Article Review

From Womb to World: Immunological Pathways Influencing Stunting and 2030 Sustainability

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Abstract

Stunting, which affects around 22% of children under five worldwide, is a serious public health issue that threatens the future of generations. Traditionally linked to poor nutrition, recent research shows that immune system imbalances and chronic inflammation also play a significant role in stunting, especially in low- and middle-income countries. This review examines how immune dysfunction and inflammation impact growth from pregnancy through early childhood, highlighting the importance of immune-related pathways in growth. Key findings reveal the significant influence of maternal immune health, neonatal immune activation, and recurrent infections on stunting. The review advocates for a shift in stunting prevention strategies, suggesting that integrating immune-targeted interventions with traditional nutritional approaches can more effectively address this issue. Policy recommendations include early health screenings to monitor inflammation and immune status, maternal supplementation with essential nutrients such as vitamin D and omega-3 fatty acids, and enhancing vaccination and breastfeeding practices. These strategies align with the United Nations' Sustainable Development Goals, particularly those focused on hunger and health. By combining nutrition and immune system interventions, we can reduce stunting and ensure healthier futures for children globally.

Keywords: *Immunological Pathways, Stunting, Sustainable Development*

INTRODUCTION

Stunting remains a major global health challenge, disproportionately affecting children in low- and middle-income countries (LMICs). The World Health Organization (WHO) defines stunting as a height-for-age measurement more than two standard deviations below the median of WHO growth standards. In Ethiopia and Nepal, stunting rates exceed 40%, while in high-income countries such as Japan, the prevalence is as low as 7% (Scott et al., 2020; Seretew et al., 2024). These disparities underscore the need for a comprehensive approach that integrates both nutritional and immunological factors.

Traditionally, stunting has been attributed primarily to malnutrition, yet emerging evidence underscores the significant role of immune dysfunction and chronic inflammation. Recurrent infections, maternal health complications, and persistent low-grade inflammation disrupt key growth pathways, particularly the growth hormone (GH) axis and osteogenesis, essential for skeletal development (Arredondo-Hernandez et al., 2022; Witkowska-Sędek & Pyrżak, 2020). Chronic inflammation increases proinflammatory cytokines such as IL-6 and TNF-α, which interfere with GH signaling and reduce the bioavailability of insulin-like growth factor-1 (IGF-1), a key mediator of bone growth (Augustus et al., 2022). Additionally, immune activation impairs intestinal barrier integrity, exacerbating nutrient malabsorption and perpetuating growth deficits. Despite these insights, immunological factors remain underexplored in mainstream stunting interventions.

Current interventions, including micronutrient supplementation programs like the SHINE and PROBIT trials, have demonstrated limited success in reducing stunting, particularly in

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environments with high infectious disease burdens (Raiten & Bremer, 2020). These programs primarily address nutritional deficiencies while neglecting immune dysfunction that exacerbates growth failure. Their continued implementation is driven by feasibility and established policy frameworks, yet the absence of scalable immunological interventions limits their effectiveness. While nutritional strategies remain essential, integrating immune-based approaches is critical for improving outcomes.

The limited incorporation of immunological strategies in stunting interventions stems from challenges such as the complexity of immune modulation, the lack of standardized immunological biomarkers for growth, and logistical constraints in resource-limited settings. However, emerging evidence suggests that combining immune modulation strategies, such as maternal and infant vaccination programs and anti-inflammatory nutritional interventions, with conventional nutritional support could enhance growth outcomes (Coppola et al., 2022). Understanding the interactions between immune function, chronic inflammation, and malnutrition is essential for developing more effective interventions.

This research addresses these gaps by adopting a comprehensive life-course approach to stunting, analyzing immunological factors from prenatal through postnatal development. Unlike prior studies focusing on isolated growth stages, it examines the interplay between immune dysfunction, chronic inflammation, and nutrition across multiple critical periods. By exploring key pathways such as GH signaling, osteogenesis regulation, and immunonutrition, this study provides a more integrated understanding of stunting mechanisms (De Vadder et al., 2021; Ozen et al., 2023). Additionally, it considers both maternal and early-life immune influences, bridging the gap between maternal and child health research.

Addressing stunting through an immunological lens is essential for shaping future health policies beyond conventional nutritional strategies. Given the link between early-life immune dysfunction and long-term health, integrating immunological considerations into global health frameworks could improve intervention effectiveness and support the 2030 Sustainable Development Goals (SDGs). This study provides a comprehensive analysis of immunological mechanisms underlying stunting and proposes an integrated approach that combines nutritional and immune-based interventions. The findings are expected to inform evidence-based policies, contributing to global efforts to reduce stunting in alignment with the SDGs.

LITERATURE REVIEW

The Complexities of Stunting: A Need for Immunological Insights

Stunting, a major public health issue, particularly affects children in low- and middle-income countries (LMICs), with a prevalence of 35% in Sub-Saharan Africa and 37% in East Africa. In contrast, countries like Japan report a much lower prevalence (7%), highlighting disparities in healthcare access, nutrition, and sanitation. These figures underscore the complex interplay of socio-economic, environmental, and immunological factors contributing to stunting, further necessitating a more integrated approach to intervention (Seretew et al., 2024; Tam et al., 2020).

Multifactorial Causes of Stunting and Health Consequences Of Stunting.

Stunting results from a complex interaction of immunological, nutritional, environmental, and socioeconomic factors. Immune dysfunction, characterized by chronic inflammation and immune activation, disrupts growth pathways, including endocrine signaling and nutrient metabolism. In low- and middle-income countries, limited access to nutrition, healthcare, and sanitation, along with recurrent infections, worsens immune health and stunting. For instance, children in impoverished areas often lack clean water, adequate food, and sanitation, increasing

their susceptibility to infections and malnutrition (Seretew et al., 2024). In contrast, high-income countries like Japan see lower stunting rates due to better nutrition, healthcare access, and preventive measures, including vaccines. Healthier behaviors, such as balanced diets and early interventions, reduce stunting risk (Augustus et al., 2022). Additionally, societal factors, such as infant feeding practices and maternal education, influence stunting outcomes. In low-income countries, inadequate maternal education can lead to poor infant feeding practices, whereas in higher-income nations, better-informed parents support optimal nutrition (De Vadder et al., 2021). Thus, while immune dysfunction is central, the socioeconomic environment, shaped by economic and social factors, greatly impacts stunting prevalence and severity.

Stunting has broad consequences, affecting both physical and immune health. It leads to immune dysregulation, increasing susceptibility to infections and chronic diseases. Additionally, stunting disrupts metabolic pathways, raising the risk of obesity, diabetes, and cardiovascular diseases later in life. Cognitive impairments also limit academic and intellectual performance, impacting future economic opportunities. In high-income countries, better healthcare and nutrition reduce these effects, while in low- and middle-income countries, the impacts are more severe, contributing to long-term health and economic disparities. Addressing stunting requires an integrated approach, combining immunological and socioeconomic interventions to improve outcomes and meet the 2030 Sustainable Development Goals (Raiten & Bremer, 2020; Scott et al., 2020)

Limitation of Current Intervention and The Need for an Immunology-Based Approach

A significant limitation of current interventions is their failure to address the complex and interconnected causes of stunting, which extend beyond nutritional deficiencies. Programs like micronutrient supplementation, as seen in the SHINE and PROBIT trials, can improve immune function and bone density but fall short in tackling immune dysfunction, chronic inflammation, and recurrent infections, which are central to the development of stunting (Augustus et al., 2022; Raiten & Bremer, 2020). These interventions primarily focus on isolated nutritional deficiencies and overlook broader immune-related factors critical to growth regulation. While cost-effective, these strategies do not adequately address immune dysfunction, which worsens stunting. In low-resource settings, where healthcare access is limited, nutrition-focused strategies alone are insufficient to tackle the multifaceted nature of stunting. Furthermore, the lack of an integrated approach that considers nutrition, immune health, and infections creates gaps in current interventions. Although nutrition and sanitation programs help, they often neglect the immune mechanisms that contribute to growth failure.

To address these gaps, a more integrated approach, combining nutrition and immune health, is needed. Targeting immune dysfunction and inflammation could lead to better outcomes, but challenges such as safety concerns and production inefficiencies hinder the broader use of immunotherapies (Coppola et al., 2022). These limitations highlight the need for a more comprehensive strategy to address stunting effectively.

Immunological Pathways Influencing Stunting: From Womb to World

Prenatal Stage: Maternal Immunity and Fetal Development

The prenatal period is essential for establishing immune balance and supporting fetal growth. Maternal immune status directly impacts fetal bone development through inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines inhibit the proliferation of chondrocytes (cartilage cells) and disrupt the process of endochondral ossification, where cartilage is gradually replaced by bone (Apostol et al., 2020; Kaur et al., 2022). Elevated maternal inflammation, commonly caused by infections or chronic conditions, increases

the production of pro-inflammatory mediators. These molecules interfere with the insulin-like growth factor 1 (IGF-1) signaling pathway, which is crucial for regulating fetal skeletal growth (Gibbs & Fairfax, 2022). This disruption leads to a condition called growth hormone (GH) resistance, where GH is less effective in stimulating IGF-1 production. As a result, the impaired GH-IGF-1 signaling pathway hinders proper bone growth (Gibbs & Fairfax, 2022). Additionally, inflammatory cytokines inhibit osteoblast differentiation, the process by which bone-forming cells mature, further compromising bone mineralization and skeletal integrity.

Clinical studies indicate that elevated maternal levels of C-reactive protein (CRP) and TNF-α are associated with lower birth weight and a higher risk of postnatal stunting (Apostol et al., 2020). Infants born to mothers with chronic inflammatory conditions, such as autoimmune diseases or persistent infections, often show impaired GH-IGF-1 axis function, highlighting the role of prenatal immune dysregulation in stunting (Kaur et al., 2022). Immunological interventions, such as TNF-α inhibitors or IL-6 blockade, have shown potential in improving fetal growth outcomes (Gibbs & Fairfax, 2022).

Natal Stage: Immunological Influences on Bone Development

The natal period marks a critical transition, with neonates moving from intrauterine immune protection to independent immune function. Inflammatory responses due to preterm birth, perinatal infections, and hypoxic-ischemic events have been associated with postnatal growth failure through their effects on the growth hormone (GH), insulin-like growth factor 1 (IGF-1) axis, and bone development pathways (Chen et al., 2024; Vogtmann et al., 2023). Systemic inflammation increases levels of pro-inflammatory cytokines, such as TNF-α and interleukin-6 (IL-6), which reduce the liver's production of IGF-1 and contribute to GH resistance (Fasoulakis et al., 2023). These cytokines also disrupt bone remodeling by inhibiting osteoblast differentiation (cells responsible for bone formation) and enhancing osteoclast activity (cells responsible for bone resorption), impairing bone growth (Apostol et al., 2020).

Clinical evidence links perinatal inflammation to growth risks. Preterm infants with high TNF-α and IL-6 levels have lower IGF-1 and reduced bone mineralization, increasing their risk of early growth failure (Nomiyama et al., 2023). Neonatal sepsis, with widespread inflammation and cytokine activation, worsens GH resistance and suppresses osteoblast activity, causing long-term skeletal deficits (Kaur et al., 2022). Early anti-inflammatory treatments, such as IL-6 blockers, show promise in improving postnatal growth (Gibbs & Fairfax, 2022).

Postnatal Stage: Immunological Influence on Bone Development and Stunting

Chronic inflammation resulting from recurrent infections, gut dysbiosis (imbalance in the gut microbiota), and environmental stressors continues to be a significant factor in postnatal stunting. Ongoing immune activation leads to growth hormone (GH) resistance, marked by increased levels of inflammatory cytokines that interfere with the availability and function of insulin-like growth factor 1 (IGF-1) and disrupt bone-forming processes (Takada et al., 2023; Zhao et al., 2022). Conditions such as chronic enteropathy, which impair gut health, further limit the absorption of essential nutrients and growth factors required for proper bone development.

Clinical studies confirm that chronic immune activation is linked to stunting. Children with high levels of IL-6 and TNF-α from recurrent infections show reduced IGF-1 and impaired bone remodeling, leading to growth deficits (Giannoni et al., 2021). Research in children with chronic inflammatory diseases like juvenile idiopathic arthritis and inflammatory bowel disease further links excessive cytokine production to growth impairment (Sarver et al., 2024).

Interventions focus on reducing inflammation and restoring GH-IGF-1 function. Vaccination against infections like measles, rotavirus, and tuberculosis helps prevent growth impairment.

Immunotherapies, such as TNF-α and IL-6 inhibitors, show promise in treating inflammatory stunting, though further trials are needed to confirm their safety and effectiveness (Widjaja et al., 2023).

In conclusion, inflammatory pathways, from prenatal to postnatal stages, contribute to stunting by disrupting the GH-IGF-1 axis and osteogenesis mechanisms (bone development), leading to impaired growth. Clinical evidence links immune activation with GH resistance, lower IGF-1 levels, and impaired osteoblast function, highlighting the need for targeted interventions. Strategies like cytokine regulation, anti-inflammatory therapies, and vaccination show promise in addressing growth impairment. A holistic approach combining maternal immune regulation, control of prenatal inflammation, and postnatal interventions is key to preventing and treating stunting.

Tabel 1. Summary of Immunological Pathways Influencing Stunting Across Growth Stages

Stage	Prenatal	Natal	Postnatal
GH-IGF-1 Disruption	↓ IGF-1 transfer due to maternal inflammation	Birth stress induces cytokines → GH resistance	Chronic inflammation → SOCS proteins ↑ → GH receptor inhibition
Osteogenesis Disruption	Maternal infections impair fetal osteoblast development	Prematurity leads to IGF-1 deficiency, impaired osteoblast differentiation	TNF-α and IL-1β inhibit osteoblasts, IL-6 promotes osteoclastogenesis
Key Inflammatory Mediators	TNF-α, IL-6, IL-1β	IL-6, TNF-α	TNF-α, IL-6, IGFBP-1
Clinical Evidence	Low birth weight, reduced IGF-1 levels, increased risk of metabolic disorders	Preterm infants show lower IGF-1, increased risk of skeletal fragility	Lower IGF-1 levels, poor bone mineralization, increased risk of osteoporosis
Potential Interventions	Maternal vaccination, infection control, cytokine modulation	Colostrum, neonatal probiotics, stress management	Childhood vaccination, anti-inflammatory nutritional therapy, microbiota-targeted interventions

Source: Kaur et al. (2022), Apostol et al. (2020), Takada et al. (2023)

Immunonutrition for Growth: A Systems-Based Approach to Child Development

Immunonutrition examines how specific nutrients, such as vitamin D, zinc, omega-3 fatty acids, and probiotics, affect immune function and growth. These nutrients enhance immune resilience, reduce inflammation, and support gut barrier integrity. For example, vitamin D regulates cytokine production by activating the vitamin D receptor (VDR) on immune cells, reducing inflammation (Xiao et al., 2023). Omega-3 fatty acids, converted into resolvins and protectins, modulate inflammatory pathways via NF-κB and PPARs, contributing to inflammation control (Pelczyńska et al., 2023). Zinc stabilizes cell membranes and supports gut integrity, which helps reduce infection risks (Yoshida et al., 2020), while probiotics enhance mucosal immunity and lower systemic inflammation (Widjaja et al., 2023). These immunonutrients are crucial for preventing growth impairments, particularly in stunted populations.

Nutrition and immune function are deeply interconnected, influencing growth outcomes. Vitamin D and omega-3 fatty acids help balance cytokines and reduce chronic inflammation, which can hinder growth. The gut-immune axis also plays a critical role, with zinc and probiotics improving gut health, enhancing nutrient absorption, and lowering infection risks, as highlighted in recent research (Inzaghi et al., 2022). Additionally, micronutrients like zinc and vitamin A support the GH-IGF-1 axis, which is vital for bone growth and overall development (Yoshida et al., 2020).

Clinical studies support the positive effects of immunonutrients on growth. Vitamin D supplementation has been shown to enhance linear growth and reduce infections in at-risk children (Xiao et al., 2023). Zinc improves gut function and promotes height gain, especially in malnourished populations (Yoshida et al., 2020). Omega-3 fatty acids help maintain bone health by modulating inflammation, while probiotics improve mucosal immunity and reduce diarrhea-related stunting (Widjaja et al., 2023). These findings underscore the importance of integrating immunonutrition into public health strategies to address stunting.

To maximize immunonutrition's benefits, interventions should be tailored to specific developmental stages. The table below outlines key nutrients, their immunological mechanisms, recommended interventions, and policy approaches.

Tabel 2. Summary of Nutrients and Immunological Interventions at Different Growth Stages

Growth Stage	Key Nutrients	Immune Mechanism	Recommended Intervention	Policy Approaches
Infancy	Probiotics, Zinc	Gut integrity, infection control	Breastfeeding support, probiotic-rich diets	Integration of probiotics into maternal programs
Early Childhood	Vitamin D, Omega-3	Anti-inflammatory, bone growth	Fortified foods, fish oil supplementation	Public health fortification initiatives
Late Childhood	Zinc, Vitamin A	GH-IGF-1 support, immune function	Micronutrient supplementation programs	School-based nutrition and supplementation policies

Source: Yoshida et al. (2020), Xiao et al. (2023), Inzaghi et al. (2022).

In conclusion, immunonutrition provides a holistic approach to preventing stunting, supporting SDG 2 (Zero Hunger) and SDG 3 (Good Health and Well-Being). Despite its potential, it is underutilized in public health strategies. Future research should assess the long-term effects and scalability of immunonutrition interventions for large-scale public health programs. Policymakers should integrate these findings to improve growth outcomes in vulnerable populations.

Connecting Immunological and Nutritional Strategies with SDGs

Integrating Immunology and Nutrition for SDG 2 and SDG 3

Integrating immunology and nutrition presents a promising approach to addressing stunting by targeting both metabolic and immune pathways. Immunonutrition strategies that leverage micronutrients, probiotics, and bioactive compounds have demonstrated potential in modulating immune function and supporting growth (Calder et al., 2020). For instance, interventions providing zinc, vitamin A, selenium, and iron have been shown to enhance immune competence while reducing the burden of infections that contribute to stunting (Demetrowitsch et al., 2020; Mitra et al., 2022). Additionally, probiotics and prebiotics play a role in maintaining gut-

immune homeostasis, which is crucial for nutrient absorption and systemic immune regulation (Chen et al., 2020). Studies have shown that providing zinc can improve immune function and growth outcomes in children facing stunting (Widjaja et al., 2023).

Policy frameworks that incorporate these immunonutrition strategies alongside conventional public health measures, such as vaccination programs, infection control, and maternal health interventions, have proven successful in reducing stunting prevalence (Fazid et al., 2024). Evidence from large-scale nutritional trials and immunological studies suggests that a synergistic approach can improve child growth outcomes more effectively than single-domain interventions (Basso et al., 2024). Comparative meta-analyses assessing the impact of integrated immunology-nutrition programs across diverse populations can further strengthen the evidence base and inform policy adaptations tailored to different demographic and socioeconomic contexts (Stenberg et al., 2021)

Incorporating these integrative strategies into national nutrition and health programs can enhance their impact on SDG 2 (Zero Hunger) and SDG 3 (Good Health and Well-Being). By bridging the gap between immunological and nutritional sciences, governments and health agencies can develop more holistic, sustainable interventions to mitigate stunting and improve overall child health (Calder et al., 2020).

Research Gaps and Policy Approaches for Immunology-Based Stunting Prevention

Despite growing evidence supporting the role of immunology in growth and development, its integration into public health policies and national stunting prevention programs remains limited (Kadia et al., 2024). To bridge this gap, policymakers must prioritize immunological screening and intervention strategies within maternal and child health frameworks. One key approach is the adoption of standardized immune health assessments, which can help identify at-risk populations and enable early, targeted interventions (Calder et al., 2020). Research suggests that detecting immune dysfunction early can improve the success of nutritional interventions aimed at preventing stunting (Chen et al., 2020).

Additionally, immuno-nutritional strategies should be embedded within existing national nutrition programs. For example, including probiotics, prebiotics, omega-3 fatty acids, and micronutrients known to modulate immune function in child nutrition programs has shown promise in improving immune function and growth outcomes (Demetrowitsch et al., 2020). These interventions should be tailored to specific population needs, particularly in regions burdened by high rates of infection and malnutrition (Fazid et al., 2024).

Furthermore, collaborations between immunologists, nutritionists, and public health experts are essential to translate scientific findings into scalable community-based programs. Successful models from pilot programs, such as those combining maternal vaccination, deworming, and nutritional support, should be evaluated for broader implementation (Kadia et al., 2024). Cost-effectiveness analyses for immune-based interventions can further strengthen their feasibility for large-scale adoption (Stenberg et al., 2021). By embedding immunological principles into national stunting prevention strategies, policymakers can develop evidence-based, sustainable interventions that align with global health priorities and SDG targets.

Table 3. Policy-Oriented Summary of Research Gaps and Approaches

Key Challenge	Policy-Oriented Approach	Implementation Considerations
Limited integration of immunology into public health programs	Standardized immune health screening for at-risk populations	Develop low-cost, scalable immune assessments for maternal and child health programs

Key Challenge	Policy-Oriented Approach	Implementation Considerations
Lack of immuno-nutritional interventions in national programs	Incorporate immunomodulatory nutrients (probiotics, prebiotics, omega-3) into child nutrition initiatives	Tailor interventions to specific regional disease burdens
Poor translation of research findings into practice	Strengthen collaboration between immunologists, nutritionists, and policymakers	Use successful community-based intervention models for wider adoption
Uncertainty regarding the cost-effectiveness of immune-based strategies	Conduct economic evaluations of immuno-nutritional interventions	Generate data to support policy recommendations and funding decisions

Source: Kadia et al. (2024), Fazid et al. (2024), Stenberg et al. (2021)

Future Directions: Strengthening The Immunology-Nutrition Nexus

To fully harness the potential of immunonutrition in stunting prevention, a multidisciplinary approach is essential. Future policy frameworks should prioritize integrating immunological insights into maternal and child health programs by incorporating immune-modulating interventions into existing nutritional strategies. This requires cross-sector collaboration between immunologists, nutritionists, and public health policymakers to translate research findings into scalable, evidence-based programs (Demetrowitsch et al., 2020). Several successful models demonstrate the feasibility of integrating immunology into stunting prevention efforts. For example, initiatives combining maternal micronutrient supplementation with infection prevention strategies have shown significant improvements in child growth outcomes (Chen et al., 2020). Similarly, community-based deworming and maternal vaccination programs in sub-Saharan Africa have led to significant reductions in infection-related growth impairments, underscoring the importance of immune health in early childhood development (Calder et al., 2020). In the context of immunonutrition, trials have shown the effectiveness of providing vitamin A and zinc in improving immune function and reducing stunting in at-risk populations (Stenberg et al., 2021).

Strengthening the immunology-nutrition nexus also involves expanding global applications beyond low- and middle-income countries (LMICs). Lessons from these interventions should inform policy adaptations in various health systems, ensuring cultural and economic feasibility (Fazid et al., 2024). Comparative meta-analyses evaluating immunological interventions across diverse populations can guide tailored policy approaches (Basso et al., 2024). Furthermore, investment in immunological monitoring within public health initiatives is crucial. Integrating immune biomarker assessments into routine maternal and child healthcare, such as C-reactive protein (CRP) and pro-inflammatory cytokine profiling in malnutrition screening, can facilitate early detection of immune dysfunction linked to stunting (Foolchand et al., 2022). Additionally, fostering public-private partnerships can accelerate the development and implementation of immunonutrition programs, ensuring sustainability and accessibility (Mitra et al., 2022).

By aligning immunological strategies with global nutrition policies, public health systems can move toward more comprehensive targeted approaches to stunting prevention, ultimately contributing to the achievement of SDG 2 (Zero Hunger) and SDG 3 (Good Health and Well-Being) (Stenberg et al., 2021).

RESEARCH METHOD

This narrative review examines the link between immune dysfunction, chronic

inflammation, and nutritional interventions in stunting, especially in LMICs. It highlights how immune dysregulation and nutritional deficiencies interact across developmental stages, contributing to stunting. By integrating biological and socio-economic factors, it supports strategies aligned with SDG 2 (Zero Hunger) and SDG 3 (Good Health and Well-Being).

To maintain methodological rigor, this review adheres to PRISMA 2020 guidelines where applicable, especially in identifying and synthesizing relevant literature (Page et al., 2021). However, as a narrative review, PRISMA serves as a framework for transparent reporting rather than strict inclusion criteria. A qualitative thematic synthesis approach was employed to integrate findings, providing a comprehensive understanding of immunological and nutritional factors in stunting.

Literature Search Strategy and Selection Criteria

A structured search was performed across Web of Science, PubMed, Scopus, and Google Scholar using keywords such as 'immunological pathways,' 'chronic inflammation,' 'nutritional interventions,' and 'stunting,' with Boolean operators (AND/OR) for refinement. Reference lists of key articles were screened using snowballing techniques. Inclusion criteria were:

1. Peer-reviewed articles in English published between 2000 and 2024.
2. Studies examining the interaction between micronutrient supplementation and immune dysfunction in stunting.
3. Research on immune-mediated inflammation's effects on growth hormone (GH) signaling, IGF-1 availability, and osteogenesis.
4. Studies focused solely on immunological or nutritional aspects without their interplay were excluded.

Data Extraction and Analysis

Data extraction followed a standardized approach, capturing study details (e.g., authors, year, design, sample size, immunological markers, and nutritional interventions). A qualitative thematic analysis identified patterns highlighting the interplay between immune dysfunction, chronic inflammation, and nutritional deficiencies in stunting.

Quantitative data from studies like SHINE and PROBIT were extracted to support qualitative findings, focusing on measurable outcomes such as immunonutrition and inflammation reduction (Raiten & Bremer, 2020). We used existing data (e.g., prevalence rates, biomarker levels) to substantiate qualitative insights rather than conducting new statistical analyses. For instance, studies reporting reduced inflammatory biomarkers after micronutrient supplementation helped confirm the immunomodulatory effects. By mapping quantitative findings to qualitative themes, we ensured consistency between statistical data and thematic conclusions, reinforcing the validity of the overall analysis.

Critical Appraisal and Reliability Assessment

Included studies were appraised using standardized tools to evaluate design, methodology, biases, and reporting quality. Observational studies and self-reported data were critically considered for their limitations. Studies showing consistent trends across populations were prioritized to enhance reliability, strengthening credibility by integrating converging findings

Ethical Considerations

Since this study only uses publicly available literature and does not involve primary data, formal ethical approval was not needed. Ethical standards were maintained by including studies from reputable journals that follow ethical publishing guidelines, with transparency in data

reporting and proper citation.

In conclusion, this methodology combines qualitative thematic analysis with quantitative evidence to synthesize immunological and nutritional pathways in stunting. By addressing research gaps through an integrated, multidisciplinary approach, this review offers insights for policymakers and practitioners. The integration of quantitative data strengthens the qualitative synthesis, enhancing transparency and reproducibility. Clear documentation of the search strategy, data extraction, and analysis methods allows future researchers to replicate or build on this work.

FINDINGS AND DISCUSSION

Key Findings from the Literature

Critical Role of Immunological Pathways in Stunting

Stunting begins in the womb and continues after birth, with chronic inflammation playing a key role (Seretew et al., 2024). High levels of inflammatory molecules, particularly TNF-α and IL-6, interfere with growth hormone and IGF-1, disrupting normal growth patterns (De Vadder et al., 2021). While past research focused on nutritional deficiencies as the primary cause, recent studies highlight immune dysfunction as a critical factor (Augustus et al., 2022). Clinical trials show that micronutrient supplementation alone does not effectively counteract inflammation-driven stunting (Scott et al., 2020). However, immunonutrition strategies, such as zinc, omega-3, and vitamin D., may help regulate inflammation, while vaccination programs and gut microbiome interventions show promise in stunting prevention (De Vadder et al., 2021). These findings suggest a shift from conventional nutrition-based approaches toward immune- and microbiome-targeted strategies for more effective stunting prevention.

Prenatal Immune Development: Foundations for Growth

Maternal immune dysregulation plays a crucial role in fetal growth and stunting risk. Intrauterine inflammation, triggered by infections and chronic conditions, disrupts GH-IGF-1 signaling, impairing bone formation and increasing susceptibility to postnatal stunting (Kaur et al., 2022). Elevated TNF-α and IL-6 levels inhibit chondrocyte proliferation and osteoblast differentiation, further compromising skeletal integrity (Apostol et al., 2020). While previous studies emphasized nutritional deficiencies, recent findings highlight immune-targeted interventions. Vitamin D and omega-3 supplementation reduces intrauterine inflammation, supporting fetal bone development. Additionally, vaccination against maternal infections mitigates immune-related growth restriction (Kaur et al., 2022). Novel therapeutic approaches, including TNF-α inhibitors and IL-6 blockade, offer potential in counteracting inflammation-induced stunting (Gibbs & Fairfax, 2022).

Neonatal Immune Dysregulation: From Womb to World

Neonatal immune dysregulation contributes to early-life stunting. The transition from intrauterine to independent immunity triggers excessive immune activation, elevating TNF-α and IL-6, which disrupts GH-IGF-1 signaling, impairs bone formation, and heightens stunting risk (Fasoulakis et al., 2023). While past studies linked stunting mainly to malnutrition, recent evidence emphasizes immune-driven mechanisms, including perinatal inflammation and neonatal stress-induced cortisol elevation, which further suppress IGF-1 secretion and hinder skeletal growth (Nomiyama et al., 2023). Chronic inflammation induces GH resistance, but emerging interventions may counteract its effects. Colostrum-based therapies and probiotics help modulate immune responses, improve nutrient absorption, and enhance postnatal growth (Kaur et al., 2022). Additionally, targeted anti-inflammatory strategies, such as IL-6 blockade, may reduce immune-related stunting risks (Gibbs & Fairfax, 2022). These findings mark a shift from nutrition-based to

immune-targeted strategies for neonatal growth.

Postnatal Infections and Chronic Immune Activation in Childhood

Chronic immune activation from recurrent infections and gut dysbiosis disrupts GH-IGF-1 signaling, impairing bone development and increasing stunting risk (Sarver et al., 2024). While past studies focused on nutrient deficiencies, recent findings highlight persistent inflammation reducing growth hormone sensitivity and weakening bone formation (Zhao et al., 2022). Gut infections cause intestinal damage, limiting nutrient absorption and essential growth factors. Inflammatory cytokines like TNF-α impair osteoblastogenesis and hinder bone growth, further exacerbating stunting (Takada et al., 2023). Innovative strategies, including targeted immunotherapies, aim to regulate inflammation and counteract growth impairments. Childhood vaccination programs also help reduce stunting by preventing infections that suppress growth. Strengthening immune resilience early in life through targeted interventions is crucial for improving child health and achieving global development goals.

Micronutrients and Immunonutrition in Stunting

Micronutrients such as vitamin D, zinc, and omega-3 play a crucial role in immune regulation and growth by modulating GH-IGF-1 signaling and bone formation (Xiao et al., 2023). Unlike previous studies that primarily focused on nutrient deficiencies as the main cause of stunting, recent findings highlight that micronutrients also contribute to controlling chronic inflammation and improving gut-immune interactions, both of which influence child growth (Inzaghi et al., 2022). Zinc has been shown to strengthen gut integrity and reduce infection risk, while probiotics enhance mucosal immunity and lower systemic inflammation (Widjaja et al., 2023). Additionally, omega-3 regulates molecular pathways that suppress excessive immune activation, which can impair growth (Pelczyńska et al., 2023). A more precise immunonutrition approach could serve as an effective strategy to improve child growth outcomes, offering a new perspective compared to previous studies that primarily linked stunting to malnutrition alone.

Integrating Immunology and Nutrition for Sustainable Growth (SDGs 2 and 3)

Integrating immunological and nutritional strategies is crucial for addressing stunting and advancing SDGs 2 (Zero Hunger) and 3 (Good Health and Well-Being). Unlike earlier studies that treated nutritional supplementation and infection control separately, recent findings highlight a synergistic approach (Basso et al., 2024). Combining vaccination programs with targeted micronutrients, such as vitamin D, zinc, and omega-3, enhances immune function, reduces chronic inflammation, and improves nutrient absorption, lowering stunting risk (Calder et al., 2020). Early immune-based diagnostics, including inflammatory biomarker profiling, offer a precise framework for individualized interventions, overcoming limitations of broad nutrition strategies (Kadia et al., 2024). While prior research linked inflammation to impaired growth, it lacked immune-targeted prevention strategies (Demetrowitsch et al., 2020). Strengthening immunonutrition with personalized, immune-responsive approaches offers a sustainable, evidence-based solution to reducing stunting (Widjaja et al., 2023).

Critical Discussion and Implication

Interpretation of Findings

This review underscores the critical role of immune dysregulation in stunting, focusing on both immune dysfunction and its impact on bone growth. Chronic inflammation, driven by prenatal and postnatal immune disruptions, impedes growth by affecting the GH-IGF-1 signaling pathway

and osteogenesis. Elevated levels of inflammatory cytokines like TNF-α and IL-6 disrupt bone formation and reduce growth hormone sensitivity, central to stunting in childhood (Fasoulakis et al., 2023; Seretew et al., 2024).

However, stunting is not a phenomenon isolated to low-resource settings or nutritional deficiencies alone. In high- and middle-income countries (MHICs), rising rates of obesity and metabolic diseases, particularly among women, contribute to a different but equally concerning pathway to stunting. In these regions, women often face high levels of chronic stress and unhealthy lifestyle choices, including the overconsumption of processed foods, which are rich in chemicals and additives. These dietary patterns lead to increased inflammation and a higher prevalence of autoimmune diseases and metabolic disorders like diabetes, obesity, and cardiovascular conditions (Fasoulakis et al., 2023).

These conditions, characterized by chronic inflammation, not only deteriorate women's immune status but also compromise pregnancy outcomes, increasing the risk of complications such as intrauterine growth restriction (IUGR) and consequently raising the potential for stunting in their children. Thus, immune dysregulation, particularly in the form of chronic inflammation, emerges as a key factor influencing stunting across diverse global settings.

This insight underscores the importance of broadening the scope of stunting prevention strategies to include not only traditional nutritional interventions but also immunological considerations, even in MHICs.

Comparison with Existing Literature

This review advances stunting research by examining the interplay between immune dysfunction, chronic inflammation, and nutrition, integrating often-overlooked immune and microbial factors. While studies identify immune dysregulation as crucial in stunting, the mechanisms connecting immune dysfunction to growth impairment, particularly through the GH-IGF-1 pathway and osteogenesis, remain underexplored. Our findings align with these studies, highlighting how inflammatory cytokines like TNF-α and IL-6 disrupt growth and bone development (Fasoulakis et al., 2023; Seretew et al., 2024).

Previous research primarily focuses on nutrition, but few investigate the synergistic effects of immunonutrition. This review demonstrates how micronutrients such as zinc, vitamin D, and omega-3 fatty acids modulate immune responses and reduce inflammation, supporting immune-targeted interventions alongside nutritional approaches (Widjaja et al., 2023; Xiao et al., 2023).

Furthermore, we address the gap in prenatal immune dysregulation research. While studies explore maternal inflammation's effects, they mainly focus on pregnancy outcomes, not long-term impacts on child growth (Kaur et al., 2022). We emphasize the need for early interventions to prevent lasting stunting consequences. In conclusion, this review bridges gaps by integrating immune dysfunction and nutrition, providing a comprehensive framework for stunting prevention, especially in LMICs.

Theoretical Implications

This review refines current theoretical models of stunting by emphasizing the dual role of immune dysfunction and the immune-inflammatory response, particularly through the GH-IGF-1 and osteogenesis pathways. By integrating these two immunological mechanisms, we provide a more comprehensive framework for understanding the biological underpinnings of stunting. The incorporation of osteogenesis into immune models highlights the importance of bone growth in stunting, an area often neglected in earlier research. Moreover, this study contributes to the theoretical understanding of immunonutrition, showing how micronutrients modulate both immune responses and bone formation pathways, offering a more nuanced approach to stunting

prevention.

Practical Implications for Public Health

Addressing stunting requires practical, actionable approaches that target the underlying causes: chronic inflammation, nutritional deficiencies, and immune dysfunction. Immunotherapy, particularly with TNF-α and IL-6 inhibitors, has shown promise in reducing inflammation, thereby potentially restoring growth-related pathways such as the GH-IGF-1 axis and improving skeletal development. These therapies could provide an immediate intervention for children suffering from inflammatory-related stunting, with clinical studies indicating the potential to mitigate growth deficits caused by persistent inflammation (Giannoni et al., 2021; Sarver et al., 2024).

While LMICs have long been the focus of stunting interventions, this issue is also increasingly relevant in MHICs, where obesity, autoimmune diseases, and metabolic disorders are contributing to stunting in children, albeit through a different pathway. In these settings, where women often experience higher stress levels and poor diet quality, chronic inflammation becomes a critical factor. To address stunting in such contexts, public health programs should integrate immunotherapeutic and immunonutritional strategies that target both the immune system and nutritional deficiencies. This approach could be especially beneficial for managing the rising prevalence of childhood stunting in countries with advanced healthcare systems, where obesity and metabolic diseases are more common.

Furthermore, in both LMICs and MHICs, integrating these immunotherapeutic and immunonutritional strategies into national health frameworks would promote a more holistic approach to stunting prevention. This integrated model could have far-reaching effects, ensuring more effective interventions that reduce stunting globally, not just in low-resource settings.

Policy Recommendations and Integration with SDGs

To combat stunting and improve child health, policy interventions must integrate immunological, nutritional, and environmental factors from preconception to early childhood. Policies should prioritize pre-pregnancy health screening to address chronic inflammation, optimize nutrition, and improve immune function, ensuring women enter pregnancy with a healthier immune status. Maternal screening for immune status, hormonal levels, and general health should be covered by accessible national health insurance schemes, such as BPJS in Indonesia, to ensure inclusivity.

Screening programs should be embedded in existing primary healthcare services like community health centers (*Posyandu*), with trained health workers to assess and manage immune-related risks. Additionally, micronutrient supplementation, especially with zinc, vitamin D, and omega-3 fatty acids, should be integrated into immunization schedules and maternal health visits, supporting immune function and reducing inflammation. Encouraging vaginal delivery to expose newborns to beneficial microbiota and promoting exclusive breastfeeding are also essential for supporting infant health and growth.

These strategies align with SDG 2 (Zero Hunger) and SDG 3 (Good Health and Well-Being), providing a holistic approach to stunting prevention. By integrating these interventions into national health programs and ensuring accessibility for marginalized populations, these recommendations can effectively reduce stunting and improve long-term health outcomes.

Strengths and Limitations of the Study

This narrative review takes a comprehensive life-course approach to stunting, exploring immunological dynamics from prenatal stages through delivery and postnatal development. Unlike single-stage studies, it examines the complex interplay of immune dysfunction, chronic

inflammation, and nutrition across multiple periods. Focusing on growth hormone (GH) signaling and osteogenesis pathways, along with immunonutrition, it provides a holistic understanding of stunting. This broad perspective offers valuable insights for more effective interventions.

However, limitations include reliance on existing literature, which introduces biases and variability, affecting consistency. The lack of systematic meta-analysis prevents precise quantification of immune dysfunction's impact. Many immunological mechanisms remain poorly understood due to limited human data. Additionally, observational and cross-sectional studies make causal conclusions difficult. Finally, while immunology and nutrition are integrated, standardized immune-based interventions for stunting remain underdeveloped, highlighting the need for further research.

Future Research Directions

Future research should integrate a more holistic approach combining immunology and nutrition to address current intervention limitations in stunting prevention. Studies should focus on developing immunomodulatory therapies, such as TNF-α and IL-6 inhibitors, to reduce chronic inflammation and support growth pathways like GH-IGF-1 (Giannoni et al., 2021; Sarver et al., 2024). Immunonutrition interventions utilizing zinc, vitamin D, and omega-3 supplements show significant potential to enhance immune function, improve nutrient absorption, and reduce infections, thereby preventing stunting (Widjaja et al., 2023).

Further research is needed to assess the effectiveness of combining these interventions in correcting immune imbalances contributing to stunting. Longitudinal studies using immune biomarkers from prenatal stages to early childhood are crucial to clarify the causal relationship between immune activation and stunting. Additionally, multi-omics approaches revealing new immune-metabolic pathways could open new therapeutic possibilities.

Finally, evaluating the implementation of immunological interventions within public health policies, particularly in resource-limited countries, is essential to achieving SDG 2 (Zero Hunger) and SDG 3 (Good Health and Well-Being).

CONCLUSIONS

This study highlights the important immune system pathways involved in stunting, providing new insights into the mechanisms behind this global health issue. By focusing on immune system dysfunction alongside poor nutrition, the research offers a deeper understanding of stunting, extending beyond just nutritional deficiencies. It emphasizes the need for a combined approach that includes both immune system and nutritional interventions to effectively tackle this challenge.

The findings suggest that immune system imbalances in mothers and early childhood immune development play a key role in determining long-term health outcomes for children, especially regarding stunting. Inflammation during pregnancy and after birth disrupts growth hormones, harms bone development, and increases the risk of stunting. This study fills gaps in existing research by exploring immune-related factors that were previously underexplored, offering new perspectives that could guide future research in both basic and clinical health studies.

From a policy standpoint, it is crucial to integrate knowledge of immune system mechanisms into strategies for reducing stunting. Current interventions that focus mostly on nutrition could be more effective if they also include monitoring and targeted interventions for the immune system, especially in vulnerable populations. Practical recommendations include adding immune system assessments to routine child health checks alongside nutrition programs to identify and address immune deficiencies that contribute to stunting. Additionally, national health programs could combine vaccination initiatives with strategies that boost nutrition and regulate

inflammation, such as vitamin D, zinc, and omega-3 supplements, to enhance growth and development outcomes. Strengthening healthcare systems to offer combined nutrition and immune health programs, particularly in maternal and child health services, would provide a more holistic approach to childhood health.

This integrated approach offers a sustainable solution to reducing stunting and contributes to achieving the United Nations' Sustainable Development Goals (SDGs), particularly SDG 2 (Zero Hunger) and SDG 3 (Good Health and Well-Being). Future research should continue exploring immune system pathways involved in stunting and how interventions can help address these pathways to prevent stunting early in life.

LIMITATION & FURTHER RESEARCH

Limitations of Current Research

This narrative review examines immunological pathways in stunting but has several limitations. First, relying on existing literature introduces selection bias and methodological variability, leading to inconsistencies in outcomes. The lack of a systematic meta-analysis prevents precise quantification of immune dysfunction's impact on stunting. Second, some immunological mechanisms, particularly immune activation, microbiota composition, and metabolic interactions, remain poorly understood due to limited human data. Third, most studies are observational or cross-sectional, limiting causal conclusions. Finally, while the review integrates immunology and nutrition, standardized immune-based interventions for stunting are underdeveloped, underscoring the need for further translational research.

Future Research Directions

To address these limitations, future studies should focus on the following research gaps:

a. Bridging the Immunology Gap
   Future research should incorporate immunological insights into stunting studies, focusing on inflammation and immune suppression. Large cohort studies are needed to assess immune activation patterns across populations.
b. Causal Links Between Immune Activation and Stunting
   Longitudinal studies tracking immune biomarkers (e.g., TNF-α, IL-6, IGF-1) from prenatal to childhood are needed to establish causality. Multi-omics approaches can uncover novel immuno-metabolic pathways.
c. Immuno-Nutritional Interventions
   RCTs should explore immune-modulating nutrients (e.g., omega-3, vitamin D, and probiotics) and their effect on inflammation and growth. Research should integrate these with existing nutrition programs.
d. Gut-Immune-Metabolic Interactions
   Research should examine how gut dysbiosis affects immune activation and growth. Long-term studies on microbiota modulation (e.g., probiotics, prebiotics) can reveal benefits for child growth.
e. Translating Research into Public Health Policy
   Studies should evaluate integrating immune health assessments into maternal-child health programs. Cost-effectiveness analyses are needed for immune-based interventions in public policies.
f. Research in Low- and Middle-Income Countries (LMICs)
   Research in LMICs should identify regional immune risk factors, assess community interventions, and examine socioeconomic and environmental influences on immune-related stunting.

Addressing these gaps will improve immunology-based stunting prevention, refine policies, and support sustainable, evidence-driven child growth interventions globally.

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