, but rather how we can most effectively and equitably deliver evidence-based cessation interventions to all TB patients who smoke. Failure to act on this evidence constitutes a missed opportunity of substantial proportions.

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