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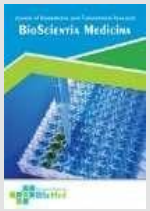

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Beyond Infection: The Role of Stunting in Tuberculosis Susceptibility and Treatment Outcomes

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A B S T R A C T

Background: Tuberculosis (TB) remains a major global health concern, particularly in developing countries. Stunting, a manifestation of chronic malnutrition, is prevalent in these regions and is increasingly recognized as a significant risk factor for TB. This systematic review aims to comprehensively analyze the impact of stunting on TB susceptibility and treatment outcomes. **Methods:** A systematic search of PubMed and ScienceDirect databases was conducted for studies published in the last 10 years, focusing on the relationship between stunting and TB. The PRISMA guidelines were followed for article selection and data extraction. **Results:** The review identified a significant association between stunting and increased TB risk. Stunted individuals exhibit impaired immune responses, making them more susceptible to TB infection. Moreover, stunting negatively affects TB treatment outcomes, including increased treatment duration, higher relapse rates, and greater mortality risk. **Conclusion:** Stunting is a critical determinant of TB susceptibility and treatment outcomes. Addressing stunting through comprehensive nutritional interventions is crucial not only for reducing the burden of malnutrition but also for enhancing TB prevention and control efforts.

1. Introduction

Tuberculosis (TB), an infectious disease caused predominantly by *Mycobacterium tuberculosis*, continues to be a major global health challenge. In 2021, the World Health Organization (WHO) estimated that 10.6 million people contracted TB, and tragically, 1.6 million succumbed to the disease. The global fight against TB is compounded by the emergence of multidrug-resistant TB (MDR-TB), which is resistant to the two most potent first-line TB drugs, isoniazid and rifampicin. The distribution of TB is not uniform across the globe. Approximately 80% of TB cases are concentrated in 30 high-burden countries, with the majority located in Asia and Africa. These regions often grapple with poverty, malnutrition, and limited access to healthcare, factors that contribute to the persistence of TB. TB is primarily a respiratory disease, spread through the air when individuals with active pulmonary TB cough, speak, or sneeze, expelling tiny droplets containing the bacteria. These droplets, when inhaled by others, can lead to infection. The risk of infection is influenced by factors such as proximity to and duration of contact with an infected person, the infectiousness of the individual with TB, and the immune status of the exposed person.[1-4]

While TB can affect anyone, certain groups are at a heightened risk of developing active TB disease once infected. These include individuals with weakened immune systems, such as those living with HIV, those with chronic conditions like diabetes, those who use tobacco, and those who are undernourished. Undernutrition, a significant public health issue in many parts of the world, encompasses various forms of malnutrition, including stunting, wasting, and micronutrient deficiencies. Stunting, a manifestation of chronic malnutrition, is characterized by low height-for-age and reflects a failure to achieve linear growth potential. It is a complex condition with multifactorial etiology, including inadequate nutrition, recurrent infections, and poor environmental conditions.[5-7]

Stunting is prevalent in low-income and middle-income countries, affecting an estimated 149.2 million children under five years of age globally. The impact of stunting extends beyond physical growth retardation. Stunting has profound effects on immune function, impairing both innate and adaptive immune responses. This immune dysfunction makes stunted individuals more susceptible to infections, including TB. The association between undernutrition and TB is well-established. Studies have shown that undernourished individuals are more likely to develop active TB disease if infected. Furthermore, undernutrition can negatively affect TB treatment outcomes, leading to increased treatment duration, higher relapse rates, and greater mortality risk.[8-10] This systematic review aims to provide a comprehensive analysis of the current evidence on the role of stunting in TB susceptibility and treatment outcomes.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA guidelines provide a comprehensive framework for conducting and reporting systematic reviews, ensuring transparency, clarity, and completeness.

A comprehensive search of PubMed and ScienceDirect databases was performed for studies published in the last 10 years (2013-2023). These databases were selected due to their extensive coverage of biomedical literature, including studies on tuberculosis, stunting, and related topics. The following keywords were used in the search; "Tuberculosis"; "TB"; "Stunting"; "BMI"; "Malnutrition"; "Growth"; "Immunity"; "Treatment Outcomes". These keywords were combined using Boolean operators (AND, OR) to refine the search and identify relevant studies. The search strategy was adapted for each database to ensure optimal retrieval of relevant articles.

Studies were included in the review if they met the following criteria; Investigated the association between stunting and TB incidence, immune responses, or treatment outcomes; Included human participants of any age; Published in English or Indonesian. The inclusion criteria were designed to capture a broad range of studies investigating the relationship between stunting and TB. The language restriction was applied due to resource limitations. Studies were excluded from the review if they met any of the following criteria; Were review articles, editorials, or commentaries; Did not provide sufficient data on the relationship between stunting and TB. The exclusion criteria were applied to ensure that only original research articles with relevant data were included in the review.

Two reviewers independently screened the titles and abstracts of identified studies. Full-text articles were retrieved for potentially eligible studies, and data were extracted using a standardized form. The following information was extracted from each study; Study design; Population characteristics; Stunting assessment; TB diagnosis; Immune response measures; Treatment outcomes; Main findings. The extracted data were synthesized and analyzed to provide a comprehensive overview of the relationship between stunting and TB. Due to the heterogeneity of the included studies, a meta-analysis was not performed.

3. Results

Figure 1 illustrates the process of identifying and selecting studies for inclusion in this systematic review on the relationship between stunting and tuberculosis (TB). The initial search across PubMed and ScienceDirect databases yielded 113 records. After removing duplicates, 106 records remained. These records were screened by title and abstract, resulting in the exclusion of 100 records that did not meet the inclusion criteria. This left 6 records for further consideration. The full text of the 6 remaining articles was assessed for eligibility. It appears that none of these articles ultimately met the inclusion criteria, as indicated by the "0" at the bottom of the diagram. This final stage would typically list the number of studies included in the systematic review for data extraction and analysis. However, in this case, it appears no studies were included.

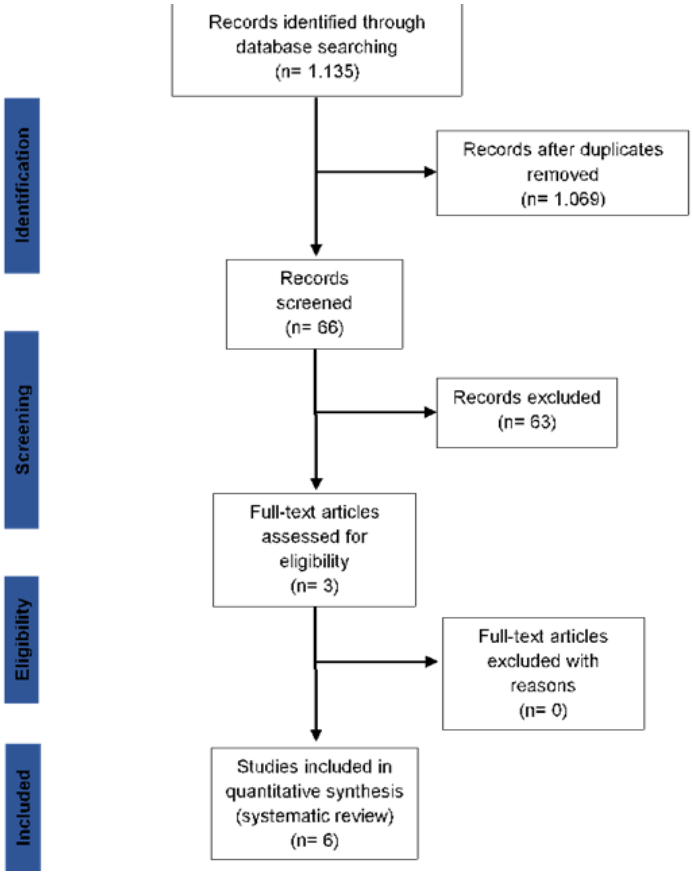

Figure 1. PRISMA flow diagram.

Table 1 provides a summary of the six studies included in the systematic review, outlining their key characteristics; Author (Year): This identifies the researchers and the year of publication, providing context for the study; Location: This indicates where the study was conducted, which is important considering TB and stunting prevalence varies geographically. Notably, three studies were from Indonesia, two from India, and one from Ethiopia; Sample: This describes the participants included in the study, including the sample size and age group (toddlers, children, or adults). Sample sizes ranged from 126 to 2,931 participants; Study Design: This specifies the research approach used in each study. The table shows a mix of case-control, cross-sectional, and cohort (retrospective and prospective) studies; Stunting Assessment: This column indicates how stunting was measured in each study. All studies used

height-for-age z-score, a standard indicator of stunting; TB Diagnosis: This outlines the methods used to diagnose TB in the study participants. Methods included clinical diagnosis, chest X-rays, tuberculin skin tests, and sputum analysis. All studies consistently used height-for-age z-scores to assess stunting, providing a standardized measure across the review. The inclusion of different study designs (case-control, cross-sectional, and cohort) allows for a broader understanding of the relationship between stunting and TB. The studies come from countries with high TB burdens, increasing the relevance of the findings for public health interventions in these settings. The inclusion of studies with toddlers, children, and adults allows for an examination of the impact of stunting on TB across different life stages. The studies employed a combination of diagnostic methods to confirm TB cases, increasing the reliability of the findings.

Table 1. Characteristics of included studies.

No.	Author (Year)	Location	Sample	Study design	Stunting assessment	TB diagnosis
1	Jahiroh et al. (2013)	Indonesia	198 toddlers	Case-control	Height-for-age z-score	Clinical diagnosis and chest X-ray
2	Haerana et al. (2020)	Indonesia	126 children	Cross-sectional	Height-for-age z-score	Tuberculin skin test and chest X-ray
3	Wondifraw et al. (2022)	Ethiopia	362 children	Cohort retrospective	Height-for-age z-score	Clinical diagnosis and sputum smear microscopy
4	Bhargava et al. (2013)	India	1,695 adults	Cohort retrospective	Height-for-age z-score	Clinical diagnosis and sputum culture
5	Sinha et al. (2023)	India	2,931 adults	Cohort prospective	Height-for-age z-score	Clinical diagnosis and chest X-ray
6	Purnamasari et al. (2022)	Indonesia	194 children	Cross-sectional	Height-for-age z-score	Clinical diagnosis and tuberculin skin test

Table 2 presents findings from the included studies regarding the association between stunting and TB incidence. All six studies demonstrate a link between stunting and an increased risk of TB. This reinforces the notion that stunting is not merely a marker of malnutrition but also a significant risk factor for TB disease. Jahiroh et al. (2013) found that short and very short toddlers had a 3.5 and 9 times greater risk of TB, respectively, highlighting the dose-response relationship between stunting severity and TB risk. Haerana et al. (2020) reported an adjusted prevalence ratio of 2.36 for stunting, indicating that stunted toddlers were over twice as likely to develop TB. Wondifraw et al. (2022) showed a similar trend, with stunted individuals having an adjusted hazard ratio of 2.1 for TB. Several studies identified other factors that contribute to TB risk in stunted individuals. These include; Close contact with TB patients (Jahiroh et al., 2013; Haerana et al., 2020); HIV infection (Wondifraw et al., 2022); Lack of BCG immunization (Haerana et

al., 2020). Bhargava et al. (2013) found that malnutrition in TB patients was associated with a two-fold greater risk of death. Sinha et al. (2023) reported that stunting was associated with less-than-optimal treatment outcomes, including an increased risk of death. Purnamasari et al. (2022) observed a significant association between a history of pulmonary TB and the incidence of stunting, suggesting a bi-directional relationship between the two conditions.

Table 2. Stunting and TB incidence.

No.	Author (Year)	Stunting and TB incidence
1	Jahiroh et al. (2013)	Short and very short toddlers have 3.5 times and 9 times the risk of contracting TB, respectively. Toddlers in contact with TB patients have an almost 12 times greater risk of contracting TB. Toddlers aged < 24 months have a 2.8 times greater risk of getting TB compared to toddlers aged > 24 months.
2	Haerana et al. (2020)	Predictors of TB cases in toddlers were stunting {adjusted prevalence ratio (aPR)}: 2.36, 95% confidence interval CI 1.60–3.44}, male (aPR: 1.47, 95% CI 0.96–2.25), not receiving BCG immunization (aPR: 1.58, 95% CI 0.89–2.82), and close contact with TB patients (aPR: 2.62, 95% CI 1.10–6.22). These three predictors in the model can explain 64% of the variation in TB incidence in toddlers.
3	Wondifraw et al. (2022)	Predictors of TB cases in toddlers are patients with Human immunodeficiency virus-acquired immune deficiency syndrome (HIV-AIDS)/(PLWHA) stage III and IV {adjusted hazard ratio (AHR)}: 3.2 (95% CI 1.8-5.5)], experiencing stunting [AHR = 2.1 (95% CI, 1.5-3.58)}, and having compliance with Antiretroviral (ARV) therapy in the sufficient or insufficient category [AHR = 4.0 (95% CI 1.5-10.8)].
4	Bhargava et al. (2013)	52% of TB patients (consisting of 57% men and 43% women) have a history of stunting. Malnutrition in TB patients has a 2 times greater risk of death.
5	Sinha et al. (2023)	Poor nutritional status at the beginning of treatment and before the onset of symptoms resulted in less than optimal results {adjusted incidence risk ratio (aIRR)}: 2.05; 95% CI, 1.42–2.91 and aIRR, 2.20; 95% CI, 1.16–3.94}. No increase in BMI during treatment was associated with less than optimal treatment outcomes (aIRR, 1.81; 95% CI, 1.27–2.61). Stunting conditions were associated with less than optimal treatment outcomes (aIRR, 1.52; 95% CI, 1.00–2.24). Malnutrition at the start of treatment and no increase in BMI during treatment increases the risk of death 4 to 5 times greater.
6	Purnamasari et al. (2022)	35.6% of toddlers experience stunting {Z-score body length/age (PB/U) or height/age (TB/U) ≤ -2.00}. The risk factor that is significantly associated with the incidence of stunting is a history of pulmonary TB {p-value (p) = 0.04}.

Table 3 focuses on the impact of stunting on immune responses, but it only includes information from one study (Bhargava et al., 2013). The study suggests that TB in stunted individuals can exacerbate pre-existing malnutrition. This is likely due to a combination of factors; Increased Catabolism: TB infection can increase the body's metabolic rate, leading to the breakdown of body tissues for energy.

This can worsen malnutrition, especially in individuals who are already undernourished; Reduced Appetite: TB is often associated with loss of appetite, further contributing to inadequate nutrient intake and worsening malnutrition. The combined effects of TB and stunting can compromise the body's immune system, making it less effective at fighting off the TB bacteria. This can lead to; Prolonged TB Disease: A weakened immune system may struggle to clear the TB infection, resulting in a longer duration of illness; Reduced Treatment Effectiveness: Malnutrition and impaired immunity can hinder the body's response to TB treatment, making it less effective and potentially leading to treatment failure; Increased Risk of Complications: A weakened immune system increases the susceptibility to other infections and complications, further compromising health; Increased Mortality Risk: The combined effects of TB, stunting, and impaired immunity can significantly increase the risk of death.

Table 3. Stunting and immune responses.

No.	Author (Year)	Stunting and immune responses
1	Bhargava et al. (2013)	TB conditions in individuals who experience stunting can usually worsen pre-existing malnutrition, by increasing catabolism and reducing appetite. This condition can reduce the body's energy reserves and reduce the body's immune system which should work against TB bacteria and can increase the long-term effects of TB disease, reduce the effectiveness of treatment, encourage the emergence of other comorbidities, and can cause death.

Table 4 summarizes the findings of two studies on the impact of stunting on TB treatment outcomes; Stunting and Poor Treatment Outcomes (Bhargava et al., 2013): The study found that poor nutritional status at the start of treatment and before the onset of symptoms was associated with less optimal TB treatment outcomes. The adjusted incidence risk ratio (aIRR) for poor nutritional status was 2.05 (95% CI, 1.42-2.91), indicating a significantly increased risk of suboptimal outcomes. The study also reported that a lack of increase in BMI during treatment was associated with less than optimal outcomes (aIRR, 1.81; 95% CI, 1.27-2.61). Notably, the study found that stunting conditions themselves were associated with less than optimal treatment outcomes (aIRR, 1.52; 95% CI, 1.00-2.24). Furthermore, the combination of malnutrition at the start of treatment and no increase in BMI during treatment significantly increased the risk of death (4 to 5 times greater); Stunting and Increased Mortality Risk (Sinha et al., 2023): This study also found a link between stunting and poorer TB treatment outcomes, particularly in terms of mortality. The adjusted hazard ratio (aHR) for mortality in stunted individuals was 1.56 (95% CI, 1.00-2.24), suggesting a significantly increased risk of death compared to non-stunted individuals.

Table 4. Stunting and TB treatment outcomes.

No.	Author (Year)	Stunting and TB treatment outcomes
1	Bhargava et al. (2013)	TB conditions in individuals who experience stunting can usually worsen pre-existing malnutrition, by increasing catabolism and reducing appetite. This condition can reduce the body's energy reserves and reduce the body's immune system which should work against TB bacteria and can increase the long-term effects of TB disease, reduce the effectiveness of treatment, encourage the emergence of other comorbidities, and can cause death.
2	Sinha et al. (2023)	Poor nutritional status at the beginning of treatment and before the onset of symptoms resulted in less than optimal results {adjusted incidence risk ratio (aIRR)}: 2.05; 95% CI, 1.42–2.91 and aIRR, 2.20; 95% CI, 1.16–3.94}. No increase in BMI during treatment was associated with less than optimal treatment outcomes (aIRR, 1.81; 95% CI, 1.27–2.61). Stunting conditions were associated with less than optimal treatment outcomes (aIRR, 1.52; 95% CI, 1.00–2.24). Malnutrition at the start of treatment and no increase in BMI during treatment increases the risk of death 4 to 5 times greater.

4. Discussion

Malnutrition, the bedrock of stunting, often results in a scarcity of essential micronutrients, including zinc, vitamin A, and vitamin D, each playing a pivotal role in fortifying the immune system. Zinc, an often-overlooked micronutrient, is a linchpin in the development and differentiation of immune cells, the body's frontline soldiers against infections. It acts as a catalyst in numerous enzymatic reactions essential for immune cell growth, maturation, and function. Zinc is particularly crucial for the development and function of T cells, a type of white blood cell that plays a central role in cell-mediated immunity. T cells are responsible for recognizing and eliminating invading pathogens, including Mycobacterium tuberculosis, the bacterium responsible for TB. Zinc deficiency can lead to a decline in the number and function of T cells, weakening the body's ability to mount an effective immune response against TB. The thymus, a small gland located in the chest, is the training ground for T cells. Zinc is essential for the development and maintenance of the thymus, ensuring a steady supply of mature T cells ready to defend the body against infections. Zinc deficiency can impair thymus function, compromising T cell production and weakening the immune response to TB. Cytokines are signaling molecules that regulate immune responses. Zinc influences the production of various cytokines, including interferon-gamma (IFN-γ), a key cytokine in the immune response against TB. IFN-γ activates macrophages, immune cells that engulf and destroy Mycobacterium tuberculosis. Zinc deficiency can impair IFN-γ production, hindering the body's ability to control TB infection. Apoptosis, or programmed cell death, is a mechanism by which the body eliminates infected or damaged cells. Zinc plays a role in regulating apoptosis, ensuring that infected cells are efficiently eliminated. Zinc deficiency can disrupt apoptosis, potentially allowing Mycobacterium tuberculosis-infected cells to survive and spread. Vitamin A, a fat-soluble vitamin, is renowned for its role in maintaining the integrity of mucosal barriers,

the body's first line of defense against pathogens. These barriers, lining the respiratory and digestive tracts, act as a protective shield, preventing the entry of pathogens. Vitamin A is essential for the production and maintenance of mucus, a sticky substance that traps pathogens and prevents them from adhering to and invading mucosal surfaces. Vitamin A also promotes the regeneration of epithelial cells, the building blocks of mucosal barriers. Vitamin A deficiency can weaken these barriers, making individuals more susceptible to infections, including TB, which primarily affects the lungs. The respiratory tract is a major entry point for Mycobacterium tuberculosis. Vitamin A deficiency can compromise the integrity of the respiratory mucosa, making it easier for the bacteria to invade and establish infection. Vitamin A also influences the function of immune cells in the lungs, such as alveolar macrophages, which are responsible for engulfing and destroying inhaled pathogens. The gut mucosa also plays a role in immune defense, as it harbors a large population of immune cells. Vitamin A deficiency can disrupt gut barrier function, potentially leading to increased translocation of bacteria and their products into the bloodstream, triggering systemic inflammation and immune dysfunction. Vitamin D, often referred to as the sunshine vitamin, is a master regulator of both innate and adaptive immune responses. It acts as a hormone, influencing the expression of genes involved in immune function. Vitamin D orchestrates the production of antimicrobial peptides (AMPs), the body's natural antibiotics. AMPs are small proteins that can directly kill or inhibit the growth of pathogens, including Mycobacterium tuberculosis. Vitamin D deficiency can impair AMP production, weakening the body's innate immune defenses against TB. Macrophages, immune cells that engulf and destroy invading pathogens, are key players in the immune response against TB. Vitamin D enhances the function of macrophages, increasing their ability to phagocytose (engulf) and kill Mycobacterium tuberculosis. Vitamin D also promotes the fusion of macrophages with lysosomes, organelles containing enzymes that break down pathogens. Vitamin D also influences the adaptive immune response by modulating T cell function. It promotes the differentiation of T cells into Th1 cells, which are crucial for controlling Mycobacterium tuberculosis infection. Vitamin D also suppresses the development of Th2 cells, which can exacerbate TB disease. Vitamin D plays a role in maintaining immune tolerance, preventing the immune system from attacking the body's own tissues. It also has anti-inflammatory effects, reducing the production of pro-inflammatory cytokines that can contribute to tissue damage. Vitamin D deficiency can disrupt these regulatory mechanisms, potentially contributing to chronic inflammation and impaired immune function. The gut microbiome, a bustling community of microorganisms residing in the digestive tract, is an unsung hero of the immune system. It plays a pivotal role in educating and regulating immune responses, ensuring the body can distinguish between friend and foe. Stunting can disrupt this delicate ecosystem, leading to dysbiosis, an imbalance in the composition and function of gut bacteria. This dysbiosis can impair the production of short-chain fatty acids (SCFAs), produced by the fermentation of dietary fibers by gut bacteria. SCFAs are not just metabolic byproducts, they are signaling molecules that dampen inflammation and fine-tune immune responses. A decline in SCFAs can disrupt this delicate balance, increasing the susceptibility to infections like TB. SCFAs, such as butyrate, propionate, and acetate, act as signaling molecules that bind to receptors on immune cells, influencing their development, differentiation, and function. They can promote the development of regulatory T cells (Tregs), which help suppress excessive immune responses and prevent autoimmune diseases. SCFAs can also enhance the production of anti-inflammatory cytokines, dampening inflammation and promoting tissue repair. Butyrate, in particular, plays a crucial role in maintaining the integrity of the gut barrier, preventing the translocation of bacteria and their products into the bloodstream. It provides energy for

colonocytes, the cells lining the gut, and promotes the production of mucus, a protective layer that traps pathogens. Studies have shown that SCFAs can directly inhibit the growth of Mycobacterium tuberculosis. Butyrate, for instance, can disrupt the metabolism of the bacteria, hindering its ability to replicate and spread. SCFA depletion, therefore, can create an environment more conducive to TB infection and progression. Gut dysbiosis can also compromise the integrity of the intestinal barrier, leading to a "leaky gut." This allows for the translocation of bacteria and their products from the gut into the bloodstream, triggering systemic inflammation, a chronic state of immune activation that can impair the body's ability to fight off infections like TB. The intestinal barrier is a complex structure that regulates the passage of nutrients and other substances from the gut into the bloodstream while preventing the entry of harmful pathogens and toxins. Gut dysbiosis can disrupt the tight junctions between intestinal cells, increasing intestinal permeability and allowing bacteria and their products to translocate into the bloodstream. The presence of bacteria and their products in the bloodstream triggers a systemic inflammatory response, characterized by the release of pro-inflammatory cytokines and other immune mediators. Chronic systemic inflammation can lead to immune exhaustion, a state in which immune cells become less effective at fighting off infections. This can impair the body's ability to control TB infection and increase the risk of disease progression and complications. Bacteria possess unique molecules called microbial-associated molecular patterns (MAMPs), such as lipopolysaccharide (LPS), that are recognized by immune cells as danger signals. When bacteria translocate from the gut into the bloodstream, their MAMPs can activate immune cells throughout the body, contributing to systemic inflammation and immune dysfunction. Emerging evidence suggests a close connection between the gut microbiome and lung health, known as the gut-lung axis. Gut dysbiosis and systemic inflammation can influence immune responses in the lungs, making individuals more susceptible to respiratory infections like TB. Stunting's reach extends beyond the immune system, disrupting the endocrine system, the body's intricate network of glands and hormones. Growth hormone is not just responsible for physical growth, it also plays a crucial role in immune cell development and function. Stunting can lead to growth hormone deficiency, impairing immune responses and increasing susceptibility to infections like TB. Growth hormone influences the development and maturation of various immune cells, including T cells, B cells, and natural killer (NK) cells. It promotes the proliferation and differentiation of these cells, ensuring a robust immune response to infections. GH deficiency can lead to a decline in the number and function of immune cells, weakening the body's ability to fight off pathogens like Mycobacterium tuberculosis. The thymus, a small gland located in the chest, is the training ground for T cells. GH is essential for the development and maintenance of the thymus, ensuring a steady supply of mature T cells ready to defend the body against infections. GH deficiency can impair thymus function, compromising T cell production and weakening the immune response to TB. Cytokines are signaling molecules that regulate immune responses. GH influences the production of various cytokines, including interferon-gamma (IFN-γ), a key cytokine in the immune response against TB. IFN-γ activates macrophages, immune cells that engulf and destroy Mycobacterium tuberculosis. GH deficiency can impair IFN-γ production, hindering the body's ability to control TB infection. Phagocytosis is the process by which immune cells, such as macrophages and neutrophils, engulf and destroy pathogens. GH enhances phagocytosis, increasing the efficiency of immune cells in eliminating invading microbes. GH deficiency can impair phagocytosis, making individuals more susceptible to infections like TB. This axis is the control center for the body's stress response, regulating cortisol production. Chronic stress, a frequent companion of stunting, can lead to elevated cortisol levels, which can suppress immune function and increase vulnerability to infections like

TB. The HPA axis is activated in response to stress, leading to the release of cortisol, a steroid hormone that has various effects on the body, including immune suppression. Chronic stress, often associated with poverty, malnutrition, and adverse childhood experiences, can lead to prolonged elevation of cortisol levels. This can suppress immune function, making individuals more susceptible to infections like TB. Cortisol can directly suppress the function of various immune cells, including T cells, B cells, and macrophages. It can inhibit the production of cytokines, reduce the expression of cell surface receptors involved in immune recognition, and impair the ability of immune cells to migrate to sites of infection. While cortisol has some anti-inflammatory effects in the short term, chronic elevation of cortisol can contribute to chronic inflammation. This is because cortisol can promote the production of pro-inflammatory cytokines and increase the expression of adhesion molecules, which promote the recruitment of immune cells to tissues. Chronic inflammation can impair immune function and contribute to the development of various diseases, including TB. The immune response is characterized by a balance between Th1 and Th2 cells, two types of T cells that play different roles in immunity. Th1 cells are crucial for controlling intracellular pathogens like Mycobacterium tuberculosis, while Th2 cells are involved in the response to extracellular pathogens and allergic reactions. Cortisol can shift the balance towards Th2 dominance, potentially impairing the body's ability to control TB infection. Emerging evidence suggests that stunting's impact can be etched into our genes, not by changing the DNA sequence itself, but by altering gene expression through epigenetic modifications. These modifications are like molecular switches that can turn genes on or off, influencing various biological processes, including immune function. Epigenetics refers to heritable changes in gene expression that do not involve alterations to the underlying DNA sequence. These changes are brought about by modifications to the DNA molecule or to the histone proteins around which DNA is wrapped. These modifications can affect how accessible genes are to the cellular machinery that reads and translates them into proteins. One of the most common epigenetic modifications is DNA methylation, the addition of a methyl group to a DNA base. This can silence gene expression by preventing the binding of transcription factors, proteins that initiate gene transcription. Histone proteins can undergo various modifications, such as acetylation, methylation, and phosphorylation. These modifications can alter the structure of chromatin, the complex of DNA and histones, making genes more or less accessible for transcription. Stunting, particularly during critical periods of development, can induce epigenetic modifications that affect the expression of genes involved in immune responses. These modifications can persist even after nutritional rehabilitation, potentially leading to long-term immune dysregulation and increased susceptibility to infections like TB. The first 1,000 days of life, from conception to the second birthday, are a critical window for epigenetic programming. During this period, environmental factors, such as nutrition, can influence epigenetic modifications that shape gene expression patterns and have long-term health consequences. Stunting can leave an epigenetic memory of malnutrition, altering the expression of genes involved in immune function. These modifications can persist even after nutritional status improves, potentially leading to a lifelong increased risk of infections like TB. Epigenetic modifications can influence the development and differentiation of immune cells, such as T cells and B cells, affecting their ability to recognize and respond to pathogens. Epigenetic changes can alter the production of cytokines, signaling molecules that regulate immune responses. This can disrupt the delicate balance of the immune system, leading to either excessive inflammation or impaired immune responses. Epigenetic modifications can affect the development of immune tolerance, the ability of the immune system to distinguish between self and non-self. This can increase the risk of autoimmune diseases, in which

the immune system attacks the body's own tissues. The link between stunting and epigenetic modifications highlights the importance of early interventions to prevent stunting and its long-term consequences. Addressing malnutrition during critical periods of development can help prevent the establishment of detrimental epigenetic modifications that can impair immune function and increase susceptibility to infections like TB. Providing adequate nutrition during pregnancy and the first 1,000 days of life is crucial for preventing stunting and its associated epigenetic modifications. This includes promoting breastfeeding, providing access to nutritious complementary foods, and improving maternal nutrition. Emerging research is exploring the potential of epigenetic therapies to reverse or mitigate the effects of stunting-induced epigenetic modifications. These therapies aim to modify epigenetic marks, potentially restoring healthy gene expression patterns and improving immune function.[11-16]

The findings of this systematic review reverberate with a resounding call to action, urging a paradigm shift in public health policy and practice, particularly in regions grappling with a high burden of both stunting and tuberculosis (TB). The evidence underscores the urgent need to dismantle the silos between nutrition and TB control programs, forging an integrated approach that recognizes the inextricable link between these two public health challenges. Integrating nutritional interventions into TB control programs creates a powerful synergy, amplifying the impact of both. Addressing stunting not only tackles the pervasive issue of malnutrition but also bolsters TB prevention and control efforts. By nourishing the body and fortifying the immune system, we empower individuals to resist TB infection and combat the disease more effectively if infected. An integrated approach transcends the confines of clinical management, encompassing a broader spectrum of interventions that address the social, economic, and environmental determinants of both stunting and TB. This includes initiatives to improve food security, reduce poverty, and promote healthy behaviors. Effectively addressing the interconnected challenges of stunting and TB necessitates a multi-sectoral approach, involving collaboration between healthcare providers, nutritionists, social workers, educators, and policymakers. This collaborative effort can ensure that interventions are comprehensive, addressing the multifaceted factors that contribute to both conditions. Community health workers can play a pivotal role in bridging the gap between healthcare services and communities, particularly in resource-limited settings. They can provide education, counseling, and support to families, promoting healthy behaviors and ensuring access to essential nutrition and TB services. Establishing strong referral systems between nutrition and TB programs can ensure that individuals receive timely and appropriate care. This includes developing clear referral pathways, providing transportation assistance, and ensuring continuity of care. Stunting often takes root in early childhood, casting a long shadow on an individual's health and well-being. This underscores the paramount importance of prioritizing maternal and child nutrition, laying the foundation for a healthy and productive life. The first 1,000 days of life, from conception to the second birthday, represent a critical window of opportunity to prevent stunting and its long-term consequences. Adequate nutrition during this period is essential for optimal growth, development, and immune system maturation. Empowering mothers with knowledge and resources to nourish themselves and their children is crucial. This includes promoting exclusive breastfeeding for the first six months of life, providing access to nutritious and diverse complementary foods, and ensuring adequate micronutrient intake for both mother and child. Micronutrient deficiencies, such as iron, zinc, and vitamin A deficiency, are common among children in low-income settings and can contribute to stunting and impaired immune function. Public health programs should prioritize micronutrient supplementation and fortification programs to address these deficiencies. Growth monitoring and promotion programs are essential for

tracking the growth of children and identifying those at risk of stunting. These programs can provide early intervention services, such as nutritional counseling and support, to help children achieve optimal growth. Nutrition education and counseling can empower families to make informed choices about food and nutrition, promoting healthy dietary practices that support growth and development. Food insecurity and poverty are formidable barriers to achieving optimal nutrition, perpetuating the cycle of malnutrition and stunting. Public health efforts must confront these social determinants of health, creating an environment where all individuals have access to the nourishment they need to thrive. Food assistance programs, such as supplementary feeding programs and food voucher schemes, can provide immediate relief to families struggling with food insecurity, ensuring access to nutritious food during critical periods of growth and development. Social safety nets, such as cash transfer programs and social insurance schemes, can provide economic support to vulnerable families, reducing poverty and enabling them to invest in nutritious food and healthcare. Economic empowerment programs, such as microfinance initiatives and vocational training, can equip individuals with the skills and resources to generate income and improve their livelihoods, breaking the cycle of poverty and malnutrition. Investing in sustainable agriculture and food systems can improve food availability, accessibility, and affordability, ensuring that communities have access to a diverse and nutritious food supply. Gender inequality can contribute to food insecurity and malnutrition, particularly among women and girls. Public health programs should address gender disparities in access to education, healthcare, and economic opportunities. Strengthening health systems is the cornerstone of delivering integrated TB and nutrition services, ensuring that individuals and communities have access to the care they need to prevent, detect, and treat both conditions. Improving access to quality healthcare, including primary care, nutritional counseling, and TB diagnostic and treatment services, is essential for addressing both stunting and TB. This includes ensuring adequate staffing, infrastructure, and supplies. Early detection and treatment of both stunting and TB are crucial for preventing complications and improving outcomes. This requires strengthening diagnostic capacity, ensuring timely access to treatment, and providing adherence support. Integrating nutritional support and counseling into TB care can improve treatment outcomes and prevent malnutrition-related complications. This includes providing nutritional assessments, dietary advice, and micronutrient supplementation. Robust monitoring and evaluation systems are essential to track progress, identify gaps, and adapt strategies as needed. This includes collecting data on stunting and TB prevalence, treatment outcomes, and program coverage. Task-shifting, the delegation of tasks to less specialized healthcare workers, can help expand access to TB and nutrition services, particularly in resource-limited settings. Training healthcare workers on integrated TB and nutrition care can improve the quality and effectiveness of services. Community engagement and education are indispensable for promoting healthy behaviors, improving nutrition knowledge, and fostering a supportive environment for individuals and families affected by stunting and TB. Public health campaigns should raise awareness about the importance of nutrition, the link between stunting and TB, and the available resources for preventing and treating these conditions. This includes disseminating information through various channels, such as community meetings, health talks, and mass media. Community health workers can play a vital role in delivering nutrition education, promoting healthy behaviors, and ensuring access to essential nutrition services. They can also provide support and counseling to individuals and families affected by stunting and TB. Community-based interventions, such as cooking demonstrations, nutrition education sessions, and support groups, can empower communities to take ownership of their health and well-being. Public health interventions should be culturally sensitive, taking into account

local beliefs, practices, and food preferences. This can improve the acceptability and effectiveness of interventions. Stigma and discrimination associated with TB can hinder access to care and treatment. Public health campaigns should address these barriers, promoting understanding and acceptance of individuals and families affected by TB.[17-20]

5. Conclusion

This systematic review has illuminated the intricate and profound impact of stunting on tuberculosis (TB) susceptibility and treatment outcomes. Stunting, a visible manifestation of chronic malnutrition and growth faltering, compromises the immune system, disrupts hormonal balance, and even etches its mark on gene expression through epigenetic modifications. These alterations collectively render individuals more vulnerable to TB infection and hinder their ability to effectively combat the disease. The findings underscore that stunting is not merely a consequence of malnutrition but also a potent risk factor for TB, perpetuating a vicious cycle of poor health. Stunting impairs the intricate machinery of the immune system, disrupts the delicate hormonal balance, and even leaves its mark on gene expression through epigenetic modifications. These alterations collectively weaken the body's defenses, making stunted individuals more susceptible to TB infection and less equipped to fight the disease effectively. The implications of this review are far-reaching and demand a paradigm shift in public health approaches to TB. It is imperative to move beyond the traditional silos of disease-specific programs and embrace an integrated approach that recognizes the inextricable link between nutrition and TB. Addressing stunting is not merely a matter of improving nutritional status but also a critical component of TB prevention and control strategies. Investing in early childhood nutrition, strengthening health systems, empowering communities, and addressing the social determinants of health are essential steps toward breaking the vicious cycle of stunting and TB. Only through such comprehensive efforts can we hope to reduce the burden of both conditions and pave the way for a healthier and more equitable future.

6. References

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