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The association between secondhand smoke exposure and risk of developing active tuberculosis in individuals with latent tuberculosis infection: a systematic literature review

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Keywords: Active tuberculosis; secondhand smoke; latent tuberculosis infection
Parole Chiave: Tubercolosi attiva; fumo passivo; infezione tubercolare latente

Abstract

Background. *Tuberculosis is one of the leading causes of death from infectious diseases in the world, with approximately 25% of the global population having latent tuberculosis infection. Secondhand smoke exposure has been recognised as a significant risk factor in the development of active Tuberculosis in individuals with latent tuberculosis infection.*
Study Design and Methods. *This study used the Systematic Literature Review method based on PRISMA guidelines. Relevant articles published between 2014-2024 were identified through PubMed, ProQuest, and Scopus databases using related keywords. A total of 13 articles met the inclusion criteria for analysis.*
Results. *Secondhand smoke exposure significantly increases the risk of latent tuberculosis infection conversion to active Tuberculosis, with a stronger effect in vulnerable groups such as children and individuals who are in close contact with active Tuberculosis patient and live in the same household with heavy smokers. This risk of exposure to secondhand smoke follows a dose-response pattern, where longer duration and higher intensity of exposure directly increase the likelihood of Tuberculosis activation in individuals with latent tuberculosis infection. The biological mechanisms involve immune suppression and lung damage caused by toxic particles in the tobacco smoke, which weaken the body's defenses against Mycobacterium tuberculosis and facilitate the progression of latent tuberculosis infection to active Tuberculosis. Therefore, reducing exposure to secondhand smoke is important to mitigate its impact on active Tuberculosis progression.*
Conclusion. *Secondhand smoke exposure has been consistently shown to increase the risk of developing active Tuberculosis in individuals with latent tuberculosis infection. To support the global Tuberculosis elimination programme, concerted efforts are needed to reduce exposure to secondhand smoke, especially in individuals with latent tuberculosis infection.*

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Introduction

As one of the most common infectious disease related causes of mortality worldwide, tuberculosis (TB) disease is a condition that people are very concerned about. Annually, millions people around the world die because of TB. From 2020 to 2023, the World Health Organization (WHO) reported fluctuations in the global TB burden. In 2023, more than 10 million people were infected with TB worldwide, and TB-related deaths remained alarmingly high, underscoring the urgent need for sustained global efforts to combat this epidemic (1-4). The rapid transmission of TB, the emergence of drug-resistant TB strains, that are difficult to treat and require longer management, as well as the health impacts such as morbidity and mortality, and economic impacts like poverty, underscore the urgency of addressing the TB epidemic immediately. In 2024, the World Health Organization (WHO) established *"The WHO End TB Strategy"* with the aim of reducing TB fatalities by 90% and TB incidence by 80% by 2030. Consequently, this disease has become a significant indicator for the success of the Sustainable Development Goals (SDGs), as it aligns with several primary SDGs objectives, including good health and well-being, no poverty, and reduced inequality. The establishment of this WHO strategy aims to reduce the burden of TB, ensuring that the target to end the tuberculosis epidemic worldwide by 2030 can be achieved in both developed and developing countries (5).

TB remains a major global health challenge, affecting millions of people each year. While not everyone exposed to TB bacteria develops active disease, certain groups are at a higher risk of progression. Among these, individuals with Latent Tuberculosis Infection (LTBI) represent a population at significant risk of developing to active TB. LTBI occurs when people infected with *Mycobacterium tuberculosis* have not yet exhibited symptoms for active TB (6). According to WHO, nearly 25% of the global population (1.7 billion people) have LTBI, and approximately 10% of those with LTBI will develop active TB during lifetime. The majority of these cases occur within the first five years after the initial infection. LTBI serves as the primary reservoir for the future development of active TB. The risk of progression increases significantly in certain groups, particularly those with compromised immune systems, including individuals living with HIV/AIDS (7). A review of 11 studies conducted in Southeast Asia found that 24.4% to 69.2% children under 15 years old, who were in close contact with individuals with active TB, became infected. Of those, 3.3% to 5.5% evolved to active TB (8).

Many factors increase a person's risk of becoming infected with TB, including exposure to the TB germ itself. Additionally, environmental factors, such as secondhand smoke exposure, can significantly contribute to the progression of LTBI into active TB (9,10). Smokers have twice the risk of developing TB compared to non-smokers. In passive smokers (individuals exposed to secondhand smoke), this risk is even 4.5 times greater compared to people who are not exposed to secondhand smoke (11). According to WHO, tobacco use is responsible for 17.6% of tuberculosis cases, highlighting the substantial impact of smoking on TB incidence globally. This alarming statistic underscores the substantial impact of tobacco on the TB epidemic (12,13). Meanwhile, according to the latest update data from *Global Tobacco Control*, approximately 1.3 billion people globally are active smokers, with 80% of them residing in low and middle income countries. The growth of the global population has contributed to higher smoking rates. Consequently, 8 million people worldwide have died from active smoking, while 1.2 million people have died due to exposure to secondhand smoke (14).

Another significant challenge in the fight against TB is the rise of multidrug-resistant tuberculosis (MDR-TB). MDR-TB occurs when the tuberculosis bacteria become resistant to at least two of the most effective anti-TB drugs, isoniazid and rifampicin. This form of TB requires longer, more complex treatment regimens, which can lead to higher treatment failure rates, prolonged infectious periods, and greater economic burden. Addressing the growing problem of MDR-TB is critical in achieving the global goal to end the TB epidemic by 2030. Meanwhile, tobacco use, a major risk factor for TB, further complicates the situation by increasing the likelihood of developing drug-resistant forms of the disease. Both active and passive smokers are more vulnerable to MDR-TB due to the exposure to tobacco smoke, which significantly contributes to the challenges in treating TB patients (12).

Tuberculosis and smoking are two "colliding epidemics" in public health issues and both of them very important to discuss. These problems contribute deaths every year, particularly in countries with high burden of TB and among populations with high use of tobacco. Both active and passive smoking are recognized as factors to increase risk of tuberculosis. While considerable research has explored the

association between secondhand smoke exposure and tuberculosis risk, there is still limited evidence and consensus on whether passive smoking increases the likelihood of progression to active tuberculosis in individuals with latent tuberculosis infection. This systematic literature review aims to explore and analyze the association between secondhand smoke exposure and risk of developing active tuberculosis in individuals with latent tuberculosis infection.

Methods

This study used the *Systematic Literature Review (SLR)* method and followed the guidelines of *Preferred Reporting Items for Systematic Reviews and Meta Analysis*.

Population, intervention, comparison, and outcome (PICO) formula was determined based on the formulation of the problem and the research question.

Identification of relevant journals was conducted through a comprehensive searchig on verified scientific search engines such as *PubMed, ProQuest*, and *Scopus* using the main keywords *"latent tuberculosis infection", "secondhand smoke", "tobacco smoke pollution"* and *"active tuberculosis"*. The journal search was limited to English-language academic journal articles published in the last 10 years, i.e. in 2014-2024 publications. The inclusion criteria used in this literature search were population-based studies in patients with latent tuberculosis infection, populations exposed to secondhand smoke and populations never exposed to secondhand smoke, population experiencing deterioration into active tuberculosis, and original research studies. Furthermore, the exclusion criteria in this study were articles that did not address the key topics of active tuberculosis (active TB), latent tuberculosis infection (LTBI), or secondhand smoke exposure, as these articles were deemed irrelevant to the PICO framework used in this systematic review.

The article search was conducted in stages through the process of identification, screening, eligibility, and synthesis of articles that were declared included (according to the criteria). A total of 471 articles were identified at the first stage (article identification). 39 duplicate articles were excluded before the screening process was carried out, so that there were 432 articles ready for screening and 392 articles excluded because they did not address to the key topics or the topics were irrelevant to the PICO for this study. After screening the title, abstract, and full text based on PICO, 40 articles entered the process of agreement test (kappa test) and feasibility test (we used the JBI Critical Appraisal Checklist for Quantitative Research). On this stage, 17 articles were excluded because not in accordance with the PICOS and 10 further articles were excluded because not eligible. After all the tests were concluded, 13 articles met the inclusion criteria for extraction as outlined in the PRISMA flowchart.

Table 1 - Inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Source	Pubmed, ProQuest, Scopus	Other databases
Year	2014-2024	Studies published before or after this period
Language	English	Other languages
Population (P)	Individuals with Latent Tuberculosis Infection (LTBI)	Individuals with other health condition
Intervention (I)	Secondhand Smoke (SHS)	Another indoor air pollution or other interventions
Comparative (C)	Exposure and without exposure to Secondhand Smoke	Other
Outcome (O)	Active Tuberculosis (TB)	Extra-pulmonary TB
Study type (S)	Original Research : cross sectional, case control, or cohort study	Study Review, Meta-Analysis, or Qualitative Study
Type of Publication	Academic Journal, open access, free, and published in the field of Public Health	Other publication (conference abstract), and paid

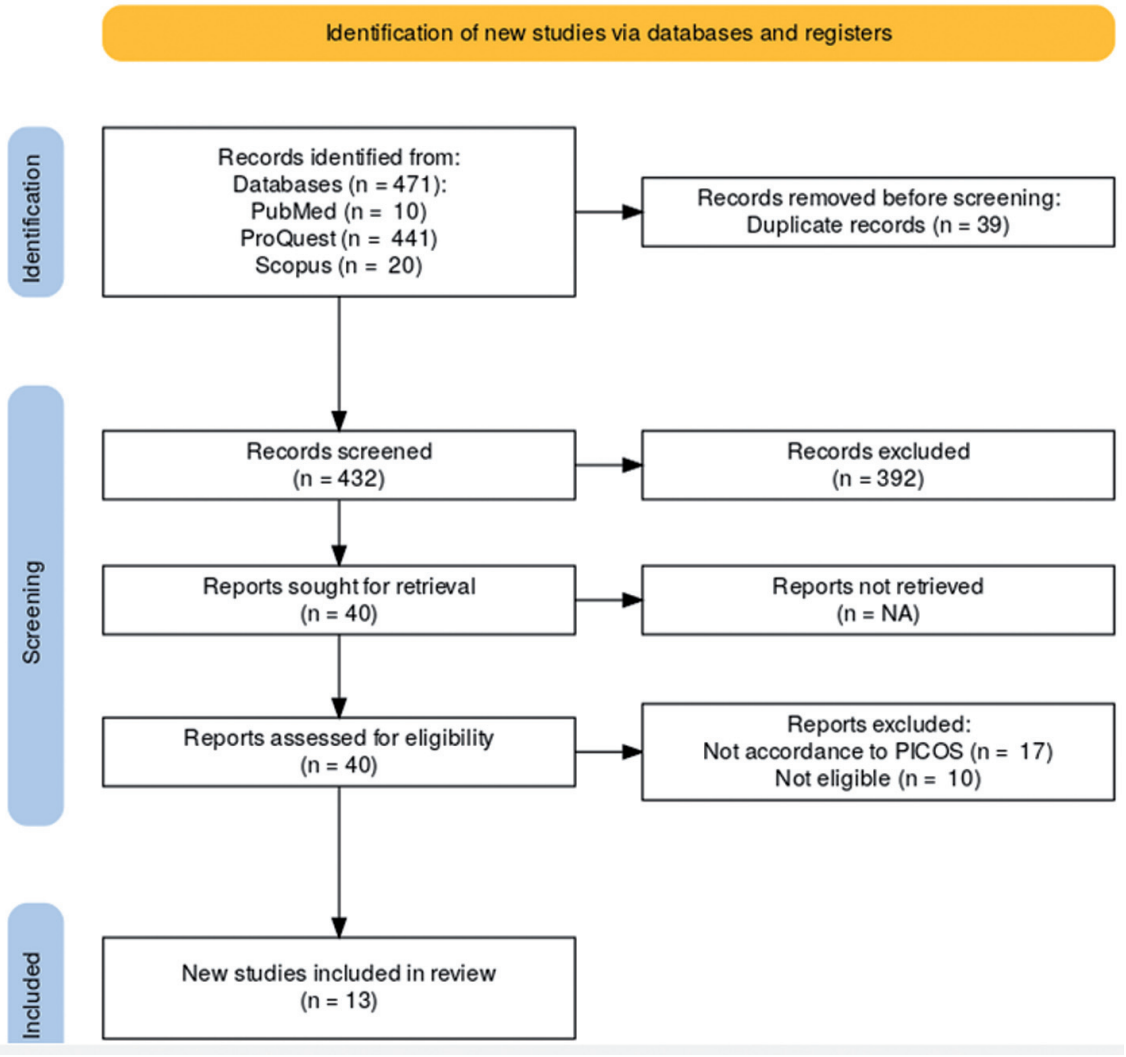

Figure 1 - PRISMA Flowchart of the bibliographic research

Results

On the basis of the table of data extraction results from the article review above, related to secondhand smoke exposure to the incidence of tuberculosis, of the 13 studies reviewed there were 6 studies with cross sectional study design, 4 studies with case control study design, and 3 studies with cohort study design. The studies were conducted both in developed countries such as the United States, California, Singapore, Spain and several developing countries such as Vietnam, Mongolia, Ethiopia, India and Pakistan that have a high burden of tuberculosis. The studies spanned the years 2014-2024 with samples ranging from paediatric to adult populations.

Findings

From the review of 13 articles, it was found that most studies identified an association between exposure to secondhand smoke and the risk of developing active TB in individuals with LTBI. A study by Burusie et al. (15) in Ethiopia revealed that household exposure to secondhand smoke increased the risk of developing active TB in children with LTBI by 3.15 times (95% CI: 1.07–9.27). This underscores that tobacco smoke exposure within the home is a significant risk factor. Kim et al. (16), through a cross-country study conducted in eight high TB burden countries, found that household exposure to secondhand smoke increased the prevalence of LTBI (aOR = 1.6; 95% CI: 1.2–2.5) and increased the risk

Table 2 - Data extraction from included studies

Author	Year	Title	Country	Method	Sample/Population	Results
Burusie Abay et al (15)	2024	Determinants of tuberculosis disease development in children in central Ethiopia: A matched case-control study	Central Ethiopia	Matched Case Control	256 cases of children diagnosed TB (pulmonary and extra-pulmonary TB). 256 controls, children without TB. Matching 1:1 based on age and study facility. Recruitment was conducted in health facilities in Ethiopia.	Household exposure to secondhand smoke increased risk of developing TB (aOR = 3.15; 95% CI: 1.07-9.27). The findings indicated a link between secondhand smoke exposure and an increased risk of active tuberculosis in children.
Kim Soyeon et al (16)	2023	Factors associated with prevalent *Mycobacterium tuberculosis* infection and disease among adolescents and adults exposed to rifampin-resistant tuberculosis in the household	Botswana, Brazil, Haiti, India Kenya, Peru, South Africa, and Thailand	Cross Sectional	712 HHCs aged ≥15 years from 279 households 63% female, 22% active smokers, 8% HIV positive.	Exposure to secondhand smoke within household significantly raises the risk of developing active TB. This exposure linked to a higher prevalence of TB infection with an adjusted OR (aOR = 1.6; 95% CI: 1.2-2.5). Individuals with history of smoking exhibited an elevated risk of active TB (aOR = 2.9 for current smokers and aOR = 4.2 for former smokers).
Kuma Diriba and Gemechu Churiso (17)	2022	The prevalence of *Mycobacterium tuberculosis* using Gene Xpert among tuberculosis suspected patients in Gedeo Zone, Southern Ethiopia	Southern Ethiopia	Cross Sectional	384 TB suspect patients in Gedeo Zone Ethiopia, aged ≥18 years. 20.8% of patients were smokers.	Exposure to secondhand smoke may increase risk of active TB (aOR 2.89; 95% CI: 2.10-3.84). Other significant risk factors were close contact with TB patients (aOR 3.42; 95% CI: 2.24-4.50), khat consumption (aOR 2.86; 95% CI: 1.28-3.79), and HIV positivity (aOR 2.01; 95% CI: 1.07-3.52).
Pavit Tewatia et al (18)	2020	Tobacco smoking as a risk factor for tuberculous pleural effusion: a case-control study	Dehradun, India	Case Control	92 cases of TB - TPE (Tuberculosis Pleural Effusion) 184 age- and sex-matched controls in India. The sample was selected from a referral hospital in Dehradun, India. 72.8% of cases were smokers; 31.5% smoked tobacco and 41.3% smoked beedi.	Secondhand smoke exposure was significantly associated with TPE (OR = 4.57; 95% CI: 2.64-7.91; $p < 0.0001$). Risk increased with number of cigarettes/beedi per day (OR = 12.26 for 11-20 cigarettes/day, $p < 0.0001$). Risk increased with duration of smoking more than 20 years (OR = 5.70; $p < 0.0001$) and pack year more than 20 (OR = 5.17; $p < 0.0001$).
Ezra Shimeles et al (19)	2019	Risk factors for tuberculosis: A case control study in Addis Ababa, Ethiopia	Addis Ababba, Ethiopia	Case Control	260 cases of newly diagnosed bacteriological (latent) pulmonary TB patients. 260 controls selected by age and gender from the same health facility in Addis Ababa, Ethiopia. Sample age >15 years.	Exposure to secondhand smoke may increase risk of active TB up to 4 times (aOR = 4.43; 95% CI: 2.10-9.3). Household exposure to secondhand smoke was particularly associated with a heightened risk of TB. Other risk factors included a home with poor ventilation (aOR = 1.81; 95% CI: 1.06-3.07), household family member with history of TB (aOR = 3.00; 95% CI:1.60-5.62), history of hospitalization (aOR = 3.39; 95% CI: 1.64-7.03).

(continue Table 2)

Author	Year	Title	Country	Method	Sample/Population	Results
Madeeha Laghari et al (20)	2019	Contact screening and risk factors for TB among household contacts of children with active TB: a way to find source and new TB cases	Hyderabad, Pakistan	Cross Sectional	443 household members of 508 children with active TB who were undergoing treatment. A total of 2,397 household members were identified, with 9.3% (223 people) screened based on symptoms (LTBI). The majority were female (53.3%).	Contact with TB patients for more than 18 hours per day elevated risk of LTBI (OR = 4.681; 95% CI: 1.198-18.294). Exposure to secondhand smoke by household members also was significantly associated with to elevated risk of active TB (OR = 7.094; 95% CI: 2.128-23.648).
Davaasambuu Ganmaa et al (21)	2019	Risk factors for active tuberculosis in 938 QuantiFERON positive schoolchildren in Mongolia: a community-based cross sectional study	Ulanbatar, Mongolia	Cross Sectional	938 QuantiFERON-TB Gold positive (positive latent TB) children Aged 6-13 years from 18 schools.	Household exposure to secondhand smoke significantly increased the risk of active TB in children (aRR = 2.40; 95% CI: 1.74-3.30, $p < 0.001$). Children who actively smoked faced an even greater risk of develop active TB (aRR 5.23; 95% CI: 2.70-10.12, $p < 0.001$).
Robert J. Blount et al (22)	2021	Indoor Air Pollution and Susceptibility to Tuberculosis Infection in Urban Vietnamese Children	Hanoi, Vietnam	Prospective Cohort	72 TB patients with paediatric household contacts (109 children aged <16 years) The study was conducted in 5 health districts in Vietnam. 58 children (53%) were diagnosed with LTBI based TST. The cohort was followed for 2 years (2017-2019)	Expose to secondhand smoke elevated risk of TB infection. The presence of each smoking household member raises the risk of latent TB infection in children by 2.56 times. (95% CI: 1.27-5.16). Children aged <5 years are at higher risk from exposure to secondhand smoke than older children.
Avril Zixin Soh et al (23)	2017	Alcohol drinking and cigarette smoking in relation to risk of active tuberculosis: a prospective cohort study	Singapore	Prospective Cohort	63,257 adult individuals (aged 45-74) from the Singapore Chinese population The cohort was followed for an average of 16.8 years.	Smokers had a significantly higher risk of developing active tuberculosis compared to non-smokers. (HR = 2.02; 95% CI: 1.78-2.30). There was no significantly increased risk in former smokers compared to non-smokers (HR = 1.08; 95% CI: 0.89-1.30). The risk of active TB increased with smoking intensity and duration.
Neus Altet et al (24)	2022	Tobacco Smoking and Second-Hand Smoke Exposure Impact on Tuberculosis in Children	Barcelona, Spain	Prospective Cohort	616 children grouped by smoking habits Children <5 years old: 148 children, 9.5% with active TB, 9.5% LTBI after WPP. Children aged 5-14 years: 468 children, 7.7% with active TB, 32.1% LTBI after WPP. The cohort was followed for 2 years (2013-2015)	Secondhand smoke exposure was significantly associated with risk of LTBI (aOR: 7.57; 95% CI: 4.79-11.94) and active TB (aOR: 3.40; 95% CI: 1.45-7.98). IGRA results indicated a higher positive rate in children exposed to secondhand smoke or active smokers. However, IGRA sensitivity decreased in active TB patients exposed to secondhand smoke. SHS exposure decreased the secretion of several cytokines such as IL-22, GM-CSF, IL-5, TNF-α, IP-10, and IL-13.

(continue Table 2)

Author	Year	Title	Country	Method	Sample/Population	Results
Ryan P. Lindsay et al (25)	2014	The Association between Active and Passive Smoking and Latent Tuberculosis Infection in Adults and Children in the United States: Results from NHANES	United States	Cross Sectional	The total sample size was 6,541 respondents. Adults (aged ≥20 years) totalled 3,598 people. Children (aged 3-19 years) totalled 2,943 people.	The prevalence of LTBI was higher among active smokers (6.0%) than non-smokers (3.3%) in adults. In foreign-born, both active smokers (aOR = 2.56; 95% CI 1.20-5.45) and passive smokers (aOR = 2.27; 95% CI 1.09-4.72) were associated with a higher risk of LTBI compared to non-smokers..
Neus Altet et al (26)	2017	Assessment of the influence of direct tobacco smoke on infection and active TB management	Barcelona, Spain	Cross Sectional	Total 525 respondents 175 active pulmonary TB patients 350 individuals from contact tracing (121 diagnosed with LTBI, 41 with secondary active TB).	Active TB patients who smoked were more likely to have cavitary lesions (aOR: 1.88; 95% CI: 1.02-3.46) and delayed culture negativity (mean 2.47 months in smokers vs. 1.69 months in non-smokers). Smoking was associated with false negative IGRA results, especially in active TB group (aOR: 3.35; 95% CI: 1.47-7.61). The prevalence of LTBI was higher in smoker contacts compared to non-smokers (aOR: 11.57; 95% CI: 5.97-22.41).
Geneé S. Smith et al (27)	2015	Cigarette smoking and pulmonary tuberculosis in northern California	California	Nested Case Control	2380 newly diagnosed cases of TB between 1996-2010. 4738 controls without TB, matched by age, sex, and race/ethnicity.	Smokers had a significantly higher risk of developing active TB compared to non-smokers (OR = 1.35; 95% CI: 1.19-1.53). Former smokers had an even greater (OR = 1.43; 95% CI: 1.23-1.67) compared to current smokers (OR = 1.26; 95% CI: 1.08-1.48). The risk of TB increased with both the duration and intensity of smoking, indicating a clear dose-response relationship.

Abbreviations : TB, tuberculosis; LTBI, latent tuberculosis infection; SHS, secondhand smoke; OR, odds ratio; aOR, adjusted odds ratio; aRR, adjusted risk ratio; HR, hazard ratio; CI, confident interval; HHC, household contact; HIV, human immunodeficiency virus; TPE, tuberculosis pleural effusion; TST, tuberculin skin test; WPP, window period prophylaxis; IGRA, interferon-gamma release assay; IL-22, interleukin-22; IL-5, interleukin-5; IL-13, interleukin-13; GM-CSF, granulocyte-macrophage colony-stimulating factor; TNF-α, tumor necrosis factor-alpha; IP-10, interferon gamma-induced protein 10.

of active TB among active smokers (aOR = 2.9) and ex-smokers (aOR = 4.2). Similarly, a study in Ethiopia by Diriba and Churiso (17) reported that secondhand smoke exposure raised the risk of active TB by 2.89 times (95% CI: 2.10–3.84). Other factors that may contribute to the progression to active TB include close contact with TB patients and individuals living with HIV.

The research conducted by Tewatia et al. (18) in India highlighted a clear dose-response association between secondhand smoke exposure and incidence of tuberculosis. The study found that the total number of cigarettes smoked per day significantly increased the risk of active TB, with individuals who smoked more than 11 cigarettes daily for 20 years having a 12.26 times higher risk. This suggests that both the quantity of cigarettes smoked and the duration of exposure to secondhand smoke can increase the risk of active TB in those previously infected with TB. In line with this, Shimeles et al. (19) in Ethiopia also found that secondhand smoke exposure in the household increased the risk of active TB by 4.43 times (95% CI: 2.10-9.3) in individuals diagnosed with LTBI. The study also identified other exacerbating factors, such as poor household ventilation, a family history of TB, and previous hospitalizations.

A study by Laghari et al. (20) in Pakistan revealed that caregivers of children at risk of active TB had a 7.09 times higher risk (95% CI: 2.12-23.64) of developing active TB due to close interaction with TB-positive children and exposure to secondhand smoke. Similarly, research in Mongolia by Ganmaa et al. (21) showed that children with LTBI who were exposed to secondhand smoke had a higher risk of developing active TB (adjusted RR = 2.40; 95% CI: 1.74-3.30). However, the study found that secondhand smoke exposure was not an independent risk factor for active TB. Blount et al. (22) in Vietnam also found that exposure to secondhand smoke in the household, elevated the risk of LTBI in children by 2.56 times (95% CI: 1.27-5.16). Soh et al. (23) in Singapore confirmed that active smokers had a 2.02 times greater risk of developing active TB than non-smokers, with the risk increasing with the duration and intensity of smoking. Additionally, Altet et al. (24) in Spain observed that secondhand smoke exposure in children with LTBI elevated the risk of developing active TB by up to 3.40 times (95% CI: 1.45-7.98), with secondhand smoke negatively affecting immune responses through decreased cytokine secretion.

Lindsay et al. (25) in the United States found a highest prevalence of LTBI in active smokers, and secondhand smoke exposure increased the risk of LTBI in adults by 2.56 times, particularly in foreign-born populations. Altet et al. (26) also demonstrated that smokers with active TB were more likely to have cavitary lesions and delayed healing, and that secondhand smoke exposure reduced IFN-γ-mediated immune responses. Lastly, study by Smith et al. (27) in California showed that smokers had 1.35 times greater risk of active TB than non-smokers, with this risk increasing with the duration and intensity of smoking, suggesting a clear dose-response effect. These articles provide consistent evidence of research findings on secondhand smoke exposure and the risk of progression to active TB in individuals with LTBI. The evidence clearly indicates that secondhand smoke significantly exacerbates the risk of LTBI progressing to active TB. The studies also emphasize that this risk is compounded by factors such as the duration and intensity of exposure, smoking habits, poor ventilation in living spaces, and close contact with individuals who have active TB.

Discussion

Tuberculosis and smoking are two dangerous health problems often combined. Secondhand smoke exposure has been recognised as one of the significant risk factors to develop active TB. Individuals with LTBI and exposure to secondhand smoke can trigger conversion to active TB through biological mechanisms that damage the immune system. The present study was conducted to explore in depth the association between secondhand smoke exposure and risk of developing active TB in individuals with LTBI, based on the results of *Systematic Literature Review* (SLR).

Study Characteristics

The study included various research designs: 6 cross sectional studies, 4 case-control studies, and 3 prospective cohort studies, conducted in regions with presence of TB burden, such as Africa (Ethiopia), Asia (India, Pakistan, Vietnam, Mongolia, Singapore), Europe (Spain), and the Americas (United States and California). The sample sizes in these studies ranged from the smallest sample of 72 in the Vietnam study to the largest sample of 63,257 in the Singapore cohort-based study. The study population included individuals with LTBI exposed to both active and passive smoke, with subgroups of vulnerable subjects such as children and adults with a history of smoking,

exposure to secondhand smoke, and people with HIV-positive status. Findings also suggest that exposure to tobacco smoke, especially long-term exposure and high intensity exposure, may increase the risk of progression of LTBI to active TB with a clear and significant dose-response association. These studies were published over the period 2014-2024, reflecting the continued global focus on the issue of tobacco smoke exposure as an important risk factor in the tuberculosis epidemic.

Overview of Latent Tuberculosis and Active Tuberculosis Conditions

LTBI is a condition where people are infected with *Mycobacterium tuberculosis* but have not yet exhibited symptoms of active TB. About 25% of the global population carries LTBI, which serves as a primary source for the development of active TB, particularly in individuals with weakened immunity or those exposed to environmental factors, such as secondhand smoke, that may trigger the infection to progress. The SLR study indicates that risk of LTBI progressing to active TB varies based on factors such as geographic location, age group, and exposure to risks. Children living in households with TB patients face a higher risk of developing active TB, as shown by Burusie et al. (15), with a 3.15 times increased risk, and Ganmaa et al. (21), with a 2.4 times increased risk. This is because children, who are in contact with active TB patients, usually also have the possibility of becaming infected with LTBI, which may eventually progress to active TB. This can occur because repeated contact, a weak and immature immune system in children, makes their bodies not ready to form an immune response strong enough to fight the germs that enter the body. As a result, they become more vulnerable to developing active TB (28). In adults, especially active smokers, the risk of active TB is doubled compared to non-smokers, as found by Soh et al. (23) in Singapore. Lindsay et al's. (25) study, also mentioned that in adults, both those who smoke actively and passively (exposed to secondhand smoke), the increased risk of LTBI becoming active TB is also high. This is due to the harmful chemicals contained in tobacco smoke. Adults who smoke or are exposed to secondhand smoke can weaken the body's immune response, impair the function of cilia in the respiratory tract, and inhibit alveolar macrophage activity. These effects reduce the body's ability to control LTBI, thereby increasing risk of the infection progressing to active TB (29).

Individuals with LTBI are more likely elevated risk progression of active TB, particularly in vulnerable populations such as childrens who live with active TB patients or adults who are exposed to secondhand smoke. Being a cohabitant of a TB-infected person, along with exposure to both active and passive tobacco smoke, notably weakens the immune system and heightens the risk of LTBI transitioning to active TB. This underscores the need for preventive measures, such as smoke control in households, reduction of risk exposure and avoidance of the rise of the number of active TB cohabitants, which could have significant public health consequences.

Overview of household secondhand smoke exposure as indoor pollution

Secondhand smoke is one of major sources of indoor air pollution, especially in households with poor ventilation, increasing the concentration of harmful substances trapped indoors. All studies show that exposure to secondhand smoke in households significantly increased the risk of LTBI progressing to active TB, as harmful chemicals in secondhand smoke can weaken the immune system and damage the respiratory tract. Shimeles et al. (19) reported that individuals infected with LTBI can elevate the risk of active TB up to 1.8 times, especially if the home is poorly ventilated. Poor ventilation exacerbates the accumulation of secondhand smoke and other harmful particles indoors, which prolongs the duration of exposure and increases the risk of active TB. This occurs because secondhand smoke is trapped in poorly ventilated rooms, increasing the duration and intensity of exposure to harmful substances that can weaken the immune response and exacerbate LTBI, allowing its transformation into active TB (30). Additionally, research by Kim et al. (16) found that exposure to secondhand smoke in the household was associated with a 1.6 times increase the prevalence of active TB infection. Similarly, Laghari et al. (20) discovered that caregivers living in households with tobacco smoke exposure had a 7.09 times higher risk of developing active TB, as this exposure can exacerbate the condition of individuals already infected with LTBI. This is because intense exposure to secondhand smoke can worsen the condition of caregivers already infected with LTBI. If caregivers are frequently exposed, their immune systems will be further offended, facilitating the transition from LTBI to active TB, especially when they care for children infected with active TB (30).

Exposure to secondhand smoke in households is a major representative of indoor air pollution,

especially in homes with poor ventilation. If LTBI individulas are present in a household, there is a risk of converting the LTBI to active TB. Secondhand smoke not only contains harmful chemicals that weaken the immune system, but also worsens the condition of individuals already infected with LTBI. Research shows that exposure to secondhand smoke in the household can increase the risk of active TB by several times, with the risk being even higher in poorly ventilated environments that trap smoke. This emphasises the need for control of exposure to tobacco smoke in households to be implemented to prevent the progression of active TB and protect vulnerable groups, including children and caregivers.

Association of secondhand smoke exposure in individuals moving from LTBI to active TB

There is a significant association between exposure to secondhand smoke and increased risk of LTBI progression to active TB. Altet et al. (24) in Spain found that children exposed to secondhand smoke had a 3.4 times higher risk of developing active TB. Similarly, Diriba & Churiso (17) in Ethiopia reported a 2.89 times increased risk of active TB in individuals exposed to secondhand smoke. Accordingly, secondhand smoke exposure can increase a child's risk of LTBI to active TB by 2.5 times, according to research conducted in Vietnam by Blount et al. in 2021 (22). These studies provide compelling evidence supporting the harmful health effects of secondhand smoke exposure. Study by Tewatia et al. (18) revealed that individuals smoking more than 11 cigarettes per day had a 12.26 times higher risk of developing active TB. Therefore, these findings demonstrate a robust correlation between smoking frequency and heightened vulnerability to active TB, particularly in those with LTBI.

Additionally, Smith et al. (27) study further demonstrated that both the duration and intensity of smoking or secondhand smoke exposure are positively correlated with the risk of active TB. The dose-response relationship suggests that the risk of active TB increases with higher levels of exposure, particularly in individuals with LTBI. The biological mechanisms behind this association include decreased cytokine production, such as TNF-α and IL-13, impaired alveolar macrophage function, and lung tissue damage caused by toxic particles in secondhand smoke (31). Exposure to secondhand smoke has not only become a risk factor for active TB progression but may also contribute to biological changes in the body in response to *Mycobacterium tuberculosis* infection. Emerging evidence suggests that tobacco smoke and its constituents, such as tar and nicotin, may directly influence the virulence of *Mycobacterium tuberculosis*, potentially exacerbating the TB epidemic. Shprykov et al. (32) demonstrated in in-vitro experiments that chronic exposure to tobacco smoke enhanced both the growth and drug resistance of *Mycobacterium tuberculosis*, highlighting a critical interaction between environmental factors and bacterial adaptation. This phenomenon may be attributed to the ability of tobacco smoke to alter the microenvironment within the lungs, creating conditions that promote bacterial survival, persistence, and mutation. Moreover, the immunosuppressive effects of tobacco smoke, such as reduced macrophage function and impaired immune cell responses, may further compromise the host's ability to contain the infection. These findings underscore the dual impact of tobacco use not only as a behavioral risk factor for active TB progression but also as a potential driver of microbial resistance, posing significant challenges for global TB control strategies (33).

Based on the study findings, it is evident that secondhand smoke not only exacerbates the condition of individuals with LTBI but also serves as a key trigger for the conversion to active TB. Furthermore, the ability of tobacco smoke to enhance *Mycobacterium tuberculosis* virulence emphasizes the urgent need for comprehensive interventions that address both behavioral risk factors and the microbial consequences of smoke exposure. Secondhand smoke can negatively affect health and worsen pre-existing conditions, including TB. Many research consistently demonstrate that secondhand smoke exposure significantly elevated the risk of LTBI progressing to active TB disease, particularly among vulnerable populations such as children and individuals who are in close contact with active TB patient and live in the same household with heavy smokers. This risk follows a dose-response pattern, with longer duration and higher intensity of exposure directly increasing the likelihood of TB activation. The biological mechanisms behind this include immune system suppression, impaired alveolar macrophage function, and lung tissue damage caused by toxic particles in tobacco smoke. Thus, it is evident that secondhand smoke not only exacerbates the condition of individuals with LTBI but also serves as a key trigger for the conversion to active TB. Therefore, interventions to reduce secondhand smoke exposure in the environment are crucial to controlling the spread of TB and mitigating the global TB burden.

Study Limitation

The results of this study have some limitations due to the variability in study design across the articles reviewed, which may impact the generalizability of the findings. To address this, employing a consistent study design and extending the review process to include a meta-analysis stage might be necessary. An approach like this could provide a more robust exploration of the strength and nuances of this relationship, ultimately enhancing the reliability and applicability of the findings.

Conclusions

Secondhand smoke exposure consistently increases the risk of developing active TB in individuals with LTBI, with biological mechanisms involving immune suppression, lung damage, dose-response effects. Furthermore, evidence suggests that tobacco smoke may enhance *Mycobacterium tuberculosis* virulence, further complicating TB prevention and control efforts. To support the global TB elimination program, targeted interventions are essential to reduce secondhand smoke exposure, particularly among vulnerable populations such as children and LTBI individuals.

Abbreviations
TB: Tuberculosis
SHS: Secondhand Smoke
LTBI: Latent Tuberculosis Infection
WHO: World Health Organization
SDGs: Sustainable Development Goals
SLR: Systematic Literature Review
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta Analysis
PICO: Population, Intervention, Comparison, Outcome

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Author 1 Soraya Permata Sujana Designed the systematic review, developed the review protocol, conducted the literature search, performed data extraction, and drafted the manuscript.
Author 2 Fadilah Habibul Hamda Analyzed the quality of the studies included in the review, contributed to writing the discussion, and revised the manuscript.
Author 3 Mufti As Siddiq M Irzal Analyzed the quality of the studies included in the review, assisted with data analysis, provided methodological input.
Author 4 Yuniko Ibnu Latif Screened articles for inclusion, contributed to the data synthesis, edited the manuscript for clarity and accuracy.
Author 5 Al Asyary Supervised the systematic review process, provided critical feedback on the review methodology and findings, and approved the final version of the manuscript.

Riassunto

L'associazione tra esposizione al fumo passivo e rischio di sviluppare tubercolosi attiva in individui con infezione tubercolare latente: una revisione sistematica della letteratura

Introduzione. La tubercolosi è una delle principali cause di morte per malattie infettive a livello mondiale, con circa il 25% della popolazione globale affetta da infezione tubercolare latente. L'esposizione al fumo passivo è stata riconosciuta come un fattore di rischio significativo per lo sviluppo di tubercolosi attiva negli individui con infezione tubercolare latente.

Disegno dello Studio e Metodi. Questo studio ha utilizzato il metodo di revisione sistematica della letteratura basato sulle linee guida PRISMA. Articoli rilevanti pubblicati tra il 2014 e il 2024 sono stati identificati tramite le banche dati PubMed, ProQuest e Scopus utilizzando parole chiave correlate. Un totale di 13 articoli ha soddisfatto i criteri di inclusione per l'analisi.

Risultati. L'esposizione al fumo passivo aumenta significativamente il rischio di conversione di infezione tubercolare latente in tubercolosi attiva, con un effetto più forte nei gruppi vulnerabili come bambini e individui che sono a stretto contatto con pazienti con tubercolosi attiva e vivono nella stessa casa con fumatori accaniti. Questo rischio di esposizione al fumo passivo segue uno schema dose-risposta, in cui una durata maggiore e una maggiore intensità di esposizione aumentano direttamente la probabilità di attivazione della tubercolosi negli individui con infezione tubercolare latente. I meccanismi biologici coinvolgono la soppressione immunitaria e il danno polmonare causato da particelle tossiche nel fumo di tabacco, che indeboliscono le difese dell'organismo contro il *Mycobacterium tuberculosis* e facilitano la progressione di infezione tubercolare latente in tubercolosi attiva. Pertanto, ridurre l'esposizione al fumo passivo è essenziale per mitigare il suo impatto sulla progressione della tubercolosi attiva.

Conclusioni. È stato costantemente dimostrato che l'esposizione al fumo passivo aumenta il rischio di sviluppare la tubercolosi attiva negli individui con infezione tubercolare latente. Per sostenere il programma globale di eliminazione della tubercolosi, sono necessari sforzi concertati per ridurre l'esposizione al fumo passivo, specialmente negli individui con infezione tubercolare latente.

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