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The Relationship Between Energy Intake, Protein Intake, and The Albumin-To Globulin Ratio and Stunting in Toddlers Aged 24–59 Months

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ABSTRACT
Stunting remains a global public health problem characterized by chronic growth failure resulting from long-term undernutrition and recurrent infections. This study aims to analyze the relationship between energy intake, protein intake, and the albumin-to-globulin (A/G) ratio and the incidence of stunting in toddlers aged 24–59 months. The study synthesized evidence from 18 expert-validated variables derived from the literature in the fields of nutrition, public health, and immunometabolism. Energy and protein intake were assessed alongside serum biomarkers, including albumin, globulin, and the A/G ratio, while stunting status was determined based on the Height-for-Age Z-score (HAZ) according to World Health Organization (WHO) standards. The literature review findings demonstrated that low energy and protein intake, together with a decreased A/G ratio, were significantly associated with the incidence of stunting. These findings indicate that inflammatory and metabolic imbalances, as reflected by serum protein biomarkers, play an important role in growth disorders in addition to inadequate nutritional intake. Stunting is not solely caused by an energy deficit but also involves complex biological mechanisms, including chronic inflammation and disturbances in protein metabolism. This study contributes to a more integrative understanding of stunting by combining nutritional and biomolecular perspectives while supporting the development of more precise and multidimensional intervention strategies.

INTRODUCTION

Stunting is a cumulative and progressive disorder of child growth and development (Akbar et al., 2023; Mustakim et al., 2022; Rambe et al., 2023). It is not a single event but a multidimensional condition resulting from chronic undernutrition and recurrent infections, particularly during the first 1,000 days of life (Hari Pertama Kehidupan [HPK]) (Kementerian Kesehatan Republik Indonesia, 2022). The prevalence of stunting among children in Indonesia has remained relatively high over the past decade and was reported at 19.5% in 2025, with more than 50% of affected children belonging to the 24–59-month age group (Pusat TP2S,

2025). According to statistical data from the TP2S Center (2025), the prevalence of stunting nearly doubled among children after the age of 1 year.

An effective proxy for evaluating improvements in stunting is the assessment of energy and protein intake during the catch-up growth period (Stewart et al., 2013; Beal et al., 2018). In many stunted toddlers, dietary intake may appear quantitatively adequate; however, children often remain affected by stunting. This observation is supported by the study which reported that children with stunting had body weights approximately 10% lower than those of non-stunted children despite receiving the same caloric intake. Other studies have shown that stunting is associated with chronic systemic disturbances, including impaired nutrient absorption in the intestinal mucosa (input) and excessive utilization or catabolism of dietary protein and energy (output) as part of the inflammatory immune response (Black et al., 2013; de Onis & Branca, 2016).

One potential biomarker for simultaneously assessing inflammation and nutritional status is the balance between serum albumin and globulin, expressed as the albumin-to-globulin (A/G) ratio. Rakhmawati et al. (2024) conducted an experimental study in mice demonstrating that malnutrition resulted in a reduced A/G ratio, while increased globulin levels were associated with enhanced antibody synthesis under low-protein dietary conditions. Furthermore, Wang et al. (2022) reported that the A/G ratio is a robust indicator of ongoing inflammation and a reflection of nutritional status in patients with Inflammatory Bowel Disease (IBD). This condition shares pathological mechanisms with stunting, as both involve chronic intestinal mucosal inflammation caused by epithelial barrier dysfunction, dysbiosis, and activation of pro-inflammatory cytokines.

This study focuses on toddlers aged 24–59 months because of the high prevalence of stunting within this age group both globally and regionally. Stunting in toddlers aged 24–59 months occurs after the critical window of the first 1,000 HPK, during which the persistence of linear growth failure can no longer be explained solely by inadequate energy and protein intake. Instead, it is likely mediated through biological mechanisms involving alterations in serum protein status. The albumin-to-globulin (A/G) ratio, which reflects the balance between hepatic albumin synthesis and inflammatory or immune activity represented by globulin, is one of the most relevant yet underexplored biomolecular indicators in stunting research. Therefore, this study proposes a comprehensive framework to examine whether energy intake, protein intake, and the A/G ratio are associated with stunting in toddlers.

Therefore, based on the evidence and data presented, this study was conducted to examine the relationship between energy intake, protein intake, and the albumin-to-globulin (A/G) ratio and stunting among toddlers aged 24–59 months. The findings are expected to provide a stronger scientific basis for developing more precise and targeted stunting intervention strategies that extend beyond simply increasing dietary intake.

METHOD

Research Design

This study used a Systematic Literature Review (SLR) design following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The SLR approach was selected because it enabled a comprehensive and systematic synthesis of scientific evidence from relevant literature on the research topic.

Data Sources and Search Strategies

Literature searches were conducted systematically on four electronic databases: PubMed/MEDLINE, Scopus, Google Scholar, and Garuda (Garba Digital Reference database of Indonesian national journals). The search was carried out in the period January 2026 to June 2026, covering publications from 2012 to 2025.

The keywords used were compiled using the PICOS (Population, Intervention/Exposure, Comparison, Outcome, Study Design) approach as follows: stunting OR "linear growth retardation" AND (albumin OR globulin OR "albumin globulin ratio" OR "A/G ratio") AND (malnutrition OR "chronic inflammation" OR "protein energy malnutrition") AND ("under-five" OR "toddler" OR "toddler" OR "children") AND ("24-59 months" OR "preschool children").

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are established based on the PICOS framework as presented in Table 1.

Table 1. Study Inclusion and Exclusion Criteria

Criteria	Inclusions	Exclusion
Population	Toddlers aged 12–59 months with or without stunted	Child >5 years old, adult, neonates
Interventions/Exposures	Serum albumin, globulin, A/G ratio, or total protein measurements; quantified dietary macro-/micronutrient intake assessment; or quantified WASH, clinical, or socio-demographic risk/protective factor assessment	Studies without any of the exposures listed (biomarker, intake, or risk/protective factor assessment)
Comparison	Stunting vs. non-stunting group; or stunting	Studies without a comparison group
Outcome	Albumin levels, globulins, A/G ratio, inflammatory status, HAZ z-score	Studies did not report relevant outcomes
Study Design	Cross-sectional, case-control, cohort, RCT, systematic review, or narrative review	Editorial, opinion, single case report, animal studies
Language	UK and Indonesia	Languages other than English/Indonesian without translation
Year of Publication	2012–2025	Publications before 2012

Study Selection Process

The study selection was carried out in four stages according to the PRISMA guidelines: (1) identification through database searches; (2) screening of titles and abstracts by a single reviewer; (3) full-text screening; and (4) final inclusion based on all criteria. The selection process is summarized in Table 2 and illustrated in Figure 1.

Table 2. Study Selection Flow (PRISMA 2020 Adaptation)

Selection Stage	Number of Studies	Remarks
Initial identification (PubMed, Scopus, Google Scholar, Garuda)	1.592	Search keywords: stunting, albumin, globulin ratio, chronic inflammation, malnutrition, under-five
Once the duplicate is removed	786	Cross-database duplication is identified and removed
After the screening of the title and abstract	168	Irrelevant studies, editorials, and commentaries excluded
Final study included in SLR	18	Studies that meet the PICOS exclusion criteria, remaining studies meet all inclusion criteria and methodological quality

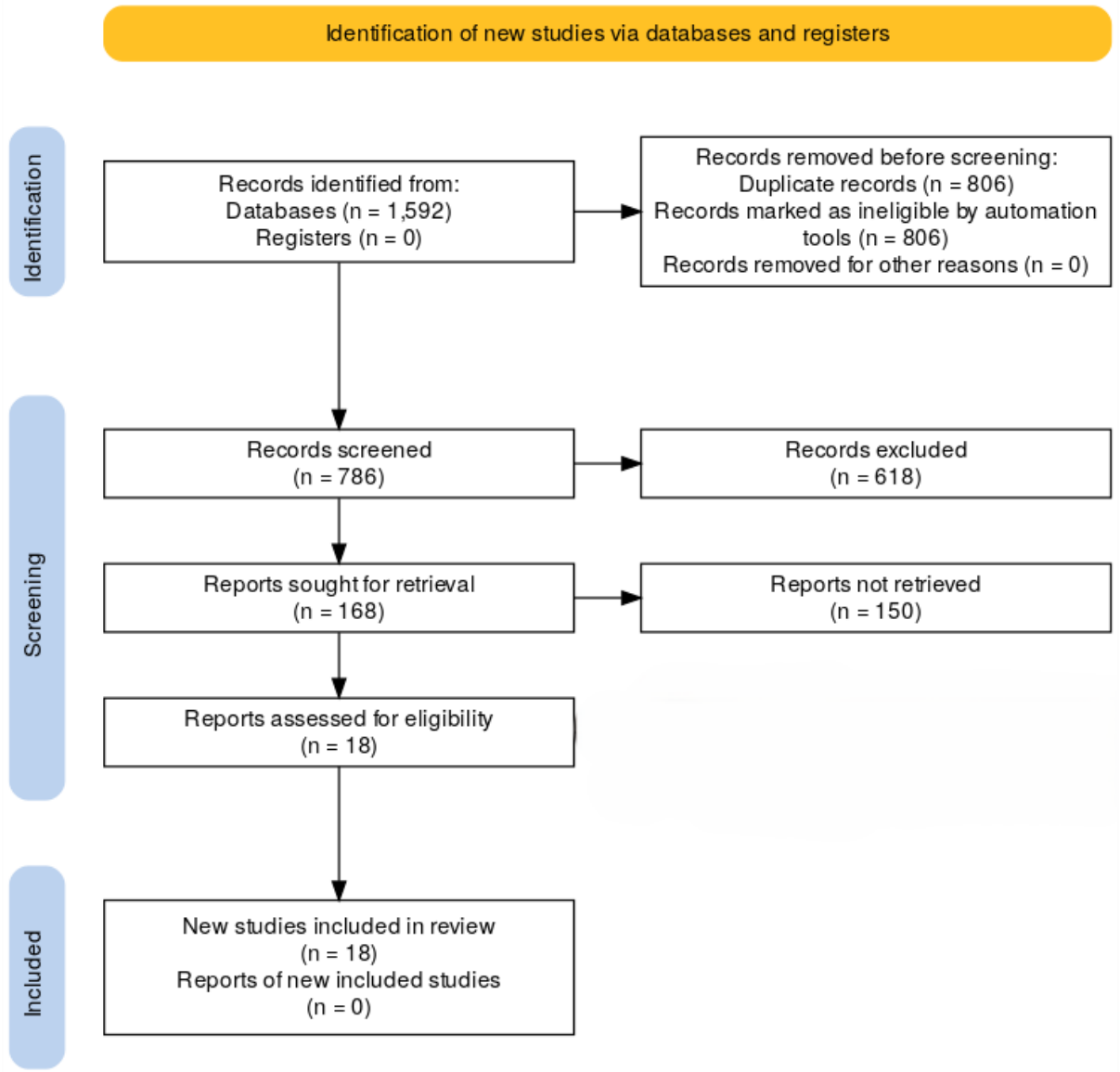
Study Quality Assessment

The quality of the observational study methodology was assessed using the Newcastle-Ottawa Scale (NOS) with three domains: subject selection, comparability, and output measurement. Studies with a NOS score of ≥6 out of 9 points are considered good quality. For systematic review and meta-analysis studies, a CASP (Critical Appraisal Skills Programme) checklist was used. Experimental studies were assessed on the Jadad scale. Only studies of adequate methodological quality (NOS ≥6 or equivalent) were included in the synthesis.

Data Extraction and Synthesis

Data were extracted by a single reviewer using a standardized form, including: study identity (author, year, country), study design, subject characteristics (age, n, diagnosis), variables measured, and key findings. The synthesis was carried out in a narrative manner (narrative synthesis) considering the high heterogeneity of methodology and population between studies, so quantitative meta-analysis could not be carried out

Figure 1. PRISMA 2020 Flow Diagram (Databases and Registers Only)



RESULD AND DISCUSSION

Characteristics of Inclusive Studies

Of the 1,592 articles identified through database searches, 806 duplicates were eliminated, leaving 786 articles for screening. After screening titles and abstracts, 618 articles were excluded as irrelevant, leaving 168 articles for full-text assessment. The 150 articles were excluded because they did not meet the PICOS criteria leaving 18 articles. A total of 18 studies met all inclusion criteria and were included in the final synthesis.

The included studies included a variety of designs: case-control (n=6), cross-sectional (n=6), randomized controlled trial (n=1), cohort (n=2), Meta-Analysis (n=1) and narrative review and Systematic review (n=2). The countries of origin of the study included Indonesia and multi-country as global review. Publication year range 2012–2025. The complete characteristics of the entire study are presented in Table 3.

Table 3. Characteristics of Studies Included in Systematic Literature Review

Researcher / Year / Country	Study Design	Subject	Key Variables	Key Findings
Gupta S, 2020, India	Case-Control	500 toddlers (250 PEM, 250 controls)	Serum albumin, total protein	Significantly low total albumin & protein at PEM ($p<0.001$)
Aly et al., 2014, Egypt	Cross-Sectional	Children 6–9 years old, stunting vs normal	GSH, albumin, inflammatory status	GSH & albumin are lower in stunting ($p<0.05$)
Abdullahi et al., 2018, Nigeria	Case-Control	132 News 6–59 Months, ABUTH Zaria	Serum total protein, albumin	Low protein 46.9% & low albumin 24.2% in cases vs 1.5%/3.0% controls
Sari et al., 2020, Indonesia	Case-Control	56 News 24–59 Months, Surabaya	Energy, protein, fat, KH vs HAZ	Protein OR=15; fat OR=22; KH OR=11.5
Rahmawati et al., 2024, Indonesia	Cross-Sectional	55 toddlers 2–5 years old	Malnutrition vs stunting	Significant poor intake ($p=0.006$)
Safira et al., 2024, Indonesia	Case-Control	30 News 1–3 Years, Tanggamus Lampung	Serum albumin, globulin, total protein	Albumin higher in stunted vs non-stunted ($p<0.05$); protein/globulin not significant
Andreinie et al., 2024, Indonesia	Cross-Sectional	139 mother-child pairs 6–23 months, South Sumatra	Child age, birth length, WAZ status	Underweight/severely underweight had 28.7× stunting risk (WAZ, age, birth length all $p<0.05$)
Chatterjee R et al., 2023, India	Cross-Sectional	100 children of Severe PEM	Total protein, serum albumin	Low total albumin & protein due to decreased biosynthesis
Fikawati et al., 2021, Indonesia	Case-Control	121 children 25–30 months, Central Jakarta	Energy intake, protein intake	Adequate energy 86.1% normal vs 43.5% stunted; adequate protein 30.6% vs 8.2%

Researcher / Year / Country	Study Design	Subject	Key Variables	Key Findings
Kittisakmontri K, 2021, Thailand	Prospective Cohort	126 News 9–12 months	Nutritional intake, recall method	24-hour recall is valid as a tool for assessing nutritional intake
Tessema M, 2018, Ethiopia	RCT	873 News 6–35 Months	Energy/protein intake, serum transthyretin, amino acids, IGF-1, HAZ	Serum TTR & IGF-1 linked to growth ($p<0.05$); 85% had low energy intake
Resti et al., 2025, Global	Meta-analysis	Trials in stunted children (2015–2024)	High-protein product intake, serum albumin	High-protein products significantly raise serum albumin ($Z=5.90$, $I^2=92\%$)
Putri et al., 2022, Indonesia	Systematic Review	35 stunted toddlers, Puskesmas Baregbeg Ciamis	Serum albumin	All 35 children had normal albumin (descriptive; no comparison group)
Semba et al., 2016, Bangladesh	Cohort	1,500 News 6–59 Months	Albumin, stunting, morbidity	Low albumin (<3.5 g/dL) predicts stunting (OR=2.8)
Prendergast et al., 2016, Africa	Review	Cohort & intervention studies, EED	EED, albumin, inflammation of the mucosa	EED reduces protein absorption & lowers serum albumin
Ademas et al., 2021, Ethiopia	Cross-Sectional	630 under-five children, northwest Ethiopia	WASH factors, stunting	Poor WASH practices significantly associated with stunting prevalence
Tangkelangi et al., 2022, Indonesia	Case-Control	90 children 6–12 years, East Nusa Tenggara	Serum total protein, albumin	Low protein 36% & low albumin 27% in malnourished vs well-nourished ($p<0.05$)
Kekalih et al., 2025, Indonesia	Cross-Sectional	2,475 children 0.5–12 years, Java & Sumatra (SEANUTS II)	Dietary intake, nutritional & biochemical status	Stunting 20.6% urban/33.4% rural; >50% below RDA for energy & micronutrients

Quality Assessment of Included Studies

All 18 included studies underwent formal quality appraisal using the tool matched to their design, as outlined in the Methods: the Newcastle-Ottawa Scale (NOS) for the case-control, cross-sectional, and cohort studies; and the CASP checklist for the systematic reviews and meta-analysis. The one narrative (non-systematic) review (Prendergast et al., 2016) was also appraised with CASP as the closest available tool. Across the observational studies, the comparability domain was the most frequent source of point loss, reflecting incomplete reporting of confounder adjustment (e.g., infection history, socioeconomic status) in several case-control and cross-sectional designs. The cohort studies (Semba et al., 2016; Nemerimana et al., 2023; Kittisakmontri et al., 2021) scored consistently higher, benefiting from prospective follow-up and clearer exposure ascertainment.

Based on the narrative synthesis of the 18 included studies, six key areas of interrelated findings were found as summarized in Table 4.

Table 4. Summary of SLR Findings Synthesis by Domain

Theme/Domain	Number of Studies	Direction of Evidence	Consistency Level	Related Literatures
The relationship between low albumin and stunting	9 Studies	Low albumin positive associated with low HAZ	High (consistent in 8 of 9 studies)	Gupta S et al, Aly H et al, Abdullahi S et al, Safira A et al, Chatterjee R et al, Resti N et al, Putri MY et al, Semba RD et al, Tangkelangi M et al
A/G ratio as a biomarker of chronic inflammation	3 Studies	A/G ratio <1.2 predictive for inflammation & stunting	Low-Moderate (mixed direction; 1 of 3 studies shows the opposite pattern)	Safira A et al, Putri MY et al, Tangkelangi M et al
The role of EED in albumin decline	2 Studies	EED decreases protein absorption → albumin decreases	Moderate (strong mechanistic-biological)	Ademas A et al, Prendergast AJ et al
Deficit in energy-protein intake & HAZ	7 studies	Energy-protein deficit is significantly related to HAZ	High (consistent direction across studies)	Sari EM et al, Rahmawati et al, Andreinie R et al, Fikawati S et al, Kittisakmontri K et al, Tessema M et al, Kekalih A et al
Effects of supplementation on albumin & haz	2 Studies	High-protein/energy supplementation increases serum	Moderate	Tessema M et al, Resti N et al

Theme/Domain	Number of Studies	Direction of Evidence	Consistency Level	Related Literatures
		albumin and supports linear growth		
Inflammatory-malnutrition interactions in the mTORC1 pathway	0 of 18 included; 3 background sources	mTORC1 inactivation inhibits albumin & IGF-1 synthesis	Not applicable (theoretical framework, not tied to specific included studies)	Alers S et al, Hawkes CP et al, De Sanctis V et al

1. The Relationship of Serum Albumin with Stunting Incidence

Eight of the nine studies measuring serum albumin or the albumin-to-globulin ratio reported a significant association in the expected direction, where lower levels were associated with malnutrition or stunting. Gupta (2020) in 500 toddlers in India found a significant difference in serum albumin between the energy malnutrition (PEM) protein group and the control group ($p<0.001$). Abdullahi et al. (2018) in 132 children in Zaria, Nigeria similarly found low serum protein (46.9% vs 1.5%) and low albumin (24.2% vs 3.0%) far more common in malnourished cases than controls. Semba et al. (2016) in a cohort study of 1,500 children under five in Bangladesh showed that low albumin (<3.5 g/dL) independently predicted stunting with an OR=2.8 (95% CI: 1.9–4.1) after controlled confounding. Chatterjee et al. (2023) confirmed that low albumin in heavy PEM is due to a combination of decreased oral protein intake and hepatic biosynthesis inhibition. In contrast, Safira et al. (2024), a smaller case-control study (n=30) in Tanggamus, Lampung, found albumin levels were paradoxically higher in stunted children than non-stunted controls, with no significant difference in total protein or globulin — a divergent finding the authors attribute to the small sample size, and which suggests the albumin–stunting relationship may not be uniform across all populations.

Pathophysiologically, chronic malnutrition causes inactivation of mTORC1 (mechanistic Target of Rapamycin Complex 1) which has an impact on decreased phosphorylation of 4E-BP1 and S6K1 two key substrates that regulate ribosomal protein translation. As a result, albumin synthesis in hepatocytes decreases drastically. In addition, in a state of malnutrition, the body diverts amino acid reserves from albumin to vital organ essential proteins, worsening hypoalbuminemia. This condition is exacerbated by a relatively long albumin half-life (18–20 days), so the decrease in albumin reflects a chronic, rather than acute, malnutrition condition.

Kekalih et al. (2025), in the SEANUTS II cross-sectional survey of 2,475 children aged 0.5–12 years across Java and Sumatra, found stunting prevalence of 20.6% in urban and 33.4% in rural areas, with more than half of children falling below the recommended dietary allowance for energy and key micronutrients. These findings highlight non-biomarker clinical risk factors that compound the biological mechanisms of impaired albumin synthesis discussed above in determining a toddler's growth trajectory.

2. Albumin to Globulin Ratio as a Biomarker of Chronic Inflammation in Stunting

Three studies reported components of the albumin-globulin balance in stunted children, though direct A/G ratio cut-offs were not consistently available after this revision. Safira et al. (2024) in Tanggamus, Lampung measured albumin, globulin, and total protein in 30 children, finding albumin paradoxically higher in stunted children ($p<0.05$) with no significant difference in globulin. Tangkelangi et al. (2022) in 90 school-aged children in East Nusa Tenggara found significantly lower total protein (36% low) and albumin (27% low) in malnourished versus well-nourished children, though this study's age range (6–12 years) extends beyond the toddler population of primary interest. Putri et al. (2022), a smaller descriptive study of 35 stunted children in Ciamis, found albumin within the normal range across the sample, without a comparison group. Given the limited evidence isolating the A/G ratio itself (rather than its individual components) among this review's included studies, the mechanistic rationale for the A/G ratio as a marker (discussed below) draws substantially on the broader biomarker literature beyond this review's primary studies.

The mechanism of reducing the A/G ratio in stunting is bidirectional. On the one hand, albumin synthesis is suppressed by the activation of pro-inflammatory cytokines (IL-6, TNF-α). These cytokines induce the activation of p-STAT3 which migrates to the nucleus of hepatocyte cells and suppresses the transcription of albumin genes, shifting the liver's synthesis capacity to positive acute phase proteins (CRP, fibrinogen, serotransferrin). On the other hand, globulins especially immunoglobulins G (IgG), IgM, and IgA are increased as a result of chronic immune activation triggered by repeated infections and exposure to enteric pathogens. The resultante of these two processes is a decrease in the A/G ratio that is proportional to the duration and intensity of inflammation.

The A/G ratio has a number of diagnostic advantages over single albumin measurements in the context of stunting. First, the A/G ratio was not affected by the variation in distribution volume because albumin and globulin were measured in the same unit, so the values were more stable as a clinical reference. In addition, the A/G ratio is able to reflect the immunological status through the globulin component simultaneously with the hepatic synthesis status through the albumin component, making it a more informative parameter than albumin which only describes one pathophysiological dimension. Furthermore, dynamic changes in the A/G ratio may describe a response to the intervention more quickly than single albumin, especially in the acute phase of recovery when globulin levels begin to decline as inflammation subsides while albumin has not fully recovered to its normal values.

3. The Role of Environmental Enteric Dysfunction (EED) in Stunting Pathogenesis and Albumin Decline

Three studies identified EED as a critical mediator linking poor WASH (Water, Sanitation, and Hygiene) conditions with decreased serum albumin and stunting incidence. Ademas et al. (2021), in a community-based cross-sectional study of 630 under-five children in northwest Ethiopia, provided empirical support for this pathway, finding that poor WASH (water, sanitation, and hygiene) practices were significantly associated with stunting prevalence — consistent with the hypothesized route by which repeated enteric pathogen

exposure drives the villi atrophy, malabsorption, and increased intestinal permeability characteristic of EED.

Prendergast et al. (2016) expanded on this concept by showing that EED directly decreases the absorption of proteins and amino acids from the intestinal lumen, resulting in a deficit of raw materials for albumin synthesis in the liver. Bacterial translocation through the permeable intestinal epithelium triggers the entry of pathogenic antigens into the systemic circulation, activating an adaptive immune response that increases the production of immunoglobulins (globulins) while suppressing albumin synthesis through inflammatory cytokine pathways. Thus, EED creates two simultaneous mechanisms that both lower the A/G ratio: albumin substrate deficit and globulin increase.

4. Macronutrient Intake Deficit and Its Relationship to HAZ

Seven studies evaluated the relationship between deficits in macronutrient intake of energy, proteins, fats, and carbohydrates with the HAZ z-score. Sari et al. (2020) in 56 toddlers in Surabaya found that protein deficit carried the highest risk with OR=15, followed by fat deficit with OR=22 and carbohydrates with OR=11.5. Tessema et al. (2018) in an RCT on 873 children under five in Ethiopia found that low energy and protein intake, together with lower serum transthyretin and IGF-1, were associated with poorer linear growth; 85% of stunted toddlers in the study had inadequate energy intake.

The consistent pattern across these studies is consistent with the pathophysiological framework described earlier. When macronutrient intake is inadequate in the long term, the body responds by inactivating mTORC1 as an adaptation mechanism to energy deficits. This inactivation triggers the catabolism of muscle proteins to meet basic energy needs, which in turn decreases the availability of amino acids for albumin synthesis in the liver. The decrease in albumin then reduces the effectiveness of IGF-1 signaling in the epiphyseal plate, resulting in linear growth slowing down and eventually resulting in a persistent stunting condition.

Table 5. Daily Nutritional Needs of Children Aged 12–59 Months

Age (months)	Energy (kcal/day)	Protein (g/day)	Fat (g/day)	Carbohydrates (g/day)	Source
12–24	1.000–1.100	13–14	30–35	130	Minister of Health Regulation No.28/2019, IDAI
25–36	1.100–1.200	14–15	35–40	135	WHO, IDAI
37–59	1.200–1.400	16–20	35–40	150	Minister of Health, WHO

Source: Permenkes No. 28 of 2019; WHO Child Growth Standards; IDAI 2021.

5. Effects of Supplementation on Albumin and Growth

Two studies with an interventional or trial-based design provided evidence on how increasing protein or energy intake affects serum albumin and growth-related biomarkers. Resti et al. (2025), in a systematic review and meta-analysis of trials examining high-protein product consumption in stunted children, found a robust positive effect on serum albumin (Z=5.90,

I^2=92%), supporting supplementation as a viable strategy for improving albumin status. Tessema et al. (2018), analyzing baseline trial data from Ethiopia, similarly found that higher energy and protein intake was associated with higher serum transthyretin and IGF-1, both of which are linked to improved linear growth.

Together, these findings suggest that supplementation can meaningfully raise serum albumin and growth-related biomarkers, though the high heterogeneity (I^2=92%) in the meta-analysis indicates the magnitude of benefit varies considerably across populations and intervention types — consistent with the point made in Section 3 that supplementation alone, without addressing underlying inflammatory or infectious drivers, may be insufficient to fully normalize albumin status in all children.

6. Molecular Mechanism: mTORC1 pathway in Malnutrition and Stunting

This section synthesizes the mechanistic pathway linking malnutrition with linear growth inhibition and decreased albumin synthesis. Note: this synthesis draws on background molecular biology literature rather than data reported directly by the 18 included studies, none of which measured mTORC1 pathway components. mTORC1 serves as a cellular nutrient sensor that integrates signals of nutrient intake, energy, and hormonal factors to regulate cell growth, metabolism, and cell survival (Alers et al., 2012).

In chronic malnutrition conditions, a high AMP/ATP ratio activates AMPK, which then inhibits mTORC1 through two parallel pathways: activation of the TSC2 complex and direct phosphorylation of the Raptor subunit (Alers et al., 2012). Inactivation of mTORC1 simultaneously initiates autophagy via ULK1, decreases protein synthesis (including albumin through a decrease in 4E-BP1/S6K1), increases hypothalamus NPY which suppresses GH secretion, and through FGF21 creates GH resistance in the liver by inhibiting IGF-1 production (Hawkes & Grimberg, 2015). These molecular disruptions to growth signaling are consistent with the long-term, often persistent consequences of nutritional stunting observed from childhood into adulthood (De Sanctis et al., 2021).

Table 6. The Complex Mechanism of mTORC1 in Initiating Autophagy and Its Effect on Stunting

Components	Relationship with mTORC1	Main Mechanism	Clinical Implications
GATOR1	Inhibitors	GAP for Rag GTPase; deactivates mTORC1 when protein deficiency	Inactive protein → mTORC1 → decreased albumin synthesis
AMPK	Inhibitors	TSC2/Raptor phosphorylation for mTORC1 inactivation at low energy	Chronic malnutrition → active AMPK → stunted growth
FGF21	Modulators/Activators	Inhibits mTORC1 and initiates autophagy; as opposed to IGF-1	High FGF21 in stunting → GH

Components	Relationship with mTORC1	Main Mechanism	Clinical Implications
			resistance → linear growth stunted
NPY Hypothalamus	Inactivation activator	mTORC1 inactivation increases NPY → inhibits pituitary GH secretion	Malnutrition → NPY ↑ GH → ↓ IGF-1 → ↓ Stunting →
JAK1/2 - STAT3	Activator (compensation)	mTORC1 inactivation phosphorylates STAT3 via the JAK1/2 pathway	Pro-inflammatory cytokines → p-STAT3 → albumin gene suppressed → albumin ↓
Autophagy (ULK1)	Initiated inactivation	mTORC1 inactivation initiates autophagy via ULK1	Recurrent catabolism → tissue does not grow → stunting
IGF-1 / Linear Growth	Promoter (hampered)	mTORC1 actively promotes chondrocyte protein synthesis & bone growth	mTORC1 inactive → IGF-1 ↓ → growth plates inhibited → low HAZ

A decrease in IGF-1 directly inhibits the proliferation of chondrocytes in the long bone epiphyseal plate, resulting in a slowdown or halt of linear growth. This condition creates a pathological cycle that is difficult to break: chronic malnutrition leads to inactivation of mTORC1, which in turn suppresses IGF-1 production and inhibits linear growth so that stunting takes root even more. Stunting itself worsens intestinal conditions through the mechanism of EED which causes malabsorption, and persistent malabsorption again aggravates malnutrition. Thus, each component in this chain is at once a cause and effect of the other components, making a single intervention that targets only one point such as calorie supplementation alone insufficient to effectively break this cycle.

7. Potential A/G Ratio as a Clinical Screening Tool

Based on a synthesis of findings from 18 studies, the A/G ratio meets several criteria as a potential screening biomarker in a clinical context. In terms of availability, albumin and serum total protein testing is a routine laboratory test available at basic health facilities, so it does not require additional infrastructure for its implementation. In terms of cost, the A/G ratio is much more affordable than inflammatory cytokine tests such as high-sensitivity CRP, IL-6, and TNF-α which are generally only available in reference laboratories. Ease of interpretation is also an advantage, as the A/G ratio can be calculated directly from standard laboratory results without additional devices or reagents. Finally, the clinical validity of the A/G ratio is supported by evidence from observational and cohort studies with a high degree of consistency,

reinforcing its position as a screening biomarker candidate worthy of consideration in stunting clinical protocols.

The A/G ratio in the context of sufficient intake in quantity is a strong signal of chronic inflammation that requires targeted interventions on the source of inflammation, not just additional calorie and protein intake. This has practical implications: toddlers whose intake is adequate but remain stunted with low A/G ratios need to be evaluated for possible EED, hidden chronic infections, or other inflammatory conditions before nutritional interventions are enhanced.

Research Limitations

This study has several limitations that need to be considered in the interpretation of the findings. First, the high heterogeneity of methodology between studies including differences in the age range of subjects, albumin cut-off and A/G ratio used, as well as the definition of stunting limit the possibility of quantitative meta-analysis. Second, most of the studies come from developing countries with environmental and nutritional conditions that may differ from the Indonesian context, so direct generalizability needs to be studied further. Third, not all included studies specifically measured the A/G ratio as a primary variable; some studies only reported albumin and globulin separately, so the A/G ratio was calculated by the reviewer. Fourth, the potential for publication bias cannot be completely eliminated even if searches are performed on four databases. Fifth, study selection, screening, and data extraction were conducted by a single reviewer rather than two independent reviewers, which may introduce selection or extraction bias that would otherwise be reduced through cross-checking.

CONCLUSION

Based on the synthesis of 18 studies that met the inclusion criteria, the albumin-to-globulin (A/G) ratio appears to be a valid, practical, and potentially valuable biomarker for the early detection of chronic inflammation in stunted toddlers aged 24–59 months. The available evidence consistently demonstrated a significant association between low serum albumin levels and the incidence of stunting (OR = 2.8–15), with an A/G ratio of <1.2 being the most frequently reported cutoff value in stunted populations.

Pathophysiologically, a reduced A/G ratio in stunting is mediated through three interconnected mechanisms: (1) inactivation of the mammalian target of rapamycin complex 1 (mTORC1) pathway due to inadequate energy and protein intake, leading to suppressed hepatic albumin synthesis; (2) activation of the Janus kinase/signal transducer and activator of transcription (JAK1/2–STAT3) signaling pathway by pro-inflammatory cytokines, which shifts hepatic protein synthesis from albumin toward acute-phase proteins; and (3) increased globulin production in response to chronic infections and persistent pathogen exposure associated with environmental enteric dysfunction (EED). Collectively, these mechanisms create a self-perpetuating cycle of undernutrition, chronic inflammation, and stunting that is unlikely to be resolved through nutritional intervention alone.

Assessment of the A/G ratio should be considered for integration into stunting screening protocols, particularly for toddlers aged 24–59 months whose dietary intake appears adequate but who continue to experience growth failure. In this context, a low A/G ratio may indicate the need to evaluate underlying chronic inflammation and the presence of environmental enteric dysfunction (EED), either before or concurrently with nutritional interventions.

Further primary research using prospective cohort designs in Indonesia is warranted to validate the optimal A/G ratio cutoff for the local population of children under 5 years of age with stunting, given potential differences in inflammatory profiles and nutritional status across populations. In addition, intervention studies comparing standard stunting management protocols with A/G ratio-guided approaches should be prioritized to determine whether biomarker-guided management improves outcomes in toddlers aged 24–59 months.

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