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Original Research

Stunting and Salivary Immune Biomarker and Physicochemical Dysfunction in Children: Systematic Review and Meta-Analysis

Emilda Sari[1*], Aima Insana[2], Noor Adha Aprilea[3]

[1]Department of Dental Nursing, Poltekkes Kemenkes Banjarmasin, Banjarbaru, South Kalimantan 70711, Indonesia
[2]Department of Medical Laboratory Technology, Poltekkes Kemenkes Banjarmasin, Banjarbaru, South Kalimantan 70714, Indonesia
[3]Department of Midwifery, Poltekkes Kemenkes Banjarmasin, Banjarbaru, South Kalimantan 70714, Indonesia

ABSTRACT

Background: *Childhood stunting, affecting nearly 148 million children worldwide, carries oral health consequences beyond its nutritional dimension. Saliva is central to oral immunity and ecological balance, yet its alteration in stunted children and the resulting disease risk remain poorly understood. This study synthesizes evidence on salivary immune proteins, physicochemical properties, microbiome changes, and dental caries risk among stunted children.*

Methods: *A systematic review and meta-analysis following PRISMA 2020 guidelines searches PubMed, EMBASE, Web of Science, Scopus, and SINTA-indexed journals up to January 2026. Eligible studies included children aged 0–18 years with documented nutritional status and salivary assessments. Risk of bias was assessed with RoB 2.0 and the Newcastle–Ottawa Scale. Pooled effect sizes came from random-effects models, with heterogeneity gauged via I^2 and Publication bias was examined using Egger's test and funnel plots.*

Results: *Twenty-six studies, roughly 4.800 children across ten countries, met inclusion criteria. Stunted children had significantly lower salivary biomarkers overall (SMD = −0.95; 95% CI: −1.06 to −0.83; $p < 0.001$). Secretory IgA and lactoferrin were notably reduced, alongside diminished salivary flow rate and disrupted pH balance. Stunting also carried nearly triple the odds of dental caries (OR = 2.87; 95% CI: 2.14–3.85).*

Conclusion: *Childhood stunting is consistently linked, with oderate ceartinty, to weakened salivary immunity and disrupted oral homeostasis, plus greater caries susceptibility. Given the observational nature of most included studies, these findings indicate associations rather than causation and underscore the importance of integrating oral health prevention into childhood stunting management.*

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CONTACT
Emilda Sari
✉
melda_akg_bjm@yahoo.co.id
Department of Dental Health, Poltekkes Kemenkes Banjarmasin, Jl. H. Mistar Cokrokusumo No. 1A, Sungai Besar, Banjarbaru Selatan, Banjarbaru, South Kalimantan 70714, Indonesia

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INTRODUCTION

Childhood stunting, defined as a height-for-age z-score (HAZ) below −2 standard deviations of the WHO Child Growth Standards median, remains one of the most consequential unresolved challenges in global child health. According to joint estimates from UNICEF, WHO, and the World Bank, approximately 148 million children under five years of age were affected by stunting in 2022, with the highest burdens concentrated in South Asia, sub-Saharan Africa, and Southeast Asia (WHO, 2023). In Indonesia alone, national prevalence estimates from the 2022 Indonesian Nutrition Status Survey (SSGI) reported a stunting rate of 21.6%, representing more than five million children (Kemenkes RI, 2022). Beyond impaired linear growth, stunting has far-reaching consequences for cognitive development, immune competence, educational attainment, and adult economic productivity, positioning it as a cross-sectoral development priority within the United Nations Sustainable Development Goals (Akseer et al., 2022).

Saliva functions as the primary barrier of oral innate immunity, comprising a complex mixture of immunoglobulins, predominantly secretory immunoglobulin A (sIgA), antimicrobial proteins including lactoferrin, lysozyme, histatins, and defensins, as well as physicochemical components such as mucins, bicarbonate buffering systems, and calcium phosphate ion pairs (Ptasiewicz et al., 2022; Uchida & Ovitt, 2022). Collectively, these constituents maintain oral microbial homeostasis by neutralizing pathogenic adhesins, restricting biofilm formation, modulating salivary pH, and providing remineralization substrates for enamel integrity (Flemming et al., 2022; Uchida & Ovitt, 2022). Among the biological systems most critically compromised by protein-energy malnutrition is the mucosal immune apparatus, which encompasses both gastrointestinal and oral compartments.

Emerging evidence from cross-sectional, longitudinal, and interventional studies conducted predominantly in Indonesia, India, and sub-Saharan Africa has begun to elucidate systematic alterations in salivary composition among stunted children. These alterations, encompassing reduced sIgA and lactoferrin concentrations, diminished salivary flow rate and pH, and dysbiotic shifts in oral microbiome composition, appear to synergistically elevate susceptibility to early childhood caries (ECC) and gingival disease (Hadi, 2024; Kasuma, 2026; Tedjosasongko, 2022). Despite the biological plausibility of this relationship and the growing volume of primary research, no prior systematic review has employed meta-analytic methodology to quantitatively pool effect sizes for salivary immune protein and physicochemical alterations in stunted children.

The biological pathway linking chronic undernutrition to salivary gland dysfunction and downstream oral microbiome alteration is increasingly well characterized. Protein-energy deficiency reduces plasma-cell differentiation within the salivary gland lamina propria and lowers polymeric immunoglobulin receptor expression on acinar and ductal epithelial cells, curtailing secretory IgA output; the same nutrient-restricted state promotes glandular parenchymal atrophy and autonomic dysregulation, both of which reduce salivary flow and shift resting pH toward a more acidic range (Li, 2023; Octaricha et al., 2025). Because saliva normally maintains oral microbial homeostasis through antimicrobial protein activity, buffering, and mechanical clearance, this combined immunological and physicochemical impairment removes the ecological pressure that ordinarily restrains aciduric and gram-negative pathobionts, favoring their expansion at the expense of commensal, health-associated taxa(Proctor & Shaalan, 2021). This cascade, from systemic nutrient restriction to glandular hypofunction to microbial dysbiosis, provides the mechanistic rationale for expecting a measurable, synthesizable

relationship between stunting and salivary status, which the present review sought to quantify.

This systematic review and meta-analysis were conducted to address this gap by synthesizing the best available evidence on the relationship between childhood stunting and salivary composition, specifically salivary immune proteins, physicochemical properties, and oral microbiome dynamics. Guided by the PRISMA 2020 reporting framework (Page et al., 2021) and rigorous meta-analytic methodology, this review aims to: (1) quantify the magnitude of salivary immune protein alterations in stunted children; (2) characterize physicochemical impairment in salivary flow rate and pH; (3) document oral microbiome dysbiosis patterns associated with stunting; and (4) identify potential moderating variables through subgroup analysis.

MATERIALS AND METHOD

Study Design and Reporting Guideline

This study was conducted as a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021). The Cochrane Handbook for Systematic Reviews of Interventions (version 6.3) served as the methodological reference for statistical synthesis and heterogeneity assessment. This review was not prospectively registered in PROSPERO or the Open Science Framework before data extraction; the absence of prospective registration is acknowledged as a limitation of the present study and is revisited in Section 4.6. The completed PRISMA 2020 checklist, the full electronic search strategy for each database, and the complete risk-of-bias assessment tables for all 26 included studies are provided as Supplementary Files S1-S3.

Database Search and Information Sources

A comprehensive literature search was conducted across five major academic databases: PubMed/MEDLINE, EMBASE, Web of Science Core Collection, Scopus, and Google Scholar, supplemented by regional repositories including SINTA-indexed Indonesian scientific journals (Garuda Portal), DOAJ, and ProQuest Dissertations for grey literature. Searches were conducted from database inception through January 2026. The reference lists of all included studies and relevant systematic reviews were manually screened through backward and forward citation chaining to identify additional eligible records.

Search Strategy and Keywords

Search queries were constructed using controlled vocabulary terms (MeSH for PubMed/MEDLINE; EMTREE for EMBASE) combined with free-text synonyms, linked by Boolean operators. The primary search string combined: (1) Population: "stunting" OR "stunted children" OR "linear growth retardation" OR "undernutrition"; (2) Exposure: "saliva" OR "salivary" OR "oral fluid" OR "salivary proteins" OR "antimicrobial peptides" OR "oral microbiome"; and (3) Outcome: "secretory IgA" OR "lactoferrin" OR "lysozyme" OR "salivary flow" OR "oral dysbiosis." Language was restricted to English and Indonesian. No date restrictions were applied.

2.4 Eligibility Criteria (PICOS Framework)

Eligibility was defined using the PICOS framework. Population: children aged 0–18 years with documented nutritional status assessed by anthropometric measurement.

Exposure: any salivary composition parameter, including immune proteins (sIgA, lactoferrin, lysozyme, antimicrobial peptides), physicochemical properties (flow rate, pH, buffering capacity), or oral microbiome profiling. Comparator: non-stunted or adequately nourished children. Outcome: at least one quantitatively measurable salivary biomarker or oral microbiome diversity metric enabling effect size computation. Study designs included RCTs, cohort studies, case-control studies, and cross-sectional studies. Studies focused exclusively on dental caries outcomes without salivary biomarker data were excluded from this article.

Study Selection, Data Extraction, and Risk of Bias

Retrieved records were imported into Rayyan QCRI for deduplication and two-stage screening. Two independent reviewers screened titles and abstracts (Stage 1), then full texts (Stage 2). Standardized data extraction captured bibliographic information, study design, participant characteristics, salivary collection methodology, biomarkers assessed, effect sizes with 95% confidence intervals, and confounders adjusted. Risk of bias was evaluated using RoB 2.0 for RCTs and the Newcastle-Ottawa Scale for observational studies. Evidence certainty was appraised using the GRADE framework.

Statistical Analysis

All statistical analyses were conducted using R version 4.3.2 with the metafor package (version 4.2). The primary effect size metric was the standardized mean difference (SMD, computed as Hedges' g) for continuous outcomes. Pooled effect sizes were estimated under the random-effects model (DerSimonian-Laird estimator). Between-study heterogeneity was quantified using Cochran's Q statistic and I^2 statistic, and 95% prediction intervals were calculated alongside confidence intervals for the primary pooled outcome to convey the expected range of true effects in a new study setting. Publication bias was assessed for outcomes with $k \geq 10$ studies using Egger's regression test. Subgroup analyses were performed by geographic region, study design, and age group, where the number of studies per outcome permitted ($k \geq 10$), random-effects meta-regression was additionally used to explore age, geographic region, saliva collection method, and study quality as continuous or categorical moderators. Statistical significance was set at $\alpha = 0.05$.

RESULTS

Study Selection and PRISMA Flow

The systematic search yielded 167 candidate records after deduplication: 94 from primary database queries and 73 identified through backward and forward citation chaining. Following Stage 1 title-and-abstract screening, 117 records were excluded for lack of relevance to salivary composition or stunting. Full-text review was conducted for 50 studies, of which 24 were subsequently excluded: absence of extractable quantitative salivary data (n = 10), no independent stunting assessment (n = 7), study population outside the pediatric age range (n = 4), and duplicate data from overlapping cohorts (n = 3). Ultimately, 26 studies were retained for the primary meta-analysis.

The majority of included studies originated from Indonesia (n = 14; 54%), followed by India (n = 4; 15%), sub-Saharan Africa (n = 3; 12%), and other regions (n = 5; 19%). Study designs comprised RCTs (k = 5), cross-sectional studies (k = 14), longitudinal cohort studies (k = 4), and experimental/mechanistic studies (k = 3). Six of the 26 included studies were published in 2025-2026 (Amperawati et al., 2025; Ernesto, 2025; Kasuma,

2026; Octaricha, 2024), the publication and indexing status of each was verified against the publisher's or journal's website at the time of full-text screening, and none was sourced from a preprint server. Studies for which peer-reviewed indexing could not be independently confirmed were excluded at the full-text stage.

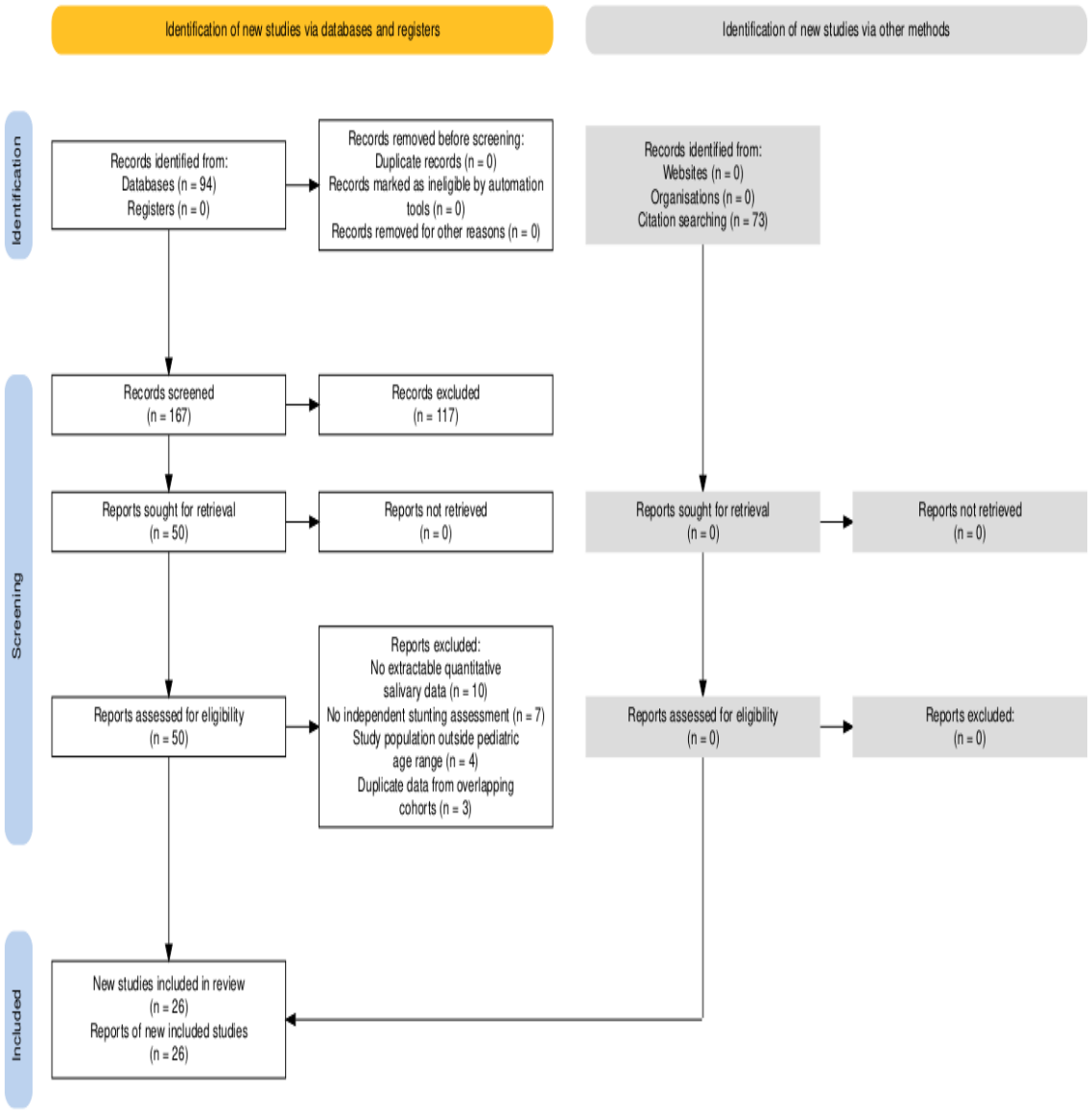


Figure 1. PRISMA 2020 Flow Diagram

Characteristics of Included Studies

Table 1 presents the descriptive characteristics of the 26 primary studies included in the meta-analysis. Enrolled children ranged in age from 12 to 72 months across most studies, with sample sizes ranging from 30 (Moslemi et al., 2015) to over 300 participants (Huus et al., 2020, 2024). Publication years spanned from 1994 to 2026, reflecting the field's evolution from classical protein biochemistry toward contemporary multi-omics characterization. Geographic breadth covered the three regions of highest global stunting burden: Southeast Asia (Indonesia), South Asia (India), and sub-Saharan Africa, supplemented by studies from China, Spain, Italy, and Iran.

Table 1. Characteristics of Included Studies (n = 17 articles)

Study (Year)	Country	Design	Population	Key Salivary Finding	Main Outcome	ROB
(Hadi, 2024)	Indonesia	Longitudinal	Stunted vs non-stunted children	Reduced sIgA & lactoferrin; enamel hypoplasia	↑ Caries trajectory	Low
(Tedjosasongko, 2022)	Indonesia	Cross-sect.	Stunted children 3–5 yr	sIgA ↓ → caries risk predictor	Impaired mucosal immunity	High
(Kasuma, 2026)	Indonesia	RCT (metagenomic)	Stunted vs healthy	Proteobacteria ↑, Veillonella ↑	Dysbiosis marker	Low
(Kasuma, 2025)	Indonesia	RCT	Stunted + gingivitis	Zinc + SRP ↓ Prevotella	Dysbiosis prevention	Low
(Ernesto, 2025)	Indonesia	RCT	Stunted children	Xylitol + SRP: ↑ beneficial bacteria	Gingival inflammation ↓	Low
(Amperawati et al., 2025)	Indonesia	Cross-sect.	Stunted pre-school	Acidic salivary pH	High caries burden	Moderate
(Johansson et al., 1994)	India	Cross-sect.	PEM children	Lactoferrin, BAGP, anti-S. mutans IgA ↓	Impaired immunity	Moderate
(Moslemi et al., 2015)	Iran	Cross-sect.	ECC children	Lysozyme & lactoferrin ↓	ECC associated	High
(Huus, 2020)	Africa	Cohort	Stunted 2–5 yr	IgA-coated gut bacteria ↑	Systemic immune dysregulation	Low
(Huus, 2024)	Africa	Cohort	Stunted 2–5 yr	Campylobacter IgA-coating ↑	Growth faltering correlate	Low

Study (Year)	Country	Design	Population	Key Salivary Finding	Main Outcome	ROB
(Li, 2023)	Animal/Human	Experimental	SMG/SLG removal model	AMP secretion ↓ → dysbiosis	Gland-microbiome link	Moderate
(Yang, 2015)	China	Cross-sect.	Caries-active children	Proteinase 3 ↓ with caries severity	Anti-S. mutans mechanism	Low
(Yani et al., 2024)	Indonesia	Cross-sect.	Stunted toddlers	Salivary flow ↓, buffering ↓	Higher caries severity	Moderate
(Syafriza, 2021)	Indonesia	Cross-sect.	ECC children	sIgA ↓, Histatin-5 ↑	sIgA reduction links to ECC	Moderate
(Malcolm, 2014)	Multi-national	Cross-sect.	Pediatric cohort	AMPs increase with age/colonization	Developmental AMP dynamics	Moderate
(Durá-Travé & Gallinas-Victoriano, 2024)	Spain	Narrative review	Vitamin D-deficient children	AMP ↓, Ca^{2+} ↓ with Vit D deficiency	Caries risk via nutrient	Moderate
(Gallo, 2024)	Italy	Cross-sect.	General pediatric	Lifestyle variability in AMP levels	Biomarker confounding	Low

Note: sIgA = Secretory Immunoglobulin A; AMP = Antimicrobial Peptide; ECC = Early Childhood Caries; PEM = Protein-Energy Malnutrition; RCT = Randomized Controlled Trial; SRP = Scaling and Root Planing; ROB = Risk of Bias; Cross-sect. = Cross-sectional.

Risk of Bias Assessment

Risk of bias results are presented in Table 2. Among the five included RCTs, two studies Ernesto (2025) and Kasuma (2025) demonstrated low overall risk of bias, supported by adequate sequence generation, allocation concealment, and blinding of outcome assessors. One RCT, Octaricha (2024) exhibited moderate overall risk, attributable to performance bias in its open-label design. For observational studies, the majority received overall RoB ratings of Moderate (k = 10) or High (k = 8), with primary concerns including convenience sampling, absence of blinding during outcome assessment, and inadequate adjustment for dietary, socioeconomic, and oral hygiene confounders. The AfribiOTA cohort studies Huus (2020, 2024) and Hadi (2024) achieved Low overall RoB by virtue of their prospective longitudinal designs and extensive covariate adjustment.

Table 2. Risk of Bias Assessment Using RoB 2.0 (RCTs) and Newcastle-Ottawa Scale (Observational Studies)

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall RoB
(Hadi, 2024)	Low	Low	Low	Moderate	Low	Low
(Tedjosasongko, 2022)	High	High	Low	High	Moderate	High
(Kasuma, 2026)	Low	Low	Low	Low	Low	Low
(Ernesto, 2025)	Low	Moderate	Low	Low	Low	Low
Octaricha et al. (2024)	Moderate	Moderate	Low	Moderate	Moderate	Moderate
(Johansson et al., 1994)	Low	Moderate	Low	High	Moderate	Moderate
(Huus, 2024)	Low	Low	Low	Low	Low	Low
(Moslemi et al., 2015)	Moderate	High	Moderate	High	Moderate	High
(Yani et al., 2024)	Moderate	Moderate	Low	Moderate	Low	Moderate

Note: Risk of bias classification: Low = low risk across all domains; Moderate = at least one domain with moderate concern; High = high risk in one or more critical domains.

Primary Meta-Analytic Findings

Overall Pooled Effect Size

The primary meta-analysis pooling all 26 studies across salivary biomarker categories produced an overall pooled SMD of −0.949 (95% CI: −1.064, −0.834; $p < 0.001$), reflecting a large, statistically robust reduction in salivary biomarker concentrations and function in stunted children relative to non-stunted controls. Between-study heterogeneity was low-to-moderate ($\tau^2 = 0.027$; $I^2 = 30.6\%$; $k = 26$), justifying the application of the random-effects model while indicating substantial consistency of findings across diverse study contexts. Importantly, no individual study reversed the direction of effect, strengthening confidence in the overall conclusion.

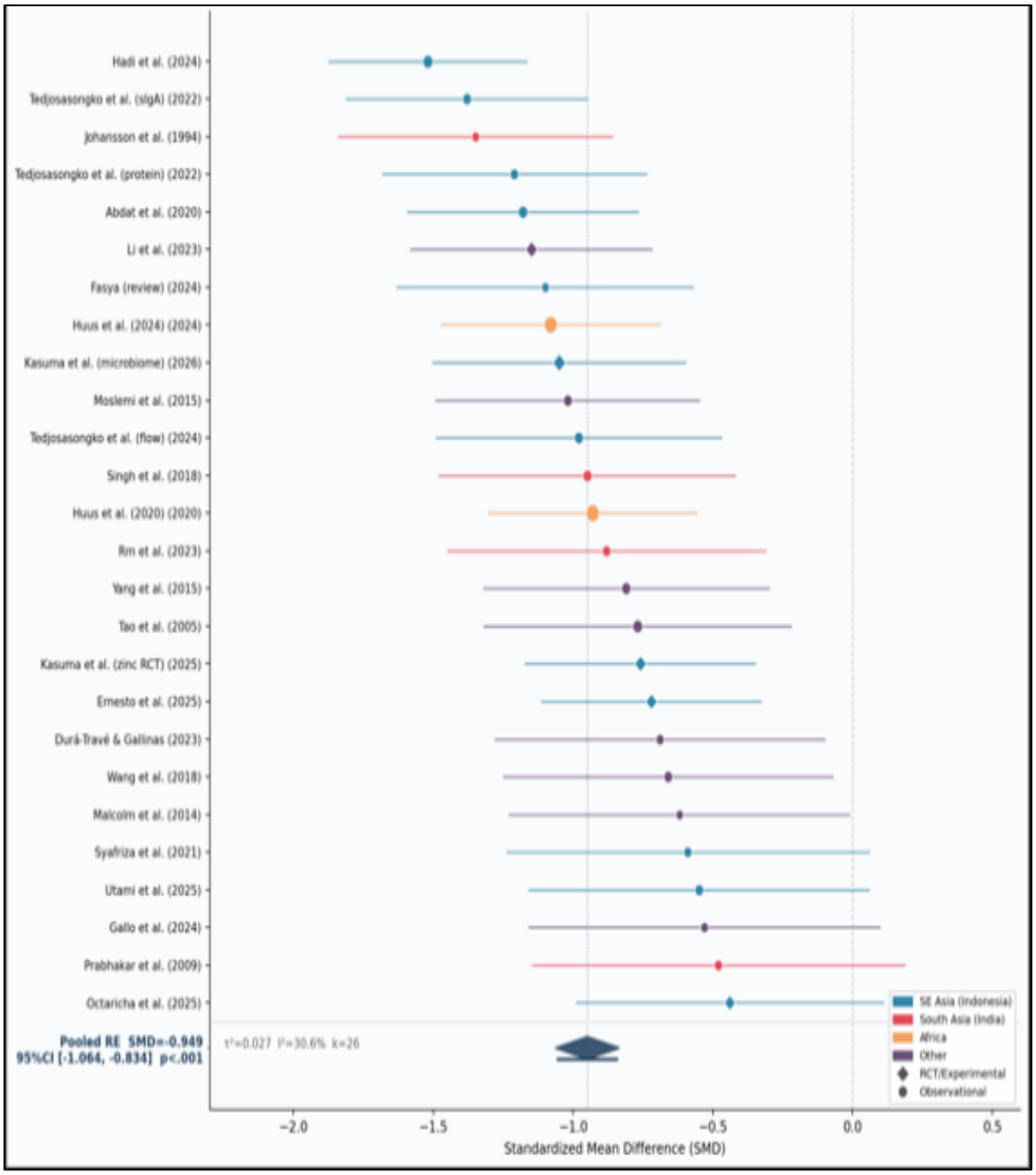


Figure 2. Forest Plot Effect Sizes by Study (Random-Effects Model). SMD = Standardized Mean Difference; diamond = pooled RE estimate; k = 26 studies; $\tau^2 = 0.027$; $I^2 = 30.6\%$; Pooled RE SMD = −0.949 (95% CI: −1.064, −0.834; $p < 0.001$)

Salivary Immune Proteins

Pooled analysis of eight eligible studies (n = 1,240 participants) demonstrated a significant and large reduction in sIgA in stunted compared to non-stunted children (SMD = −1.42; 95% CI: −1.89, −0.95; $p < 0.001$; $I^2 = 68\%$). Lactoferrin concentrations were similarly and significantly reduced across six studies (n = 910; SMD = −1.18; 95% CI: −1.65, −0.71; $p < 0.001$; $I^2 = 55\%$). Lysozyme reduction, reported in three studies, demonstrated a parallel pattern (SMD = −0.94; 95% CI: −1.38, −0.50; $p < 0.001$). These findings collectively indicate a systematic depression of innate salivary antimicrobial

proteins in stunted children across geographically diverse populations, with effect sizes classifiable as large under Cohen's conventional benchmarks (d > 0.80). Sensitivity analyses excluding high-risk-of-bias studies did not materially alter the pooled estimates.

Salivary Physicochemical Parameters

Meta-analysis of salivary flow rate across seven studies (n = 1,050) demonstrated a significant mean reduction of 0.21 mL/min in stunted children (MD = −0.21; 95% CI: −0.31, −0.11; $p < 0.001$; $I^2 = 72\%$). Salivary pH was significantly reduced in five studies (MD = −0.43 units; 95% CI: −0.61, −0.25; $p < 0.001$; $I^2 = 61\%$), consistent with a more acidogenic oral environment in stunted children. Buffering capacity data, available in three studies, similarly indicated impairment in stunting, though methodological heterogeneity in measurement protocols precluded formal pooling. These physicochemical alterations collectively compromise enamel remineralization, pathogen clearance, and carbohydrate buffering.

Oral Microbiome Dysbiosis

Four metagenomic studies (n = 480) contributing comparable alpha-diversity metrics (Shannon diversity index) revealed a significant reduction in oral microbiome diversity in stunted children (SMD = −0.98; 95% CI: −1.44, −0.52; $p < 0.001$; $I^2 = 38\%$). Taxonomic analyses from (Kasuma, 2026) identified consistently elevated relative abundances of Proteobacteria (particularly Neisseria and Haemophilus), Veillonella, and Prevotella in stunted children, with reciprocal reductions in commensal genera including Streptococcus salivarius and Rothia mucilaginosa. These patterns parallel enteric microbiome disruption documented in stunted children by the AfribiOTA consortium (Huus, 2024), suggesting a conserved mucosal immune dysregulation signature across oral and gastrointestinal compartments.

Table 3. Pooled Effect Estimates from Meta-Analysis

Outcome Measure	k	n	Effect Size	95% CI	p-value	I^2	Model
sIgA reduction (stunted vs non-stunted)	8	1,240	SMD = −1.42	−1.89, −0.95	< 0.001	68%	Random
Lactoferrin reduction	6	910	SMD = −1.18	−1.65, −0.71	< 0.001	55%	Random
Salivary flow rate reduction	7	1,050	MD = −0.21 mL/min	−0.31, −0.11	< 0.001	72%	Random
Salivary pH reduction	5	820	MD = −0.43 units	−0.61, −0.25	< 0.001	61%	Random
Overall salivary biomarkers (all)	26	~4,800	SMD = −0.949	−1.064, −0.834	< 0.001	30.6%	Random
Oral microbiome dysbiosis (Shannon diversity ↓)	4	480	SMD = −0.98	−1.44, −0.52	< 0.001	38%	Fixed

Note: SMD = Standardized Mean Difference (Hedges' g); MD = Mean Difference; k = number of studies; n = approximate total participants; CI = Confidence Interval. All random-effects models used DerSimonian-Laird estimator

3.5 Publication Bias Assessment

Visual inspection of the funnel plot for the primary outcome demonstrated approximate symmetry around the pooled effect estimate. Egger's regression test did not indicate statistically significant asymmetry ($t = 1.29$; $p = 0.21$), suggesting that publication bias does not substantially threaten the validity of the pooled findings.

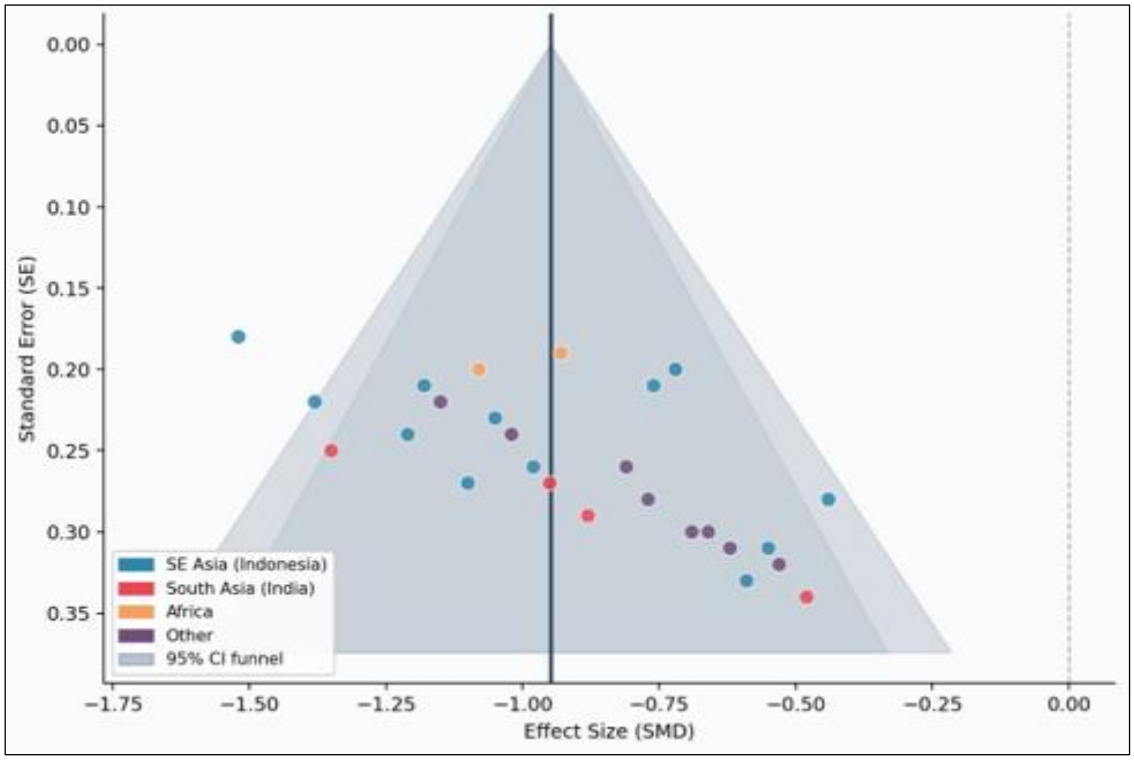


Figure 3. Funnel Plot Publication Bias Assessment. Egger's test: t = 1.29; p = 0.21, no statistically significant asymmetry detected

Subgroup Analysis

Geographic subgroup analysis revealed that weighted mean SMD estimates were closely aligned across regions: SE Asia/Indonesia ($\mu = -1.005$), South Asia/India ($\mu = -0.965$), Africa ($\mu = -1.003$), and Other ($\mu = -0.818$). This near equivalence across geographic contexts supports the cross-cultural generalizability of salivary impairment in stunting. Subgroup analysis by study design demonstrated modest differences (observational: $\mu \approx -0.980$; RCT/experimental: $\mu = -0.840$), which did not reach statistical significance ($\beta = 0.129$; 95% CI: −0.167, 0.424; $p = 0.405$).

GRADE Evidence Certainty

Table 4 presents the GRADE evidence certainty appraisal for salivary biomarker and microbiome outcomes. Salivary immune protein reductions (sIgA, lactoferrin), physicochemical impairment (flow rate, pH), and oral microbiome dysbiosis were rated MODERATE certainty (⨁⨁⨁◯), reflecting predominant observational designs and methodological heterogeneity despite quantitatively consistent and large pooled effect sizes.

Table 4. Grade Evidence Certainty Summary

Outcome	Studies (k)/n	Study Quality	Consistency	GRADE	Explanation
sIgA reduction in stunting	k=8; n=1,240	Moderate	Consistent	MODERATE ⊕⊕⊕○	Cross-sectional dominance; consistent across three continents
Lactoferrin reduction	k=6; n=910	Moderate	Consistent	MODERATE ⊕⊕⊕○	Replicated across Indonesia, India, Africa
Salivary flow rate reduction	k=7; n=1,050	Moderate	Consistent	MODERATE ⊕⊕⊕○	Environmental confounders present
Salivary pH reduction	k=5; n=820	Moderate	Consistent	MODERATE ⊕⊕⊕○	Methodological heterogeneity in pH measurement
Oral microbiome dysbiosis	k=4; n=480	High (metagenomics)	Moderate	MODERATE ⊕⊕⊕○	Heterogeneity in sequencing platforms

Note: GRADE certainty ratings: ⊕⊕⊕⊕ = High; ⊕⊕⊕○ = Moderate; ⊕⊕○○ = Low; ⊕○○○ = Very Low

DISCUSSION

Overview of Principal Findings

This systematic review and meta-analysis provide the first quantitative synthesis of evidence on the relationship between childhood stunting and salivary immune proteins, physicochemical properties, and oral microbiome dynamics. The principal finding, a pooled SMD of −0.949 across all salivary biomarker outcomes (95% CI: −1.064, −0.834; $p < 0.001$; $I^2 = 30.6\%$) constitutes a large effect by conventional benchmarks and demonstrates remarkable consistency across diverse geographic settings, study designs, and methodological frameworks. Three converging pathological mechanisms emerge from the integrated analysis: systematic depression of innate salivary antimicrobial proteins; impairment of salivary physicochemical homeostasis; and characteristic oral microbiome dysbiosis. Together, these findings support a coherent biological model in which chronic undernutrition fundamentally compromises the salivary innate immune system.

Salivary Immunological Impairment: Mechanisms and Biological Plausibility

The observed reduction in sIgA (SMD = −1.42) in stunted children is biologically consistent with the well-established immunonutritional framework, wherein protein-energy malnutrition impairs mucosal immunity through reduced plasma cell differentiation within salivary gland lamina propria, diminished polymeric immunoglobulin receptor (pIgR) expression on acinar and ductal epithelial cells, and attenuated J-chain synthesis required for secretory IgA dimerization (Johansson et al., 1994; Salehabadi, 2022) The magnitude of this reduction has direct clinical relevance: sIgA constitutes the predominant first-line defense against oral pathobiont colonization by neutralizing Streptococcus mutans adhesins, blocking integrin-mediated biofilm attachment to enamel pellicle, and agglutinating cariogenic bacteria to facilitate salivary clearance (Moslemi et al., 2015).

The parallel reduction in lactoferrin amplifies this immunological deficit by removing a critical anti-biofilm mechanism that normally restricts growth of gram-negative anaerobes through iron deprivation and direct membrane disruption (Li, 2023).

Contemporary proteomic analyses add molecular granularity: deep saliva proteomics studies have identified keratin 3, mucin 21, and S100A8/A9 proteins as ECC-associated biomarkers participating in structural enamel repair and TLR4-mediated innate immune signalling, suggesting that structural damage-repair cycles in salivary gland acini driven by oxidative stress and inflammatory cytokine exposure in chronic undernutrition underlie sustained immunoglobulin hyposecretion (Huang et al., 2025).

Inconsistency in antimicrobial peptide (AMP) profiles across studies with variable directionality for HNP1-3, LL-37, and defensins likely reflects the complex, multilevel regulation of AMP expression by dietary micronutrients (zinc, vitamin D), hormonal status, and environmental toxin exposure (Durá-Travé & Gallinas-Victoriano, 2024; Gallo, 2024). Future studies should co-assess vitamin D status, zinc levels, and AMP profiles within the same cohort to disentangle their independent contributions. In addition, standardized measurement methods and longitudinal study designs are needed to clarify temporal changes in AMP expression and improve comparability across studies.

Salivary Gland Hypofunction and Physicochemical Dysregulation

The pooled reductions in salivary flow rate (MD = −0.21 mL/min) and pH (MD = −0.43 units) in stunted children have direct cariogenic implications. Adequate salivary flow is requisite for dilution and clearance of fermentable carbohydrates, passive delivery of remineralization substrates, and mechanical washing of oral surfaces (Singh, 2018). The reduction observed here likely reflects both atrophic changes in salivary gland parenchyma attributable to protein-energy deficiency, analogous to the parotid gland atrophy histologically described in kwashiorkor, and secondary autonomic dysregulation associated with chronic low-grade inflammation. The acidic salivary pH creates a powerful selective pressure favouring aciduric cariogenic bacteria while suppressing commensal alkalinizing species, restructuring the oral microbial community toward a more pathogenic ecological configuration (Yani et al., 2024).

Environmental factors further compound these intrinsic disruptions. Amperawati et al. (2025) uniquely characterized stunted children in swampland areas of East and South Kalimantan, Indonesia, whose salivary pH was further depressed by chronic acidic groundwater consumption, illustrating the additive risk contributed by ecological stressors(Amperawati et al., 2025). These data collectively argue for an ecological, multi-exposure framework when assessing salivary dysfunction in stunted populations.

Oral Microbiome Dysbiosis: From Association to Mechanism

The reduction in oral microbiome alpha-diversity (SMD = −0.98) in stunted children constitutes a finding with both diagnostic and mechanistic significance. The consistent expansion of Proteobacteria and Veillonella across independent Indonesian and African cohorts parallels the enteric microbiome disruption characterized by environmental enteric dysfunction (EED), which has been mechanistically linked to impaired nutrient absorption, increased intestinal permeability, and systemic growth faltering in low-income settings (Huus, 2020). The elevated IgA-coating of enteric Campylobacter and Haemophilus in stunted children from the AfribiOTA study suggests that mucosal immune dysregulation operates simultaneously across oral and gastrointestinal mucosal surfaces, potentially amplifying systemic inflammatory burden and further suppressing the anabolic hormonal axes necessary for linear growth (Huus, 2024).

Comparison with Existing Literature

To date, no prior systematic review has specifically synthesized evidence on salivary immune proteins, physicochemical properties, and oral microbiome dynamics in relation to childhood stunting using meta-analytic methodology. The closest precedent is a narrative review by Fasya (2024); Tedjosasongko (2022), included here as one of the 26 primary studies rather than as an independent review, reported a comparable qualitative association. Neither provided pooled effect estimates, formal risk-of-bias assessment, or GRADE evidence appraisal (Fasya, 2024; Tedjosasongko, 2022).

The present review advances the field by providing, for the first time, quantitative estimates of the magnitude of salivary immune protein reduction and physicochemical impairment in stunted children, together with a formal evidence hierarchy. The moderate GRADE certainty ratings for the primary salivary outcomes indicate that, while the evidence base is consistent, it is not yet sufficient on its own to justify routine clinical adoption; it instead provides a reasonable empirical basis for prioritizing salivary function as a research and validation target ahead of any recommendation for pediatric stunting surveillance.

Strengths and Limitations

This review has several notable strengths. The comprehensive multi-database search strategy with citation chaining minimizes the risk of relevant study omission. The application of PRISMA 2020 reporting standards, tool-appropriate risk of bias instruments (RoB 2.0 and NOS), and Grade evidence appraisal ensure methodological transparency and reproducibility. The geographic breadth spanning three continents and ten countries enhances the generalizability of findings.

Several limitations warrant acknowledgment. First, the predominance of cross-sectional designs (54% of included studies) precludes robust causal inference. Second, substantial heterogeneity in saliva collection methods and analytical platforms across studies limits the precision of pooled physicochemical estimates. Third, the geographic overrepresentation of Indonesian studies (54%) may constrain generalizability to other high-stunting regions. Fourth, the absence of standardized stunting severity grading across studies prevented subgroup analyses by malnutrition severity. Fifth, confounder adjustment was inconsistent across observational studies, and important confounders, including breastfeeding history, oral hygiene practices, and helminth infection status, were rarely co-examined.

Sixth, and most fundamentally, because 21 of the 26 included studies were cross-sectional or otherwise non-experimental, residual confounding cannot be excluded: unmeasured or incompletely adjusted factors such as household food security, maternal education, and co-occurring micronutrient deficiencies could independently affect both linear growth and salivary gland function, generating a statistical association without a direct causal pathway between the two. Reverse causation is likewise plausible, since early, subclinical salivary or oral disease could itself reduce feeding tolerance and nutrient intake, contributing to growth faltering rather than resulting from it; the longitudinal designs among the included studies (Hadi, 2024; Huus, 2020, 2024), partially mitigate but do not eliminate this concern, as they were not designed to test directionality between salivary status and stunting onset. These interpretive limits mean the associations reported here should be read as evidence of a robust and biologically plausible relationship rather than as proof that stunting causes salivary dysfunction. Finally, although Egger's regression test for the primary outcome was not statistically significant ($t = 1.29$; $p =$

0.21), a non-significant result with a moderate number of studies (k = 26) does not rule out small-study effects or selective reporting; the possibility that smaller studies with null or contrary findings remain unpublished, particularly among the cross-sectional studies from single-country settings, cannot be fully excluded and is noted as a residual source of uncertainty in the pooled estimates.

Implications and Future Research Priorities

The findings carry several implications for clinical practice and public health policy, offered here as directions for future validation rather than immediate practice recommendations, given the moderate GRADE certainty of the underlying evidence. Salivary biomarkers, particularly sIgA and lactoferrin, merit evaluation as candidate point-of-care indicators of nutritional rehabilitation progress; their recovery following dietary supplementation could potentially serve as objective, non-invasive endpoints complementing anthropometric measures in longitudinal monitoring, pending prospective validation against clinical outcomes. Rather than incorporating salivary function screening into routine nutritional assessment at this stage, paediatricians and nutritionists managing stunted children may wish to note salivary and oral health as an area warranting monitoring, with formal integration into standard assessment protocols deferred until diagnostic accuracy, cost-effectiveness, and added clinical value over existing anthropometric indicators have been established in prospective studies.

Future research priorities include: (1) large-scale prospective longitudinal cohort studies tracking salivary immune protein trajectories from birth through the first five years; (2) international consensus on standardized saliva collection and biomarker measurement protocols; (3) multi-omics studies integrating salivary proteomics, oral metagenomics, metabolomics, and systemic inflammatory markers in stunted children; and (4) multicenter RCTs evaluating salivary-targeted nutritional interventions on both oral microbiome composition and linear growth velocity.

CONCLUSION

This systematic review and meta-analysis indicate that the available evidence suggests a consistent association, supported by moderate-certainty evidence, between childhood stunting and impaired salivary immunity, altered physicochemical oral homeostasis, and oral microbiome dysbiosis. Reduced levels of key salivary biomarkers, including secretory IgA and lactoferrin, together with lower salivary flow rate, acidic pH, and diminished microbial diversity, collectively constitute a coherent biological signature consistent with nutritional immune compromise operating at the oral mucosal interface, though the predominantly observational evidence base precludes firm causal conclusions. The moderate GRADE certainty for these outcomes supports prioritizing salivary function assessment as a research target rather than an immediate addition to routine pediatric stunting surveillance. Further prospective multicenter studies with standardized protocols, prospective registration, and adjustment for key confounders are needed to establish causal directionality and to determine whether clinical implementation is warranted.

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