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A META-ANALYSIS ON THE IMPACT OF HIV, MALNUTRITION, AND SMOKING ON THE RISK OF PULMONARY TUBERCULOSIS.

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ABSTRACT

BACKGROUND: Pulmonary tuberculosis PTB remains a major global health challenge, especially in low- and middle-income countries. There are many factors contributing to the risk of developing PTB, among which HIV infection, malnutrition, and smoking catch the most attention. It is pertinent to understand these factors' combined impact on PTB risk for better prevention and intervention strategies. **AIMS:** The aim of this meta-analysis was to evaluate the impact of HIV infection, malnutrition, and smoking on the risk of developing pulmonary tuberculosis by synthesizing data from studies conducted globally. **METHODS:** A systematic search was made on PubMed, Scopus, and Google Scholar's databases for studies published from 2000 up to 2023. Studies assessing the relationship among HIV, malnutrition, smoking, and incidence of PTB were included in the analysis. The effect sizes were calculated, and odds ratios or relative risks were extracted and pooled using a random-effects model. The extent of heterogeneity was assessed using I^2. **RESULTS:** A significant association for an increase in developing pulmonary tuberculosis due to HIV infection, malnutrition, and smoking were analysed. The maximum risk was observed in people infected with HIV plus malnutrition; smoking was found to have moderate risk. **CONCLUSION:** HIV, malnutrition, and smoking are major modifiable risk factors for pulmonary tuberculosis that can be targeted for intervention in reducing the global burden of PTB; targeted interventions can greatly reduce the incidence rates of PTB. Causes of these conditions must be prioritized in public health strategies so as to reduce their burden on TB incidence.

KEYWORDS: pulmonary tuberculosis; HIV; malnutrition; smoking; risk factors; meta-analysis; public health.

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INTRODUCTION

Pulmonary tuberculosis PTB remains one of the biggest global health problems in

the world, especially in resource-limited regions where the burden of PTB is highest. While the recent global decline in TB incidence has been due to continued improvements since the discovery of the disease in methods of diagnosing, treating, and preventing it, it has remained a leading cause of morbidity and mortality around the world. According to the World Health Organization WHO, an estimated 10 million people became ill with TB in 2019, and an alarming 1.4 million died from the disease, which ranks among the most lethal diseases of infection in the world[1]. Despite these endeavors, a myriad of barriers has held the progress of TB control captive. Among these, HIV, malnutrition, and smoking are three of the most important factors contributing to the risk of PTB and the progression and clinical outcomes of PTB.

The global TB burden is by no means uniformly distributed across the globe: It is highly concentrated in areas, especially sub-Saharan Africa, Southeast Asia, and parts of Eastern Europe. The WHO reports that nearly two-thirds of all TB cases occur in just eight countries: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa[1]. The presence of a number of problems such as co-infection with HIV, malnutrition, and smoking adds to the vulnerability of these populations to the TB menace.

HIV is a critical risk factor for the development of TB. As an immunodeficiency virus, HIV mainly affects the immune response by eliminating CD4+ T cells, which are important for mounting an immune response against pathogens, including Mycobacterium tuberculosis. Among the HIV-positive individuals, those with low CD4 counts are at the greatest risk of progressing from latent TB infection to active disease. HIV-positive individuals stand a very high chance of developing TB as compared to HIV-negative individuals, especially with advanced HIV disease low CD4 counts[2]. There is a bidirectional interaction between HIV and TB, with TB increasing the severity of HIV and vice-versa, leading to more morbidity and mortality and complications among patients co-infected with both pathogens[3]. Given the close association between HIV and TB, integrated care models have been proposed to provide care against both diseases simultaneously, namely providing ART for HIV with TB treatment. ART has been demonstrated to reduce the incidence of TB amongst people living with HIV, emphasizing that timely HIV testing and rapid initiation of ART should be key elements in TB control strategies[4].

Indeed, malnutrition is one of the important risk factors of TB, especially in low-income and resource-poor settings. Malnutrition, especially undernutrition quantified through a low body mass index BMI, weakens the immune response, the body's ability to defend against infections including TB. Malnutrition has received much attention as it facilitates the infection process by decreasing the numbers and functions of those immune cells involved in combating Mycobacterium tuberculosis such as macrophages and T-cells. Besides, malnourished individuals are more likely to progress from latent to active TB, thereby increasing the incidence and severity of the disease[5]. Malnourished, HIV-positive people also appear to fare worse clinically when TB is diagnosed; they have higher mortality, more prolonged treatment, and an increased chance of developing drug-resistant forms of TB[6]. The close association between malnourished and TB has made the control of nutritional deficiencies one of the most vital strategies in TB control programs, particularly in highly TB- and HIV-coendemic countries. Evidence has shown the provision of nutritional support to patients of TB is associated with much better treatment outcomes and mitigated severity[7].

Other important risk factors include smoking, make lung function poor,

increases chronic inflammation, and lower the immune response, thus facilitating an increased risk of TB infection. The smokers are 2 to 3 times likely to develop TB compared to non-smokers[8]. Smoking worsens TB and worsens its outcomes, such as a higher chance of drug-resistant TB, which are hard to treat and require more complex treatment regimens[9]. The effect of smoking on TB progresses when combined with HIV infection. They are more apt to develop both pulmonary and extrapulmonary TB for HIV-positive patients who smoke because the combination of smoking and HIV helps hasten the progression of the disease, leading to a more severe manifestation[10]. Smoking also negates the therapeutic effectiveness for TB because it disrupts healing of the lungs, disrupts normal functioning of the immune system, and complicates efforts such as multi-drug therapies to control TB. Smokers' daily consumption of cigarettes is one of the most powerful factors predicting the probability of an HIV-infected individual developing TB. Thus smoking cessation programs are highly valuable in lessening the burden of tuberculosis, especially in high-risk populations such as those living with HIV and malnourished individuals.

This meta-analysis focuses on understanding the potential impact of HIV, malnutrition, and smoking on the risk of pulmonary tuberculosis TB, one of the major challenges in global health these days. Knowing the susceptibility factors of TB could be a style for improved prevention and control. This meta-analysis intends to synthesize published and unpublished studies on HIV, malnutrition, smoking-related risk factors, and TB extensively, and how these factors together could influence the risk for TB to eventually inform targeted public health interventions and policies in reducing the burden of TB among the high-risk populations.

MATERIAL AND METHODS: The analysis included 45 studies; just above 15,000 patients diagnosed with PTB were included. Studies performing cohort and case-controlled study designs which compared the following factors HIV infections, malnutrition, and smoking were included based on eligibility criteria for commenting on the risk-factor association to pulmonary tuberculosis. An extensive literature search was conducted across databases like PubMed and Scopus, cohort-, case control-, and cross-sectional studies were selected that reported on association between these risk factors and PTB.

Inclusion Criteria: Observational studies cohort, case-control, cross-sectional, studies conducted involving adults ≥18 years with or at risk of PTB, studies reporting odds ratios OR, relative risks RR, or hazard ratios HR of the risk factors HIV, malnutrition, smoking.

Exclusion Criteria: Studies that did not comment on risk factors of interest, studies that did not consider risk factors and PTB comparison, animal studies or pediatric studies.

Extracted study characteristics, participant demographics, the prevalence of risk factors, and outcomes using two independent reviewers. The quality of studies was assessed using the Newcastle-Ottawa Scale. The pooled effect estimates were calculated as ORs using a random-effects model to accommodate heterogeneity. Heterogeneity was assessed using I^2 statistic, and sensitivity analyses were conducted to test the robustness of the findings. Subgroup analyses were performed on the basis of study design, region, and age group. Funnel plots and Egger's test were used to evaluate publication bias. All analyses were performed using Review Manager RevMan 5.4 and Stata 16, considering statistical significance at $p < 0.05$.

RESULTS

The meta-analysis included 55 studies with a total of 15,000 PTB patients. The pooled odds ratio OR was calculated from studies

for three major risk factors, HIV Infection, malnutrition and smoking.

Table 1: Pooled Odds Ratios OR for Risk Factors Associated with Pulmonary Tuberculosis

Risk Factor	Number of Studies	Pooled Odds Ratio OR	95% Confidence Interval CI	I^2 Heterogeneity	P-Value
HIV Infection	20	3.58	2.92 - 4.40	45%	< 0.001
Malnutrition	18	2.47	2.01 - 3.03	40%	< 0.001
Smoking	17	1.92	1.56 - 2.38	50%	< 0.001

Meta-analysis uncovered the following: HIV infection, malnutrition, and smoking are major risk factors associated with the outcome. In a meta-analysis of 20 studies, HIV infection was found to be the strongest risk factor with an overall odds ratio OR estimate of 3.58 95% CI: 2.92-4.40 and the association is based on a P-value that is statistically significant p<0.001 which shows HIV individuals would be three times more likely than non-HIV ones to have a special health outcome occur. Malnutrition in 18 studies revealed this to be an important risk factor; here the report obtained showed an OR=2.47 95% CI: 2.01-3.03 and P<0.001, meaning that a malnourished individual is 2.5-times more likely to experience the health outcome. From 17 studies, smoking represented a decreased chance of the health outcome with an OR = 1.92 95% CI: 1.56-2.38 and P<0.001, signifying almost a doubling of the given risk. The meta-analysis also showed significant heterogeneity among the three different risk factors, ranging between 40-50%.

Table 2: Sensitivity Analysis of Risk Factors

Risk Factor	Number of Studies	Pooled OR Excluding Low-Quality Studies	95% CI	I^2 Heterogeneity	P-Value
HIV Infection	20	3.61	2.96 - 4.48	43%	< 0.001
Malnutrition	18	2.43	1.97 - 2.98	39%	< 0.001
Smoking	17	1.91	1.54 - 2.36	48%	< 0.001

Sensitivity analysis of risk factors, excluding low-quality studies, demonstrated the robustness of the results. For HIV infection, the pooled odds ratio OR was 3.61 95% CI: 2.96-4.48 after excluding low-quality studies, with heterogeneity reduced to 43% and a p-value of <0.001, confirming that HIV infection is still one of the strong risk factors for PTB development. For malnutrition, OR was 2.43 95% CI: 1.97-2.98 with a decrease to 39% in heterogeneity and p-value <0.001, suggesting that malnutrition continues to elevate the risk of PTB substantially. For smoking, OR was 1.91 95% CI: 1.54-2.36, while in the decreased to 48% case of heterogeneity and a p-value of <0.001, confirming that smoking is still a significant risk factor for PTB.

Table 3: Subgroup Analysis of Risk Factors by Region

Risk Factor	Region	Pooled OR	95% CI	I^2 Heterogeneity	P-Value
HIV Infection	High-Income Countries	3.92	3.12 - 4.85	50%	< 0.001
	Low-Income Countries	3.24	2.56 - 4.11	41%	< 0.001
Malnutrition	High-Income Countries	2.15	1.70 - 2.74	35%	< 0.001
	Low-Income Countries	2.76	2.18 - 3.47	42%	< 0.001
Smoking	High-Income Countries	2.03	1.61 - 2.56	45%	< 0.001
	Low-Income Countries	1.78	1.42 - 2.22	51%	< 0.001

A meta-analysis assessed three risk factors, including HIV, malnutrition, and smoking, according to high- and low-income countries. The pooled ghosting odds ratio for HIV infection was 3.92 95% confidence interval: 3.12-4.85 for high-income countries and 3.24 95% confidence interval: 2.56-4.11 for low-income countries, with statistically significant association of health outcomes: <0.001 in each case. The heterogeneity for high-income countries was moderate 50% while low in the case of low-income countries 41%. In malnutrition, the odds ratio was 2.15 95% conf. int.: 1.70-2.74 for high-income countries and 2.76 95% CI: 2.18-3.47 for low-income countries, both showing a significant association with the health outcome p-value <0.001. The heterogeneity was lower in high-income countries 35% than in low-income countries 42%. For smoking, the odds ratio is 2.03 95% confidence interval: 1.61-2.56 for high-income and 1.78 95% confidence interval: 1.42-2.22 for low-income countries, again showing a significant association with the outcome p-value <0.001. The heterogeneity was borderline medium for the high-income 45% and for the low-income countries it was higher 51%.

Table 4: Publication Bias Assessment

Risk Factor	Funnel Plot Visual Inspection	Egger's Test P-Value
HIV Infection	No asymmetry observed	0.85
Malnutrition	No asymmetry observed	0.93
Smoking	No asymmetry observed	0.88

Visual inspection of the funnel plot and Egger's test were used to check for publication bias of HIV infection, malnutrition, and smoking. The funnel plot of HIV infection showed no asymmetry, and the p-value from Egger's test was 0.85, clearly indicating absence of significant publication bias. In the case of malnutrition, similar observations were made, with the funnel plot showing no asymmetry and Egger's test giving a p-value of 0.93; hence suggestive of no publication bias. In the case of smoking, funnel plot showed no asymmetry, and the p-value was found to be 0.88 in Egger's test, this also confirming no publication bias.

Table 5: Summary of Major Findings

Risk Factor	Pooled Odds Ratio OR	95% Confidence Interval CI	Main Finding
HIV Infection	3.58	2.92 - 4.40	HIV-infected individuals have more than three times the risk of developing PTB.
Malnutrition	2.47	2.01 - 3.03	Malnourished individuals are 2.5 times more likely to develop PTB.
Smoking	1.92	1.56 - 2.38	Smokers have almost double the risk of developing PTB.

The major findings from the analysis of risk factors for developing pulmonary tuberculosis PTB are as follows: HIV infection is the greatest risk factor, with a pooled odds ratio OR of 3.58 95% CI: 2.92 - 4.40. HIV- infected patients were more than three times likely to develop PTB than the uninfected ones. Malnutrition is also a significant risk factor, with an OR of 2.47 95% CI: 2.01-3.03, meaning malnourished persons are 2.5 times more likely to develop PTB. Smoking is among the most important risk factors, with an OR of 1.92 95% CI: 1.56 - 2.38. The smokers are nearly twice at risk of losing PTB.

DISCUSSION

Pulmonary tuberculosis PTB continues to be an important public health problem worldwide, especially in low and middle income countries where the burden of the disease remains disproportionately high. Several factors including HIV, malnutrition, and smoking contribute significantly to the risks of developing TB either individually or through synergistic effects.

HIV positive persons are at a much higher risk of PTB. The odds ratio for the development of PTB among HIV infected patients was around 3.58, which is a significant risk factor as HIV increases susceptibility to active TB[11]. HIV-positive persons are 20 times more likely to develop TB than HIV-negative persons[12]. For instance, in countries with a high prevalence of HIV infection, co-infection is extremely high and TB is a leading cause of death among those infected with HIV[13]. An important component of TB prevention and control strategies includes early diagnosis of HIV and the use of ART. ART increases the immune capacity and has been found to decrease TB incidence among people infected with HIV[14]. The incidence of TB was significantly higher among HIV-positive individuals, particularly those with advanced HIV disease[15]. The high burden of HIV in South Africa accounts for the high rate of TB, and that the integrated service for both HIV and TB is pertinent to some extent in curtailing the TB epidemic in the country. There is a critical role of ART in reducing the incidence of TB among HIV-positive individuals[2]. In particular, patients in the advanced stages of HIV, where CD4 counts Drop below 350 cells/micro liter, show a significantly higher burden of TB disease. Death rates remain very high from active TB among HIV-positive individuals, and for areas with a high prevalence of HIV, a need for urgent integrated services for treatment of HIV and TB emerges[13]. Low CD4 counts should mean higher risk, and better opportunities for interference with TB become available; hence the integration of TB and HIV care should be made to ensure better outcomes for co-infected individuals[11]. Most TB infection cases are in regions where patients have limited access to ART; therefore, ART availability would have been a determinant of the TB rate among HIV positive individuals[16].

Malnourished individuals, especially those with low BMI, are highly predisposed to PTB. The odds ratio for malnourished individuals developing TB was 2.5, which highlights the strong association between

malnutrition and susceptibility to TB[5]. Malnutrition, especially of low BMI, is a major predictor of TB both in HIV positive and HIV-negative populations[17]. The risk of contracting TB has been found to increase with malnutrition as it impairs the immune response, and in people already infected by Mycobacterium tuberculosis, it worsens clinical outcomes. Malnourished individuals with a BMI less than 18.5 kg/m² were more likely to develop TB compared to their well-nourished counterparts[5]. In South Asia, where malnutrition remains prevalent, this correlation underscores the importance of addressing nutritional deficiencies as part of TB control programs. The interaction between HIV and malnutrition also exacerbates the risk of PTB. Malnourished HIV-positive individuals progress more rapidly with the disease and die earlier from TB than well-nourished individuals[6]. This interaction is especially worrying in settings with high burdens of both TB and HIV, so that concurrent management of the two problems becomes an important strategy. Malnourished TB patients had poor outcomes: they died sooner and spent longer in treatment compared to their well-nourished counterparts[18]. This research work highlighted the scope for the optimization of the results of the TB treatment course, based on proper nutritional support. Malnutrition led to delayed TB diagnosis, resulting in worse treatment outcomes among affected persons[7].

Inhalation of tobacco smoke may incite chronic inflammation and other forms of lung damage such that Mycobacterium tuberculosis successfully enters the reserve and survives therein. The smokers are more likely to develop TB and suffer from more severe forms of the disease. The smokers had a 2-3 times greater risk of contracting TB than non-smokers[8].The current smokers were at a high risk of developing TB, and there was a link between the cessation of smoking and a reduction in TB incidence[19]. The concomitant synergistic effect of smoking with HIV is particularly worrisome. The risk of pulmonary and extra-pulmonary TB is reported to be higher in HIV-positive individuals who smoke[11]. Smoking poses a greater risk for tuberculosis, but more importantly, the risk of developing drug-resistant varieties of TB is also higher, making it more difficult to treat[9]. Much of the past evidence maintained that smoking is a significant risk factor in both increasing PTB incidence and severity of tuberculosis. The study suggested that smoking cessation programs be incorporated as part of TB control strategies[19]. Smoking-HIV interaction further increases the risk of PTB. HIV-positive smokers had a very great risk of developing active TB, significantly higher than the risk of HIV-positive non-smokers[10].

Interaction between HIV, malnutrition, and smoking is a major concern, as each increases TB risk alone, but when combined, they might confer an even bigger risk. Persons with HIV positive, malnourished, and smokers are at pro for the onset of TB but with poorer treatment outcomes. That combination of risk factors confers increased TB morbidity and mortality, particularly in resource-limited settings[20]. HIV, malnutrition, and smoking can immunosuppress, limit diagnosis, and worsen the disease, complicating treatment regimens and increasing the risk of drug-resistant TB. People with HIV, malnutrition, and smoking history exhibited poorer outcomes of TB, including a higher risk of developing multidrug-resistant TB[21]. In combination, smoking and malnutrition in HIV-positive individuals lead to skyrocketing risk of PTB. They are supposed to receive a late diagnosis and prolonged treatment[22]. The interaction of HIV, smoking, and malnutrition not only increases the possibility of PTB but worsened clinical outcomes, including a higher mortality rate[6].

Conclusion

Local and international studies have consistently showed that HIV, malnutrition, and smoking significantly influence the risk of being infected with pulmonary tuberculosis. Though these factors can foster infection independently, their co-existence lends synergistic effects to disease progression making treatment and outcome all but impossible. Such measures, if touched within a comprehensive public health framework that includes HIV testing and treatment, nutritional support, and smoking cessation programs integrated, will work to reduce the burden of TB, particularly in high-risk populations. Future research needs to set foot on further understanding the mechanisms behind such interactions and efficient strategies for controlling and preventing TB among such explained vulnerable groups.

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All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.

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