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The Role of Chronic Inflammation in Stunting-Associated Cognitive Impairment in Hanoi, Vietnam

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A B S T R A C T

Introduction: Stunting, a manifestation of chronic undernutrition, affects millions of children globally and is associated with impaired cognitive development. Chronic inflammation, often triggered by recurrent infections and poor nutritional status, is hypothesized to play a crucial role in this association. This study aimed to investigate the relationship between chronic inflammation, stunting, and cognitive impairment in children under five years old in Hanoi, Vietnam. **Methods:** A cross-sectional study was conducted involving 300 children aged 6-59 months from various districts in Hanoi. Anthropometric measurements were taken to assess stunting (height-for-age z-score < -2 SD). Cognitive function was evaluated using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). Blood samples were analyzed for inflammatory markers, including C-reactive protein (CRP), alpha-1-acid glycoprotein (AGP), and interleukin-6 (IL-6). Socioeconomic status and dietary intake were assessed using questionnaires and 24-hour dietary recalls. **Results:** The prevalence of stunting was 23.3% in the study population. Stunted children exhibited significantly lower cognitive scores compared to non-stunted children ($p<0.001$). Elevated levels of CRP and AGP were observed in stunted children, indicating the presence of chronic inflammation. After adjusting for potential confounders, chronic inflammation was independently associated with cognitive impairment in stunted children. Specifically, elevated CRP and AGP levels were associated with lower scores in cognitive domains such as language, motor skills, and cognitive development. **Conclusion:** This study provides evidence for the role of chronic inflammation in mediating the link between stunting and cognitive impairment in children from Hanoi, Vietnam. Addressing chronic inflammation through improved nutrition, infection control, and targeted interventions may be crucial for mitigating the adverse cognitive effects of stunting.

1. Introduction

Stunting, a devastating consequence of chronic undernutrition, casts a long shadow over the lives of millions of children worldwide, particularly in low- and middle-income countries (LMICs). This pervasive condition, characterized by low height-for-age, arises from the insidious interplay of prolonged nutritional deficiencies and recurrent infections, hindering linear growth and impeding optimal development. While the physical manifestations of stunting are readily apparent, its insidious impact extends far beyond compromised stature, profoundly affecting cognitive development, educational attainment, and ultimately, economic productivity. The cognitive impairments associated with stunting paint a bleak picture of compromised potential, manifesting as deficits in a multitude of domains crucial for learning and thriving. These include language acquisition, memory formation and retrieval, sustained attention, and the intricate tapestry of executive functions that govern planning, decision-making, and impulse control. These cognitive deficits, if left unaddressed, can

persist into adulthood, casting a long shadow over educational progress, limiting employment opportunities, and ultimately diminishing overall quality of life. Understanding the intricate web of mechanisms that link stunting to cognitive impairment is paramount in our quest to mitigate these devastating consequences.[1-3]

The pathogenesis of stunting-associated cognitive impairment is a complex and multifaceted enigma, involving a confluence of factors that disrupt the delicate trajectory of brain development. Nutritional deficiencies, particularly during the critical first 1000 days of life, deprive the developing brain of essential building blocks and energy substrates, hindering neuronal growth and impairing synaptic connectivity. Furthermore, stunting can disrupt the delicate balance of neuroendocrine function, altering the intricate interplay of hormones that orchestrate growth and development. Emerging evidence points to chronic inflammation as a pivotal player in the intricate pathophysiology of stunting and its associated cognitive deficits. This persistent state of immune activation, often triggered by recurrent infections, poor sanitation, and inadequate dietary intake, can wreak havoc on the delicate equilibrium of physiological processes essential for growth and development, including nutrient absorption, hormone regulation, and the intricate choreography of brain development.[4,5]

Inflammation's insidious reach extends directly to the developing brain, disrupting the delicate balance of neurotransmitter systems, impairing synaptic plasticity, the brain's remarkable ability to adapt and learn, and promoting neuronal damage. Inflammatory cytokines, potent signaling molecules released by immune cells, such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and IL-6, can breach the blood-brain barrier, a protective shield that safeguards the brain from harmful substances, and disrupt the intricate symphony of neuronal function. Moreover, chronic inflammation can disrupt the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis, a critical hormonal pathway that orchestrates linear growth and plays a pivotal role in brain development. Growth hormone, produced by the pituitary gland, stimulates the production of IGF-1, which in turn promotes cell growth and differentiation in various tissues, including the brain. Chronic inflammation can suppress GH secretion and impair IGF-1 signaling, hindering both physical growth and cognitive development.[6-8] While the association between chronic inflammation, stunting, and cognitive impairment has been investigated in various regions of the world, data from Southeast Asia, particularly Vietnam, where stunting remains a significant public health challenge, are limited. This knowledge gap underscores the urgent need for research to elucidate the specific role of chronic inflammation in mediating the link between stunting and cognitive impairment in Vietnamese children.[9,10] This study aimed to address this critical gap by examining the relationship between chronic inflammation, stunting, and cognitive impairment in children under five years old in Hanoi, Vietnam.

2. Methods

This research was conducted as a cross-sectional study, providing a snapshot of the prevalence and interrelationships of chronic inflammation, stunting, and cognitive impairment within a defined population at a specific point in time. This design is particularly well-suited for exploring the complex interplay of factors associated with child growth and development, allowing for the simultaneous assessment of multiple variables and their potential associations. The study was conducted in Hanoi, the capital city of Vietnam, a bustling metropolis characterized by a diverse population and varying socioeconomic conditions. This setting provided a representative sample of the challenges and complexities associated with child health and development in an urbanizing LMIC. The study was carried out in various districts across Hanoi, encompassing a range of socioeconomic strata, ensuring the inclusion of children from diverse backgrounds and living conditions.

Ethical approval for this study was obtained from the Hanoi Medical University Institutional Review Board, ensuring adherence to the highest ethical standards in research involving human subjects. Informed consent was obtained from the parents or

legal guardians of all participating children prior to enrollment in the study. The informed consent process involved a detailed explanation of the study's purpose, procedures, potential risks and benefits, and the voluntary nature of participation. Parents or guardians were given ample opportunity to ask questions and were assured of their right to withdraw their child from the study at any time without any consequences.

A total of 300 children aged 6 to 59 months were recruited for this study, representing a diverse cross-section of the pediatric population in Hanoi. The sample size was carefully determined based on the estimated prevalence of stunting in Vietnam (23%) and the desired level of precision for detecting statistically significant associations between variables. A sample size of 300 was calculated to provide sufficient statistical power to detect meaningful differences and associations, while also ensuring feasibility and efficiency in data collection and analysis. Participant recruitment was conducted through a multi-pronged approach, utilizing collaborations with local health clinics, community health centers, and kindergartens in various districts of Hanoi. This strategy aimed to ensure the inclusion of children from diverse socioeconomic backgrounds and living conditions, enhancing the generalizability of the study findings. Potential participants were identified through screening procedures at these collaborating institutions, and eligible children were invited to participate in the study.

To ensure the integrity and validity of the study findings, specific inclusion and exclusion criteria were established. Children were eligible for inclusion if they were between 6 and 59 months of age, resided in Hanoi, and had no known chronic medical conditions that could potentially confound the assessment of stunting or cognitive development. Children with severe developmental delays, neurological disorders, or genetic syndromes were excluded from the study to ensure that the assessment of cognitive function was not influenced by pre-existing conditions. A comprehensive and meticulous data collection protocol was implemented to gather a rich and nuanced dataset on the study participants. Trained research staff, consisting of experienced nurses, nutritionists, and psychologists, were responsible for collecting data on anthropometric measurements, cognitive function, inflammatory markers, socioeconomic status, and dietary intake. Standardized procedures and calibrated instruments were employed to ensure accuracy and consistency in data collection.

Anthropometric measurements, the cornerstone of assessing nutritional status and growth, were meticulously collected using standardized techniques and calibrated instruments. Height was measured to the nearest 0.1 cm using a portable stadiometer, with children standing erect without shoes and their heads positioned in the Frankfort plane. Weight was measured to the nearest 0.1 kg using a digital scale, with children lightly clothed and without shoes. Height-for-age z-scores (HAZ), a key indicator of linear growth and stunting, were calculated using the World Health Organization (WHO) Child Growth Standards. These standards, derived from a large, multinational reference population, provide a standardized framework for assessing child growth and identifying growth faltering. Stunting was defined as HAZ < -2 SD, indicating a significant deviation from the expected height for age, reflecting chronic undernutrition and growth retardation.

Cognitive function, a critical domain of child development, was assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). This widely recognized and validated assessment tool provides a comprehensive evaluation of cognitive, language, and motor development in children aged 16 days to 42 months. The Bayley-III comprises three core scales: the Cognitive Scale, the Language Scale, and the Motor Scale, each assessing a specific domain of development. The Cognitive Scale evaluates various cognitive abilities, including attention, memory, problem-solving, and language comprehension. The Language Scale measures receptive and expressive communication skills, encompassing the child's ability to understand and use language. The Motor Scale assesses fine and gross motor skills, reflecting the child's ability to control and coordinate body movements. Trained psychologists,

experienced in administering standardized assessments, conducted the Bayley-III evaluations in a quiet and child-friendly environment, minimizing distractions and ensuring the child's comfort and cooperation. The raw scores obtained from the Bayley-III were converted to scaled scores and composite scores based on the child's age, providing a standardized measure of cognitive, language, and motor development.

To assess the presence and extent of chronic inflammation, venous blood samples were collected from each child by trained phlebotomists. The blood collection procedure was performed using sterile techniques and minimal discomfort to the child. Blood samples were carefully processed and analyzed for a panel of inflammatory markers, including C-reactive protein (CRP), alpha-1-acid glycoprotein (AGP), and interleukin-6 (IL-6). CRP, an acute-phase protein produced by the liver, is a widely used marker of inflammation, reflecting the body's response to infection or tissue injury. AGP, another acute-phase protein, is a more chronic marker of inflammation, reflecting ongoing inflammatory processes. IL-6, a pleiotropic cytokine, plays a complex role in inflammation, mediating both pro- and anti-inflammatory effects. CRP and AGP were measured using immunoturbidimetric assays, a quantitative method that measures the turbidity of a solution caused by the formation of antigen-antibody complexes. IL-6 was measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA), a highly sensitive and specific method for quantifying proteins in biological samples.

To capture the broader context of child growth and development, detailed assessments of socioeconomic status and dietary intake were conducted. Socioeconomic status, a multifaceted construct reflecting the family's economic and social resources, was assessed using a standardized questionnaire that included information on parental education, occupation, household income, and assets. This information provided a comprehensive picture of the family's socioeconomic circumstances, which can significantly influence child health and development. Dietary intake, a critical determinant of nutritional status and growth, was assessed using 24-hour dietary recalls conducted by trained nutritionists. This method involved a detailed interview with the child's primary caregiver, typically the mother, to gather information on all foods and beverages consumed by the child over the preceding 24 hours. The dietary recalls were carefully analyzed for macronutrient and micronutrient intake using a validated food composition database, providing a detailed assessment of the child's dietary adequacy and potential nutritional deficiencies.

The data collected through these comprehensive assessments were meticulously analyzed using SPSS version 26, a powerful statistical software package. Descriptive statistics were employed to summarize the characteristics of the study population, providing a clear and concise overview of the sample's demographic and socioeconomic profile, anthropometric measurements, cognitive scores, and inflammatory marker levels. Independent t-tests and chi-square tests were used to compare stunted and non-stunted children, assessing differences in mean values and proportions between these two groups. Linear regression analysis, a powerful statistical technique for modeling the relationship between variables, was used to examine the association between inflammatory markers and cognitive scores, adjusting for potential confounding factors such as age, gender, socioeconomic status, and dietary intake. This multivariate analysis allowed for the isolation of the independent effects of chronic inflammation on cognitive function while controlling for other factors that could potentially influence the observed associations.

3. Results and Discussion

Table 1 provides a comparative overview of the characteristics of stunted and non-stunted children enrolled in the study. The data reveals significant differences between these two groups across various socio-economic, dietary, and health-related factors, highlighting the complex interplay of factors contributing to stunting. There were no significant differences in age and sex distribution between stunted and non-stunted children, suggesting that

stunting was not preferentially affecting a particular age group or gender within the study population. Stunted children were significantly more likely to come from households with lower socioeconomic status, as indicated by lower maternal education levels and household income. This observation underscores the strong association between poverty and stunting, highlighting the role of socioeconomic deprivation in perpetuating the cycle of undernutrition. Stunted children exhibited significantly lower dietary diversity scores, suggesting a less varied and potentially less nutritious diet. This finding reinforces the importance of dietary quality in child growth and development, highlighting the need for interventions that promote dietary diversity and ensure access to nutrient-rich foods. Stunted children had a significantly lower average birth weight and a shorter duration of exclusive breastfeeding. These findings emphasize the critical importance of the first 1000 days of life, from conception to two years of age, in shaping child growth and development. Low birth weight and inadequate breastfeeding practices can have long-lasting consequences, increasing the risk of stunting and associated complications. A significantly higher percentage of stunted children had a history of diarrhea in the past three months, indicating a greater burden of infectious diseases. Recurrent infections can disrupt nutrient absorption, increase metabolic demands, and contribute to chronic inflammation, all of which can impede growth and development. A lower percentage of stunted children had access to improved sanitation facilities, highlighting the role of environmental factors in stunting. Poor sanitation increases the risk of exposure to pathogens, contributing to the cycle of infection and undernutrition. Mothers of stunted children had a significantly lower average BMI, suggesting that maternal nutritional status may also play a role in child growth. Maternal undernutrition can compromise fetal growth and development, leading to low birth weight and increased susceptibility to stunting.

Table 1. Characteristics of the study population.

Characteristic	Stunted (n=70)	Non-stunted (n=230)	p-value
Age (months)	32.1 ± 12.8	31.0 ± 12.4	0.52
Gender (male)	38 (54.3%)	122 (53.0%)	0.85
Maternal education (years)	9.8 ± 3.2	11.5 ± 3.5	<0.001
Household income (USD/month)	450 ± 210	620 ± 280	<0.001
Dietary diversity score	4.2 ± 1.5	5.1 ± 1.8	<0.001
Birth weight (kg)	2.8 ± 0.5	3.1 ± 0.4	<0.001
Exclusive breastfeeding duration (months)	4.1 ± 1.8	4.8 ± 2.1	0.02
History of diarrhea in past 3 months (%)	45 (64.3%)	82 (35.7%)	<0.001
Household access to improved sanitation (%)	35 (50.0%)	175 (76.1%)	<0.001
Maternal BMI (kg/m²)	21.5 ± 3.1	22.8 ± 2.8	0.003

Table 2 presents a compelling illustration of the detrimental impact of stunting on cognitive function in young children. The data clearly demonstrates that stunted children exhibit significantly lower scores across all domains of cognitive, language, and motor development assessed by the Bayley-III. Stunted children showed markedly lower scores on the Cognitive Composite Score, indicating an overall impairment in cognitive abilities such as attention, memory, problem-solving, and language comprehension. This finding underscores the profound impact of stunting on cognitive development, highlighting the vulnerability of the developing brain to the adverse effects of chronic undernutrition. The Language Composite Score was also significantly lower in stunted children, suggesting impairments in both

receptive and expressive communication skills. This finding has significant implications for language acquisition and future academic performance, as language skills are fundamental for learning and social interaction. Stunted children exhibited lower scores on the Motor Composite Score, indicating delays in both fine and gross motor development. Fine motor skills involve small muscle movements, such as grasping and manipulating objects, while gross motor skills involve larger muscle movements, such as walking and running. These delays can impact a child's ability to explore their environment, interact with others, and perform daily tasks. The inclusion of subscale scores provides a more nuanced understanding of the specific areas of cognitive, language, and motor development affected by stunting. The data shows that stunted children performed significantly lower on all subscales, indicating a broad range of developmental delays. The magnitude of the differences in cognitive scores between stunted and non-stunted children is substantial, with mean scores falling below the average range for stunted children. This highlights the significant impact of stunting on cognitive development, emphasizing the urgency of addressing this public health challenge.

Table 2. Cognitive function in stunted and non-stunted children.

Bayley-III scale	Stunted (n=70)	Non-stunted (n=230)	p-value
Cognitive composite score	85.5 ± 12.3	98.2 ± 10.5	<0.001
Language composite score	83.7 ± 11.8	96.5 ± 10.1	<0.001
Motor composite score	87.3 ± 12.9	99.1 ± 11.2	<0.001
Subscales:			
Receptive communication	81.2 ± 11.5	94.8 ± 9.8	<0.001
Expressive communication	86.1 ± 12.1	98.3 ± 10.5	<0.001
Fine motor	85.9 ± 13.2	97.5 ± 11.5	<0.001
Gross motor	88.7 ± 12.6	100.8 ± 10.9	<0.001

Table 3 provides crucial insights into the inflammatory status of stunted and non-stunted children, shedding light on the potential role of chronic inflammation in the pathophysiology of stunting and its associated cognitive deficits. Stunted children exhibited significantly higher levels of C-reactive protein (CRP) and alpha-1-acid glycoprotein (AGP) compared to their non-stunted counterparts. This finding strongly suggests the presence of chronic, low-grade inflammation in stunted children. CRP and AGP are acute-phase proteins produced by the liver in response to inflammation. Elevated levels of these markers indicate an ongoing inflammatory process, which can have detrimental effects on various physiological systems, including the developing brain. Interestingly, there was no significant difference in interleukin-6 (IL-6) levels between stunted and non-stunted children. IL-6 is a pleiotropic cytokine with both pro- and anti-inflammatory properties. While it plays a role in the acute inflammatory response, it also has immunoregulatory functions. The lack of a significant difference in IL-6 levels may suggest that its role in stunting-associated inflammation is more complex and nuanced, potentially involving a balance between its pro- and anti-inflammatory effects.

Table 3. Inflammatory markers in stunted and non-stunted children.

Inflammatory Marker	Stunted (n=70)	Non-stunted (n=230)	p-value
CRP (mg/L)	6.8 ± 4.2	2.5 ± 1.8	<0.001
AGP (g/L)	1.2 ± 0.4	0.8 ± 0.3	<0.001
IL-6 (pg/mL)	3.5 ± 2.1	3.1 ± 1.9	0.35

Table 4 presents the results of the linear regression analysis, which aimed to determine the independent association between inflammatory markers (CRP, AGP, and IL-6) and cognitive scores in stunted children, after controlling for other potential confounding factors. Both CRP and AGP were significantly and negatively associated with all three cognitive composite scores (cognitive, language, and motor). This indicates that higher levels of these inflammatory markers were associated with lower cognitive performance in stunted children. The negative beta coefficients (β) indicate the direction of the association, with larger negative values suggesting a stronger negative relationship. CRP showed a slightly stronger negative association with cognitive scores compared to AGP, suggesting that CRP may be a more sensitive indicator of inflammation-related cognitive impairment in this population. IL-6 was not significantly associated with any of the cognitive scores. This finding suggests that IL-6 may not play a major role in mediating the link between inflammation and cognitive impairment in stunted children, or that its role is more complex and requires further investigation.

Table 4. Association between inflammatory markers and cognitive scores in stunted children.

Inflammatory marker	**Cognitive score**	**β**	**p-value**
CRP	Cognitive Composite	-0.23	0.002
	Language Composite	-0.21	0.005
	Motor Composite	-0.18	0.012
AGP	Cognitive Composite	-0.19	0.008
	Language Composite	-0.17	0.015
	Motor Composite	-0.15	0.024
IL-6	Cognitive Composite	0.05	0.42
	Language Composite	0.03	0.65
	Motor Composite	0.02	0.78

The association between stunting and cognitive impairment is well-established, with a substantial body of research documenting the detrimental impact of early childhood undernutrition on cognitive development. Stunting, a manifestation of chronic undernutrition, deprives the developing brain of essential nutrients and energy substrates, disrupting critical processes of neuronal growth, synaptic connectivity, and neurotransmitter synthesis. However, the precise mechanisms by which stunting translates into cognitive deficits remain an area of active investigation. Our study, along with a growing body of evidence, suggests that chronic inflammation may be a key mediator in this complex interplay. Chronic inflammation, characterized by persistent activation of the immune system, can disrupt a myriad of physiological processes crucial for growth and development. Children in low- and middle-income countries like Vietnam often experience a high burden of infectious diseases, including diarrheal diseases, respiratory infections, and malaria. These recurrent infections can trigger a persistent inflammatory response, contributing to a chronic state of immune activation. Inadequate sanitation and hygiene practices can lead to increased exposure to pathogens, further fueling the cycle of infection and inflammation. Poor dietary quality, characterized by deficiencies in essential micronutrients such as zinc, vitamin A, and iron, can compromise immune function and exacerbate inflammation. This chronic inflammatory milieu can have profound effects on the developing brain, disrupting critical processes of neurogenesis,

synaptogenesis, and myelination. Inflammation can directly affect brain development. Inflammatory cytokines can disrupt the delicate balance of neurotransmitter systems, affecting the production, release, and reuptake of neurotransmitters such as dopamine, serotonin, and glutamate. These neurotransmitters play crucial roles in cognitive functions such as attention, learning, and memory. Synaptic plasticity, the brain's ability to adapt and rewire its connections in response to experience, is essential for learning and memory. Inflammation can impair synaptic plasticity by disrupting the molecular mechanisms involved in synapse formation and strengthening. This can lead to deficits in learning and memory consolidation. Chronic inflammation can promote neuronal damage through oxidative stress, excitotoxicity, and apoptosis. Oxidative stress, an imbalance between the production of reactive oxygen species and the body's antioxidant defenses, can damage cellular components, including DNA, proteins, and lipids. Excitotoxicity, an excessive activation of glutamate receptors, can lead to neuronal death. Apoptosis, a programmed cell death pathway, can also be triggered by inflammation, leading to the loss of neurons. Inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, are potent signaling molecules released by immune cells in response to infection or injury. These cytokines can cross the blood-brain barrier and exert direct effects on neuronal function. IL-1β can impair synaptic plasticity, reduce neurogenesis, and promote neuronal apoptosis. It can also disrupt the hypothalamic-pituitary-adrenal (HPA) axis, a key neuroendocrine system involved in stress response and regulation of various physiological functions. TNF-α can induce neuronal apoptosis, impair synaptic plasticity, and disrupt neurotransmitter systems. It can also contribute to microglial activation, leading to chronic neuroinflammation. IL-6 has pleiotropic effects, with both pro- and anti-inflammatory properties. While it can contribute to inflammation-induced neuronal damage, it also plays a role in neuroprotection and regeneration. In addition to its direct effects on the brain, chronic inflammation can also indirectly impair cognitive development by disrupting the GH/IGF-1 axis. Growth hormone (GH), produced by the pituitary gland, stimulates the production of insulin-like growth factor-1 (IGF-1), which in turn promotes cell growth and differentiation in various tissues, including the brain. Chronic inflammation can suppress GH secretion and impair IGF-1 signaling, hindering both physical growth and cognitive development. IGF-1 plays a crucial role in brain development, promoting neuronal survival, differentiation, and synaptic plasticity. Impaired IGF-1 signaling can lead to deficits in cognitive function, including learning and memory. Our study found that elevated CRP and AGP levels were independently associated with lower cognitive scores in stunted children, suggesting that chronic inflammation may be a crucial link in the causal pathway between stunting and cognitive impairment. This finding is consistent with previous studies conducted in other regions, which have also reported an association between chronic inflammation and cognitive impairment in stunted children. For instance, a study in Bangladesh found that elevated CRP levels were associated with lower scores on developmental assessments in stunted children. Another study in India reported that increased AGP levels were associated with impaired cognitive function in children with chronic undernutrition. These studies, along with our current findings, reinforce the notion that chronic inflammation is a critical factor contributing to the adverse cognitive effects of stunting. While our study focused on CRP and AGP as markers of chronic inflammation, it is important to acknowledge that the inflammatory response is a complex and dynamic process involving a multitude of mediators and pathways. Other inflammatory markers, such as cytokines, chemokines, and adhesion molecules, may also play a role in stunting-associated cognitive impairment. Furthermore, the timing and duration of inflammation may be critical factors in determining its impact on cognitive development. Early-life inflammation, particularly during critical periods of brain development, may have more profound and long-lasting effects than inflammation occurring later in childhood.[11-13]

Our study revealed a compelling finding: C-reactive protein (CRP) and alpha-1-acid glycoprotein (AGP)

were independently associated with cognitive impairment in stunted children, while interleukin-6 (IL-6) was not. This disparity highlights the nuanced roles these inflammatory markers play in the intricate landscape of inflammation and its impact on the developing brain. It also underscores the potential of CRP and AGP as sensitive indicators of inflammation-related cognitive dysfunction in this vulnerable population. To fully appreciate the significance of this finding, it's crucial to understand the distinct characteristics of each inflammatory marker. CRP is an acute-phase protein produced by the liver in response to inflammation. It acts as a rapid responder, with levels rising dramatically within hours of an inflammatory insult. This swift response makes CRP a valuable marker for detecting acute infections and inflammatory conditions. However, its rapid rise and fall also mean that it may not adequately reflect the persistence of inflammation over time. AGP, also an acute-phase protein, exhibits a more gradual and sustained response to inflammation. Its levels rise more slowly than CRP and remain elevated for a longer duration, making it a valuable marker for monitoring chronic inflammatory states. In the context of stunting, where inflammation often persists due to recurrent infections, poor sanitation, and inadequate nutrition, AGP may provide a more accurate reflection of the ongoing inflammatory burden. IL-6 is a pleiotropic cytokine, meaning it has diverse and often opposing effects. It plays a role in both pro- and anti-inflammatory processes, making its interpretation in the context of chronic inflammation more complex. While IL-6 can contribute to inflammation-induced neuronal damage, it also has neuroprotective and regenerative properties. This duality may explain why we did not observe a significant association between IL-6 and cognitive impairment in our study. The fact that CRP and AGP were more strongly associated with cognitive impairment than IL-6 suggests that these markers may be more sensitive indicators of inflammation-related cognitive dysfunction in stunted children. Stunting is often associated with chronic, low-grade inflammation, which may be better reflected by the sustained elevation of AGP rather than the more transient changes in CRP. While CRP may capture acute inflammatory episodes, AGP provides a more integrated measure of the cumulative inflammatory burden over time. CRP and AGP may have specific effects on the brain that contribute to cognitive impairment. For instance, CRP has been shown to activate microglia, the resident immune cells of the brain, leading to neuroinflammation and neuronal damage. AGP can bind to various receptors in the brain, potentially affecting neuronal function and synaptic plasticity. CRP and AGP may interact with other factors that contribute to cognitive impairment in stunted children, such as nutritional deficiencies and environmental exposures. For example, CRP has been shown to exacerbate the neurotoxic effects of lead.[14,15]

While our study provides compelling evidence for the role of chronic inflammation in mediating the link between stunting and cognitive impairment, it is crucial to acknowledge that stunting is a complex and multifactorial condition. It's not merely a consequence of a single isolated factor, but rather a culmination of intertwined biological, social, and environmental influences. These factors interact in intricate ways, creating a web of adversity that can significantly impair cognitive development in children. While chronic inflammation plays a significant role, other crucial factors contribute to the cognitive deficits observed in stunted children. Stunting often coexists with micronutrient deficiencies, particularly of iron, zinc, and iodine. These micronutrients are essential for brain development and function. Iron is crucial for oxygen transport, myelination, and neurotransmitter synthesis. Iron deficiency can lead to impaired cognitive function, including deficits in attention, learning, and memory. Zinc plays a vital role in neurogenesis, synaptogenesis, and neurotransmission. Zinc deficiency can impair cognitive development, leading to deficits in learning, memory, and executive function. Iodine is essential for thyroid hormone production, which is critical for brain development. Iodine deficiency can lead to impaired cognitive function, including deficits in intelligence, motor skills, and language development. Inadequate intake of macronutrients, such as protein and essential fatty acids, can also impair brain

development and function. Protein is essential for building and repairing tissues, including brain tissue. Essential fatty acids, such as omega-3 fatty acids, are crucial components of neuronal membranes and play a role in neurotransmission and synaptic plasticity. Exposure to lead, a potent neurotoxin, can have devastating effects on cognitive development. Lead can interfere with neurotransmitter function, disrupt synaptic plasticity, and impair neuronal development. Children living in poverty are often at higher risk of lead exposure due to factors such as living in older housing with lead-based paint and residing in areas with industrial pollution. Exposure to other environmental toxins, such as pesticides, air pollutants, and industrial chemicals, can also have neurotoxic effects. These toxins can disrupt brain development and function, leading to cognitive deficits. Poverty creates a cascade of stressors that can negatively impact child development. Poverty often leads to food insecurity, inadequate housing, limited access to healthcare and education, and increased exposure to violence and adversity. These stressors can disrupt brain development and function, leading to cognitive deficits. Food insecurity, the lack of consistent access to enough food for an active, healthy life, can have profound effects on cognitive development. Children experiencing food insecurity may suffer from malnutrition, which can directly impair brain development. Food insecurity can also lead to stress and anxiety, which can further disrupt cognitive function. Access to quality early childhood education is crucial for cognitive development. Early childhood education provides stimulating learning environments and opportunities for social interaction, which promote cognitive, language, and motor development. Children living in poverty often have limited access to quality early childhood education, which can exacerbate the cognitive deficits associated with stunting. Maternal mental health, including depression and anxiety, can also impact child development. Maternal mental health problems can affect parenting practices, the quality of the mother-child relationship, and the home environment, all of which can influence cognitive development. Emerging evidence suggests that the gut microbiome, the community of microorganisms residing in the digestive tract, plays a crucial role in brain development and function. Stunting can disrupt the gut microbiome, leading to dysbiosis, an imbalance in the composition and function of the gut microbiota. This dysbiosis can affect the production of neuroactive metabolites, such as short-chain fatty acids, which can influence brain development and function. Epigenetic modifications, heritable changes in gene expression that do not involve alterations to the underlying DNA sequence, can also contribute to the cognitive deficits associated with stunting. Stunting can alter epigenetic patterns, affecting the expression of genes involved in brain development and function. These epigenetic changes can have long-lasting effects on cognitive development, even after nutritional rehabilitation. The multifaceted nature of stunting and cognitive impairment underscores the need for a holistic approach to intervention. Ensuring adequate intake of macro- and micronutrients through dietary diversification, food fortification, and supplementation programs. Reducing the burden of infectious diseases through improved sanitation and hygiene, vaccination programs, and prompt treatment of infections. Reducing exposure to environmental toxins, such as lead and other pollutants, through environmental remediation and public health education. Providing access to quality early childhood education programs that promote cognitive, language, and motor development. Implementing social protection programs that address the underlying causes of poverty, such as food insecurity and lack of access to education and healthcare. Providing support for maternal mental health, including screening and treatment for depression and anxiety. By addressing these multiple determinants of stunting and cognitive impairment, we can strive to break the intergenerational cycle of poverty and undernutrition, improving the cognitive potential and overall well-being of children.[16,17]

The findings of this study, highlighting the detrimental impact of stunting and chronic inflammation on cognitive development, carry profound implications for public health interventions. It's clear that a single solution won't suffice. Instead, a

comprehensive and integrated strategy is needed to tackle the multifaceted nature of stunting and its associated cognitive deficits. This multi-pronged approach should encompass interventions aimed at improving nutrition, controlling infections, addressing environmental risks, and fostering early childhood development. By targeting these interconnected factors, we can strive to break the intergenerational cycle of poverty and undernutrition, paving the way for improved cognitive potential and overall well-being of children in Vietnam and other LMICs. Nutrition plays a foundational role in child growth and development, particularly in the context of stunting. Our study underscores the importance of providing adequate macro- and micronutrients to support optimal brain development and reduce inflammation. Promoting dietary diversity is crucial for ensuring adequate intake of essential nutrients. This can be achieved through nutrition education programs that empower families to make informed food choices, emphasizing the inclusion of nutrient-rich foods from various food groups. Community gardens and agricultural initiatives can also improve access to diverse and affordable food sources. Targeted micronutrient supplementation can address specific deficiencies that contribute to stunting and cognitive impairment. For instance, iron, zinc, and iodine supplementation programs can be implemented to address deficiencies prevalent in specific regions or populations. Fortifying staple foods with essential micronutrients can be an effective strategy to improve the nutritional quality of the diet. For example, fortifying rice with iron or flour with folic acid can help to address widespread deficiencies. Promoting nutrition-sensitive agriculture can improve access to nutrient-rich foods and promote sustainable food systems. This approach involves integrating nutrition considerations into agricultural policies and practices, encouraging the production and consumption of diverse and nutritious crops. Regular growth monitoring and promotion programs can help to identify children at risk of stunting and provide timely interventions. These programs can also provide education and counseling to families on appropriate feeding practices and nutrition. Addressing maternal nutrition is crucial for preventing stunting and promoting optimal child development. Interventions should focus on improving the nutritional status of women of reproductive age, including during pregnancy and lactation. This can be achieved through nutrition education, supplementation programs, and access to antenatal and postnatal care. Recurrent infections are a major contributor to chronic inflammation and stunting. Public health interventions aimed at controlling infections are essential for mitigating the adverse effects of inflammation on cognitive development. Promoting access to clean water and sanitation facilities is crucial for reducing exposure to pathogens and preventing infections. This can be achieved through community-led total sanitation programs, construction of latrines and handwashing stations, and hygiene education campaigns. Expanding access to vaccination programs can protect children from preventable infectious diseases. Immunization against diseases such as measles, pneumonia, and diarrhea can significantly reduce the burden of infections and inflammation. Ensuring prompt and effective treatment of infections is essential for preventing complications and reducing the duration of inflammation. This can be achieved through strengthening healthcare systems, improving access to healthcare facilities, and providing training to healthcare workers on appropriate diagnosis and treatment of infections. IMCI is a comprehensive approach to child health that focuses on the integrated management of common childhood illnesses, including pneumonia, diarrhea, malaria, and measles. IMCI programs can help to improve early diagnosis and treatment of infections, reducing the risk of complications and chronic inflammation. Environmental exposures, particularly to neurotoxins such as lead, can have detrimental effects on cognitive development. Public health interventions should prioritize the reduction of environmental risks to protect the developing brain. Implementing lead abatement programs to reduce lead exposure in homes and communities. This can involve removing lead-based paint from older housing, replacing lead pipes, and educating families about the dangers of lead exposure. Implementing policies and regulations to

reduce air and water pollution. This can involve promoting cleaner transportation options, reducing industrial emissions, and improving waste management practices. Ensuring access to safe drinking water to reduce exposure to contaminants that can affect cognitive development. This can involve implementing water treatment programs and promoting safe water storage and handling practices. Educating communities about environmental risks and promoting safe practices to reduce exposure to toxins. This can involve community outreach programs, school-based education, and public awareness campaigns. Early childhood development programs provide stimulating learning environments and opportunities for social interaction, which are crucial for promoting cognitive, language, and motor development. Investing in early childhood development can help to mitigate the cognitive deficits associated with stunting and provide children with a strong foundation for future learning. Establishing early learning centers that provide quality early childhood education programs. These centers can offer stimulating learning environments, age-appropriate activities, and opportunities for social interaction. Implementing parent-child interaction programs that empower parents to engage in stimulating activities with their children. These programs can provide guidance on age-appropriate play, language stimulation, and early literacy activities. Providing home visiting programs that offer support and education to families on child development and parenting practices. These programs can help to create a nurturing home environment that promotes cognitive development. Organizing community-based playgroups that provide opportunities for children to interact and learn through play. Playgroups can promote social-emotional development, language skills, and cognitive development. Integrating early childhood development programs with other services, such as nutrition and health programs, can enhance their impact and reach. This can involve co-locating early learning centers with health clinics or providing nutrition education within early childhood development programs. Stunting is deeply intertwined with poverty and social inequities. Addressing the social determinants of health, such as poverty, food insecurity, and lack of access to education and healthcare, is crucial for breaking the intergenerational cycle of stunting and cognitive impairment. Implementing poverty reduction programs that provide economic opportunities and social safety nets to vulnerable families. This can involve cash transfer programs, microfinance initiatives, and skills training programs. Ensuring food security through programs that improve access to nutritious food. This can involve food assistance programs, school feeding programs, and community-based food security initiatives. Promoting access to quality education for all children, including early childhood education. This can involve expanding access to preschool programs, improving the quality of primary education, and providing scholarships and financial assistance to families. Ensuring access to quality healthcare services, including antenatal and postnatal care, immunization programs, and treatment for childhood illnesses. This can involve strengthening healthcare systems, improving access to healthcare facilities, and providing financial protection against healthcare costs. Empowering women through education, economic opportunities, and access to healthcare. Empowered women are more likely to have healthy pregnancies and raise healthy children, breaking the cycle of intergenerational poverty and stunting.[18-20]

4. Conclusion

This study provides compelling evidence for the detrimental impact of chronic inflammation on cognitive development in stunted children under five years old in Hanoi, Vietnam. Elevated levels of CRP and AGP were independently associated with lower cognitive scores, highlighting the role of chronic inflammation in mediating the link between stunting and cognitive impairment. These findings underscore the urgent need for comprehensive public health interventions that not only address the immediate nutritional needs of children but also target the underlying inflammatory processes that can hinder their cognitive potential.

5. References

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