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Associations of The Gut Microbiota on Respiratory Disease in Children : A Systematic Review

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ABSTRACT

Background: The gut-lung axis represents a critical pathway linking early-life gut microbiota to pediatric respiratory diseases, but comprehensive synthesis of associations, mechanisms, and therapeutic evidence is lacking.

Methods: This systematic review synthesized 80 studies (RCT, etc) examining gut microbiota associations with pediatric respiratory outcomes including asthma, allergic rhinitis, respiratory tract infections (RTIs), bronchiolitis, bronchopulmonary dysplasia (BPD), and cystic fibrosis (CF) lung disease.

Results: Early-life gut dysbiosis during the first 100 days—characterized by reduced *Lachnospira* , *Veillonella*, *Faecalibacterium*, *Rothia* (FLVR taxa) —consistently associated with increased asthma risk (Arrieta et al., 2015). Short-chain fatty acids

(SCFAs), particularly acetate and butyrate, emerged as central immunomodulatory mediators (Yang et al., 2025). Mendelian randomization confirmed causal roles for *Collinsella* and *Ruminococcaceae* UCG014 in childhood asthma (Li et al., 2023). In CF, *Bifidobacterium* - dominant gut microbiota associated with 45% fewer pulmonary exacerbations (Ray et al., 2022). Probiotics reduced RTI incidence (42% vs 59% in controls) and acute asthma exacerbations (RR 0.38) but showed no benefit for primary asthma prevention. Cesarean delivery, antibiotic exposure (HR for asthma 1.21), and breastfeeding cessation were key moderators. Apparent diversity–disease contradictions resolved when considering community composition rather than diversity metrics alone.

Conclusion: Gut microbiota composition in early life is causally associated with pediatric respiratory disease risk through SCFA-mediated immune modulation, with the first 100 days as a critical window. Probiotics show strain-specific efficacy for RTI prevention and asthma treatment but not primary prevention.

Keywords: Gut microbiota; pediatric respiratory disease; gut-lung axis; short-chain fatty acids; probiotics; asthma

INTRODUCTION

The human gastrointestinal tract harbors a complex microbial ecosystem—the gut microbiota—that plays a fundamental role in immune system development, metabolic regulation, and protection against pathogens (Druszczyńska et al., 2024). Over the past decade, the concept of the "gut-lung axis" has emerged, describing bidirectional communication between the intestinal microbiota and the respiratory mucosa through systemic immune, metabolic, and neuroendocrine pathways (Yang et al., 2025). Disruption of this axis, termed gut dysbiosis, has been increasingly implicated in the pathogenesis of diverse pediatric respiratory diseases, including asthma, allergic rhinitis, bronchiolitis, respiratory tract infections (RTIs), bronchopulmonary dysplasia (BPD), and cystic fibrosis (CF)-related lung disease (Aldriwesh et al., 2023; Caley et al., 2023; Woodall et al., 2022).

Background: Childhood respiratory diseases represent a major global health burden. Asthma affects approximately 10–15% of children in industrialized countries, while RTIs are the leading cause of pediatric hospitalization worldwide (Zhao, 2026). Despite advances in pharmacotherapy, primary prevention remains elusive, and disease modification strategies are limited. The gut microbiota, which is established at birth and shaped by delivery mode, feeding practices, antibiotic exposure, and environmental factors, has been proposed as a modifiable determinant of respiratory health (Grier et al., 2019; Liu et al., 2023). Early-life microbial perturbations during critical developmental windows may permanently alter immune set points, increasing susceptibility to respiratory disease (Arrieta et al., 2015; Durack et al., 2018).

Key mechanistic pathways linking gut microbiota to respiratory outcomes include short-chain fatty acid (SCFA) production (e.g., acetate, propionate, butyrate), which signals through G-protein-coupled receptors (GPR41, GPR43) on immune cells, promoting regulatory T-cell (Treg) differentiation and suppressing Th2-mediated inflammation (Yang et al., 2025; Druszczyńska et al., 2024). Additionally, gut dysbiosis can increase intestinal permeability, allowing bacterial lipopolysaccharide (LPS) and other metabolites to enter the systemic circulation and propagate low-

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grade inflammation that affects the lung (Caley et al., 2023). The importance of specific taxa—particularly *Faecali bacteriumprausnitzii*, *Roseburia*, *Bifidobacterium*, and *Lachnospiraceae* Members—has been highlighted in multiple observational cohorts (Arrieta et al., 2015; Galazzo et al., 2020; Nasir & Gul, 2025).

Research Gap: Although numerous primary studies and systematic reviews have examined gut microbiota–respiratory disease associations, several critical gaps remain. First, the directionality of associations—particularly whether high or low gut diversity is protective—appears inconsistent across different respiratory outcomes (Moroishi et al., 2022; Fu et al., 2025), and a unifying framework explaining these contradictions is lacking. Second, while probiotic interventions have been extensively tested, results are conflicting: some meta-analyses show clear benefits for RTI prevention (Liu et al., 2013; Langenneger et al., 2025) and asthma treatment (Liu et al., 2025; Fan et al., 2025), whereas others find no effect for primary asthma prevention (Azad et al., 2013; Zuccotti et al., 2015; Abrahamsson et al., 2013). The reasons for this discrepancy remain poorly understood. Third, the role of the gut–lung axis in specific pediatric respiratory conditions beyond asthma—such as BPD, CF, and RSV bronchiolitis—has been less systematically integrated. Fourth, the causal nature of observed associations has only recently been addressed using Mendelian randomization (Li et al., 2023), and mechanistic evidence from human studies remains sparse.

Novelty: This systematic review provides several novel contributions. First, it synthesizes evidence across a broad spectrum of pediatric respiratory outcomes (asthma, allergic rhinitis, RTIs, RSV, BPD, CF, neonatal respiratory distress syndrome [NRDS], obstructive sleep apnea) within a single analytic framework. Second, it explicitly addresses apparent contradictions (e.g., high vs low diversity, prevention vs treatment effects) and proposes resolution mechanisms. Third, it integrates observational, interventional, and Mendelian randomization evidence to assess causality. Fourth, it provides a detailed thematic analysis of moderating factors (delivery mode, breastfeeding, antibiotics, air pollution) and their effect modification. Fifth, it evaluates disease-specific gut–lung axis dynamics, particularly in CF as a high-resolution model.

Objectives: The primary objective of this systematic review is to comprehensively assess the associations between gut microbiota composition, diversity, and function and pediatric respiratory

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disease outcomes. Secondary objectives are: (1) to evaluate the effects of probiotic, prebiotic, and synbiotic interventions on respiratory outcomes in children; (2) to identify moderating factors (delivery mode, feeding, antibiotics, environmental exposures) that influence these associations; (3) to elucidate proposed biological mechanisms, focusing on SCFAs and immune modulation; and (4) to identify critical time windows for microbiota effects on respiratory health.

Hypotheses: The following hypotheses guided this review: (1) Early-life gut dysbiosis—specifically depletion of SCFA-producing commensals—is associated with increased risk of childhood asthma and allergic respiratory diseases. (2) The direction of association between gut alpha diversity and respiratory disease risk depends on whether diversity reflects protective commensals or pathobiont enrichment. (3) Probiotic interventions show strain-specific, moderate efficacy for RTI prevention and asthma treatment but not for primary asthma prevention due to differences in immune programming windows. (4) Moderating factors (cesarean delivery, formula feeding, antibiotic exposure) increase respiratory risk through predictable effects on gut microbiota composition.

Benefits: This review benefits multiple stakeholders. For clinicians, it provides evidence-based guidance on the role of gut microbiota in pediatric respiratory diseases and the potential indications for probiotic/prebiotic supplementation. For researchers, it identifies critical knowledge gaps and proposes standardized methodological approaches. For policymakers, it highlights modifiable early-life exposures (breastfeeding, rational antibiotic use) as targets for primary prevention. For patients and families, it offers practical insights into lifestyle and dietary factors that may influence respiratory health.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the Associations of The Gut Microbiota on Respiratory Disease in Children.

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Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Children	Gut microbiota	Healthy controls	Respiratory disease
Keyword 2	Pediatric	Gut microbiome	Disease-free children	Asthma
Keyword 3	Infants	Gut–lung axis	Placebo group	Wheezing
Keyword 4	0–18 years	Early-life colonization	No probiotic use	Respiratory tract infections

The Boolean MeSH keywords inputted on databases for this research are: *("Children" OR "Pediatric" OR "Infants" OR "0–18 years") AND ("Gut microbiota" OR "Gut microbiome" OR "Gut–lung axis" OR "Early-life colonization") AND ("Healthy controls" OR "Disease-free children" OR "Placebo group" OR "No probiotic use") AND ("Respiratory disease" OR "Asthma" OR "Wheezing" OR "Respiratory tract infections")*

Screening

Abstract screening

We screened in sources based on their abstracts that met these criteria:

- **Pediatric Population**: Does the study include children aged 0-18 years (with particular focus on infants and early childhood)?
- **Gut Microbiota or Probiotic Focus**: Does the study examine gut microbiota composition, diversity, or function in relation to respiratory outcomes OR investigate probiotic interventions for respiratory disease prevention or treatment?
- **Respiratory Outcomes**: Does the study include respiratory outcomes such as asthma, allergic rhinitis, respiratory infections, wheezing, or other clinically diagnosed respiratory conditions?

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- **Gut Microbiota Assessment Methods**: Does the study use clearly defined gut microbiota assessment methods (16S rRNA sequencing, metagenomics, culture-based methods, or validated probiotic interventions)?
- **Study Design**: Is the study an observational study (cohort, case-control, cross-sectional), randomized controlled trial, systematic review, or meta-analysis?
- **Non-Adult Population**: Does the study include participants other than exclusively adult populations (>18 years)?
- **Gut Microbiota Specificity**: Does the study examine gut microbiota (not exclusively oral, skin, or other non-gut microbiota)?
- **Human Participants**: Does the study include human participants (not exclusively animal studies, in vitro studies, or mechanistic studies without human participants)?
- **Respiratory Disease Focus**: Does the study assess respiratory disease outcomes (not solely gastrointestinal outcomes without respiratory disease assessment)?

Papers that failed any strict criterion were automatically excluded. For the remaining papers, we considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Full-text screening

We then screened papers based on their full text using these additional criteria:

- **Pediatric Population**: Does the study include children aged 0-18 years (with particular focus on infants and early childhood)?
- **Gut Microbiota or Probiotic Focus**: Does the study examine gut microbiota composition, diversity, or function in relation to respiratory outcomes OR investigate probiotic interventions for respiratory disease prevention or treatment?

- **Respiratory Outcomes**: Does the study include respiratory outcomes such as asthma, allergic rhinitis, respiratory infections, wheezing, or other clinically diagnosed respiratory conditions?
- **Gut Microbiota Assessment Methods**: Does the study use clearly defined gut microbiota assessment methods (16S rRNA sequencing, metagenomics, culture-based methods, or validated probiotic interventions)?
- **Study Design**: Is the study an observational study (cohort, case-control, cross-sectional), randomized controlled trial, systematic review, or meta-analysis?
- **Non-Adult Population**: Does the study include participants other than exclusively adult populations (>18 years)?
- **Gut Microbiota Specificity**: Does the study examine gut microbiota (not exclusively oral, skin, or other non-gut microbiota)?
- **Human Participants**: Does the study include human participants (not exclusively animal studies, in vitro studies, or mechanistic studies without human participants)?
- **Respiratory Disease Focus**: Does the study assess respiratory disease outcomes (not solely gastrointestinal outcomes without respiratory disease assessment)?

Papers that failed any strict criterion were automatically excluded. For the remaining papers, we considered all screening questions together and made a holistic judgement about whether to include each paper in the final analysis.

Data extraction

- **Study Design & Child Population**:

  Extract study design and characteristics of the child population relevant to gut microbiota-respiratory disease associations, including:

  - Study design (RCT, etc)

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- Child age range and sample size
- Geographic location and setting
- Key inclusion/exclusion criteria related to children's health status
- Follow-up duration (for longitudinal studies)
- Data collection timepoints for microbiota and respiratory outcomes

- **Gut Microbiota Measures**:

  Extract all gut microbiota characteristics assessed in relation to childhood respiratory diseases, including:

  - Sampling method and timing (stool collection age/timepoint)
  - Analysis method (16S rRNA sequencing, shotgun metagenomics, culture-based)
  - Specific microbiota measures (alpha diversity indices, beta diversity, relative abundance of specific taxa, metabolites)
  - Taxonomic level of analysis (phylum, family, genus, species)
  - Key bacterial genera/species specifically mentioned in relation to respiratory outcomes

- **Respiratory Disease Outcomes**:

  Extract all respiratory disease outcomes and symptoms studied in children, including:

  - Specific respiratory conditions (asthma, wheezing, upper/lower respiratory tract infections, pneumonia, etc.)
  - Outcome definitions and diagnostic criteria used

- Age at outcome assessment
- Measurement methods (parent report, medical records, clinical diagnosis, prescription data)
- Severity measures or symptom frequency
- Follow-up duration for respiratory outcome tracking

- **Microbiota-Respiratory Associations**:

  Extract all associations found between gut microbiota and childhood respiratory diseases, including:

  - Direction of association (increased/decreased microbiota diversity or specific taxa associated with higher/lower respiratory disease risk)
  - Statistical measures (odds ratios, risk ratios, correlation coefficients, p-values, confidence intervals)
  - Specific bacterial taxa associated with respiratory outcomes (with effect sizes)
  - Proposed biological mechanisms linking gut microbiota to respiratory health (immune modulation, metabolite production, gut-lung axis pathways)
  - Strength and significance of associations
  - Dose-response relationships if reported

- **Interventions & Effects**:

  Extract details about any microbiota-targeted interventions and their effects on childhood respiratory outcomes, including:

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- Type of intervention (probiotics, prebiotics, bacterial supplementation, dietary modifications)
- Specific bacterial strains or compounds used
- Intervention timing, dosage, and duration
- Respiratory outcomes measured post-intervention
- Effect sizes and statistical significance of intervention effects
- Control group comparisons
- Note if study was observational only (no interventions)

- **Moderating Factors**:

  Extract factors that influenced the gut microbiota-respiratory disease associations in children, including:

  - Mode of delivery (cesarean vs. vaginal birth)
  - Feeding practices (breastfeeding vs. formula feeding duration)
  - Antibiotic exposure timing and frequency
  - Environmental factors (rural vs. urban, allergen exposure, siblings)
  - Child characteristics (sex, genetic factors, comorbidities)
  - Critical time windows for microbiota effects on respiratory health
  - Factors that strengthened or weakened observed associations

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Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Children" OR "Pediatric" OR "Infants" OR "0–18 years") AND ("Gut microbiota" OR "Gut microbiome" OR "Gut–lung axis" OR "Early-life colonization") AND ("Healthy controls" OR "Disease-free children" OR "Placebo group" OR "No probiotic use") AND ("Respiratory disease" OR "Asthma" OR "Wheezing" OR "Respiratory tract infections")*	138
Semantic Scholar	*("Children" OR "Pediatric" OR "Infants" OR "0–18 years") AND ("Gut microbiota" OR "Gut microbiome" OR "Gut–lung axis" OR "Early-life colonization") AND ("Healthy controls" OR "Disease-free children" OR "Placebo group" OR "No probiotic use") AND ("Respiratory disease" OR "Asthma" OR "Wheezing" OR "Respiratory tract infections")*	1
Springer	*("Children" OR "Pediatric" OR "Infants" OR "0–18 years") AND ("Gut microbiota" OR "Gut microbiome" OR "Gut–lung axis" OR "Early-life colonization") AND ("Healthy controls" OR "Disease-free children" OR "Placebo group" OR "No probiotic use") AND ("Respiratory disease" OR "Asthma" OR "Wheezing" OR "Respiratory tract infections")*	1,268
Google Scholar	*("Children" OR "Pediatric" OR "Infants" OR "0–18 years") AND ("Gut microbiota" OR "Gut microbiome" OR "Gut–lung axis" OR "Early-life colonization") AND ("Healthy controls" OR "Disease-free children" OR "Placebo group" OR "No probiotic use") AND ("Respiratory disease" OR "Asthma" OR "Wheezing" OR "Respiratory tract infections")*	16,100
Wiley Online Library	*("Children" OR "Pediatric" OR "Infants" OR "0–18 years") AND ("Gut microbiota" OR "Gut microbiome" OR "Gut–lung axis" OR "Early-life colonization") AND ("Healthy controls" OR "Disease-free children" OR "Placebo group" OR "No probiotic use") AND ("Respiratory disease" OR "Asthma" OR "Wheezing" OR "Respiratory tract infections")*	1,486

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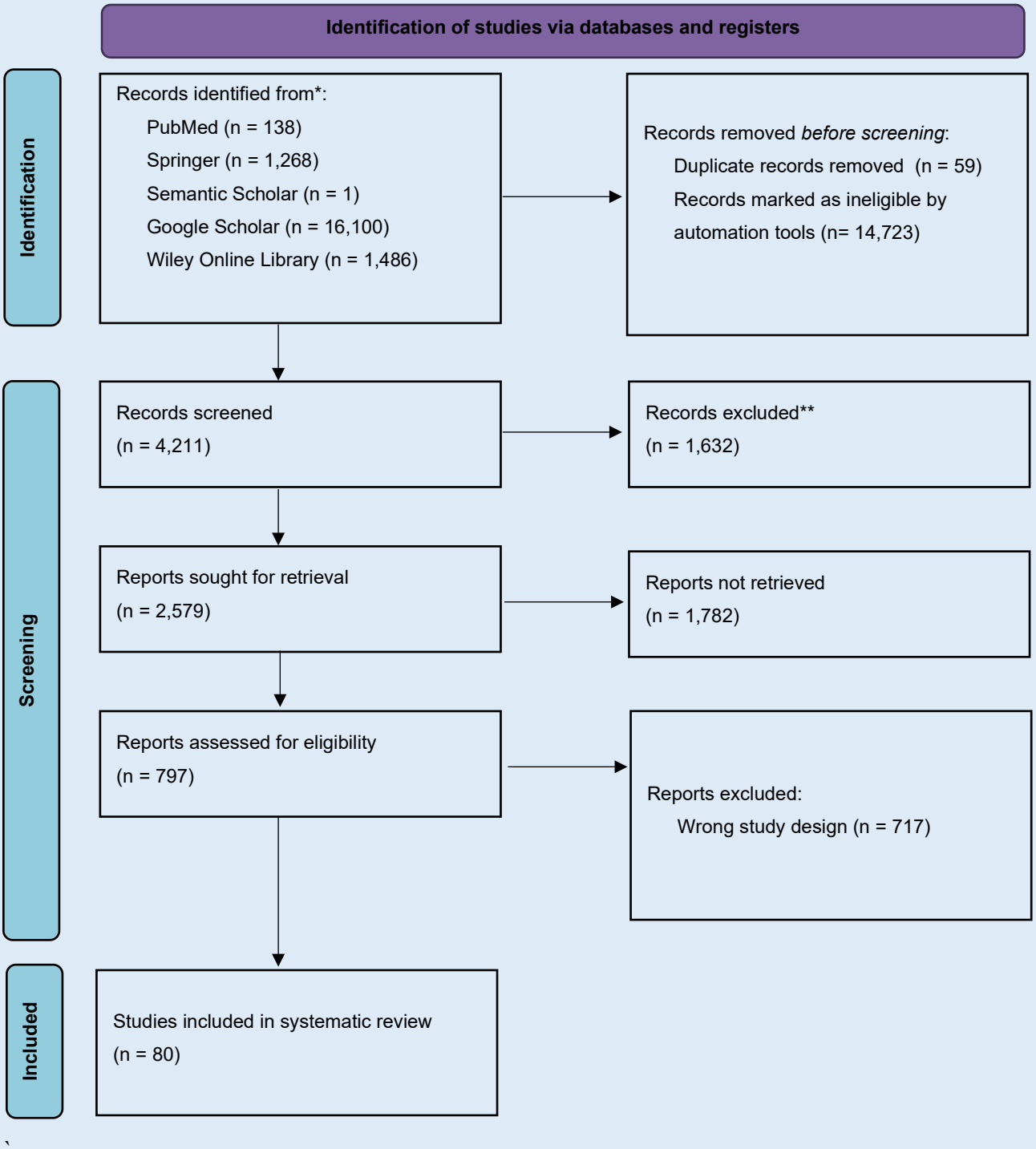


Figure 1. Article search flowchart

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Risk of Bias

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Arrieta et al. 2015 [1]	Low	Moderate	Low	Low	Low	Low
García-Mauriño Alcazar et al. 2022 [2]	Low	Low	Low	Low	Low	Low
Galazzo et al. 2020 [3]	Low	Moderate	Low	Low	Low	Low
Li et al. 2023 [4]	Low	Low	Low	Low	Low	Low
Cabrera-Rubio et al. 2024 [5]	Moderate	Moderate	Low	Moderate	Low	Moderate
Woodall et al. 2022 [6]	Low	Low	Low	Low	Low	Low
Yagi et al. 2024 [7]	Low	Low	Low	Low	Low	Low
Ray et al. 2022 [8]	Low	Moderate	Low	Moderate	Low	Moderate
Liu et al. 2023 [9]	Low	Moderate	Low	Low	Low	Low
Sameeha et al. 2025 [10]	Low	Low	Low	Low	Low	Low
Liu et al. 2013 [11]	Low	Low	Low	Low	Low	Low

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Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Hojsak et al. 2010 [12]	Low	Low	Low	Moderate	Low	Low
Liu et al. 2025 [13]	Low	Low	Low	Low	Low	Low
Liu et al. 2026 [14]	Low	Unclear	Low	Low	Low	Moderate
Zuccotti et al. 2015 [15]	Low	Low	Low	Low	Low	Low
Azad et al. 2013 [16]	Low	Low	Low	Low	Low	Low
Zhao 2026 [17]	Low	Low	Low	Low	Low	Low
Yang et al. 2025 [18]	Low	Low	Low	Low	Low	Low
Caley et al. 2023 [19]	Low	Low	Low	Low	Low	Low
Zheng et al. 2019 [20]	Moderate	Moderate	Low	Moderate	Low	Moderate
Druszczyńska et al. 2024 [21]	Low	Low	Low	Low	Low	Low
Moroishi et al. 2022 [22]	Low	Moderate	Low	Low	Low	Low
Aldriwesh et al. 2023 [23]	Low	Low	Low	Low	Low	Low

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Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Durack et al. 2018 [24]	Low	Low	Low	Moderate	Low	Low
Esposito et al. 2022 [25]	Moderate	Moderate	Low	Moderate	Low	Moderate
Nasir & Gul 2025 [26]	Moderate	Unclear	Unclear	Moderate	Moderate	Moderate
Price et al. 2023 [27]	Low	Moderate	Low	Low	Low	Low
Filardo et al. 2022 [28]	Low	Low	Low	Low	Low	Low
Bruzzese et al. 2014 [29]	Low	Low	Low	Moderate	Low	Low
Gallant et al. 2025 [30]	Low	Low	Low	Low	Low	Low
Langenneger et al. 2025 [31]	Low	Low	Low	Low	Low	Low
Thatrimontrichai et al. 2025 [32]	Moderate	Moderate	Low	Moderate	Low	Moderate
Vael et al. 2011 [33]	Moderate	Unclear	Unclear	Moderate	Low	Moderate

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Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Lau et al. 2017 [34]	Low	Low	Low	Moderate	Low	Low
Chen et al. 2010 [35]	Low	Low	Low	Moderate	Low	Low
Jenkins et al. 2022 [36]	Low	Low	Low	Low	Low	Low
Venter et al. 2022 [37]	Low	Low	Low	Low	Low	Low
Grier et al. 2019 [38]	Low	Moderate	Low	Low	Low	Low
Fan et al. 2025 [39]	Low	Low	Low	Low	Low	Low
Miraglia del Giudice et al. 2025 [40]	Low	Low	Low	Low	Low	Low
Sjödin et al. 2023 [41]	Low	Low	Low	Low	Low	Low
Sazawal et al. 2010 [42]	Low	Low	Low	Moderate	Low	Low
Rashidi et al. 2021 [43]	Low	Low	Low	Low	Low	Low
Abrahamsson et al. 2013 [44]	Low	Low	Low	Moderate	Low	Low

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Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Lif Holgerson et al. 2022 [45]	Low	Moderate	Low	Low	Low	Low
Vidal et al. 2019 [46]	Moderate	Unclear	Unclear	Moderate	Low	Moderate
Piloquet et al. 2024 [47]	Low	Low	Low	Low	Low	Low
Ouwehand et al. 2009 [48]	Low	Low	Low	Moderate	Low	Low
Milani et al. 2024 [49]	Low	Low	Low	Low	Low	Low
Ranucci et al. 2018 [50]	Low	Low	Low	Moderate	Low	Low
Hjelmsø et al. 2020 [51]	Low	Low	Low	Low	Low	Low
Darbandi et al. 2021 [52]	Low	Low	Low	Low	Low	Low
Price et al. 2022 [53]	Low	Moderate	Low	Low	Low	Low
Rutten et al. 2015 [54]	Low	Low	Low	Moderate	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Soldi et al. 2019 [55]	Low	Low	Low	Moderate	Low	Low
Berni Canani et al. 2017 [56]	Low	Low	Low	Moderate	Low	Low
Elazab et al. 2013 [57]	Low	Low	Low	Low	Low	Low
Zhang et al. 2022 [58]	Moderate	Moderate	Low	Moderate	Low	Moderate
Duvallet et al. 2018 [59]	Moderate	Unclear	Unclear	Moderate	Low	Moderate
Zuhair et al. 2025 [60]	Low	Low	Low	Low	Low	Low
Guo et al. 2025 [61]	Low	Low	Low	Low	Low	Low
Hong et al. 2025 [62]	Moderate	Unclear	Unclear	Moderate	Low	Moderate
Hu et al. 2021 [63]	Moderate	Moderate	Low	Moderate	Low	Moderate
Hu et al. 2024 [64]	Low	Low	Low	Low	Low	Low
Li et al. 2025 [65]	Low	Low	Low	Low	Low	Low
Fu et al. 2025 [66]	Moderate	Moderate	Low	Moderate	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Mo et al. 2022 [67]	Moderate	Unclear	Unclear	Moderate	Low	Moderate
Nashed et al. 2022 [68]	Low	Moderate	Low	Low	Low	Low
Lin et al. 2009 [69]	Low	Low	Low	Moderate	Low	Low
Uwaezuoke et al. 2022 [70]	Low	Low	Low	Low	Low	Low
Richmond et al. 2025 [71]	Low	Low	Low	Moderate	Low	Low
Rautava et al. 2008 [72]	Low	Low	Low	Moderate	Low	Low
Venter et al. 2021 [73]	Low	Low	Low	Low	Low	Low
Flygel et al. 2025 [74]	Low	Low	Low	Moderate	Low	Low
Paganini et al. 2017 [75]	Low	Low	Low	Moderate	Low	Low
Huang et al. 2018 [76]	Low	Low	Low	Moderate	Low	Low
Das et al. 2013 [77]	Low	Low	Low	Low	Low	Low

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Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Drago et al. 2022 [78]	Low	Low	Low	Moderate	Low	Low
Garaiova et al. 2014 [79]	Low	Moderate	Low	Moderate	Low	Moderate
Nocerino et al. 2017 [80]	Low	Low	Low	Moderate	Low	Low

RESULTS

Characteristics of Included Studies

Study	Research Focus	Population	Geographic Setting
Cristina García-Mauriño Alcazar et al., 2022 [2]	Infant gut microbiota and childhood respiratory disease	Infants 0–12 months; outcomes to age 18 years; N per study 76–917	Europe, USA (primarily urban)
R. Cabrera-Rubio et al., 2024 [5]	Gut and respiratory microbiota in bronchiolitis vs healthy infants	Infants <12 months; N=96 (cases=57, controls=39)	Madrid, Spain
M. Druszczyńska et al., 2024 [21]	Gut–lung axis mechanisms and respiratory disease	Mixed pediatric and adult populations	International (multi-country)

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Study	Research Focus	Population	Geographic Setting
Y. Moroishi et al., 2022 [22]	Infant gut microbiome at 6 weeks and risk of respiratory infections in year 1	N=465 (16S); N=185 (metagenomics); New Hampshire, USA	USA (community-based)
M. Aldriwesh et al., 2023 [23]	Airway and gut microbiome and pediatric asthma	Children up to 18 years; 25 studies	International (North America, Europe, Asia, Middle East)
C. Woodall et al., 2022 [6]	Gut microbiome alterations in RTI patients vs healthy controls	Children >3 years and adults; 11 studies	Predominantly China; one USA study
M. Arrieta et al., 2015 [1]	Early-life gut dysbiosis and childhood asthma risk	N=319 infants; CHILD Study; outcomes to age 3	Canada (4 sites)
Kazuma Yagi et al., 2024 [7]	Microbiome alterations during RSV infection	Infants/young children <3 years; 12 studies	Industrialized countries (USA, Spain, Italy, Netherlands, China)
J. Durack et al., 2018 [24]	Gut microbiota development and LGG supplementation in high-risk infants	High-risk n=25 (LGG/placebo); healthy controls n=29; birth to 12 months	USA (San Francisco)
Gianluca Galazzo et al., 2020 [3]	Gut microbiota maturation and atopic/asthma outcomes	N=440 children; stool at 5–31 weeks and school age 6–11 years	Germany

Study	Research Focus	Population	Geographic Setting
F. Sameeha et al., 2025 [10]	Antibiotic exposure, gut microbiome, and allergic disease in children	Prenatal to 10 years; N=1,530,914 across 15 studies	International
Shan Liu et al., 2013 [11]	LGG supplementation and respiratory infection prevention	Children 0–18 years; N=1805 across 4 RCTs	Europe (Finland, Croatia)
S. Esposito et al., 2022 [25]	Oral bacterial lysate OM-85 and microbiota in preschoolers with recurrent RTIs	Children aged 1–6 years; N=288	Milan, Italy
Faseeha Nasir & Sarooj Gul, 2025 [26]	Gut microbial signatures in pediatric asthma and eczema	N=180 (60 asthma, 60 eczema, 60 controls); ages 1–12 years	Faisalabad, Pakistan
Ping Zheng et al., 2019 [20]	Air pollution effects on gut microbiome in asthmatic vs healthy children	N=21 (11 asthmatic, 10 healthy); mean age 7.8 years	Beijing, China
Rong Zhao, 2026 [17]	Early-life exposures, probiotics, and asthma/wheeze risk	Multiple pediatric cohorts and RCTs; 51 studies	International
G. Zuccotti et al., 2015 [15]	Probiotics and prevention of atopic diseases including asthma and wheeze	N=4755 children across 17 RCTs	International

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Study	Research Focus	Population	Geographic Setting
Courtney E. Price et al., 2023 [27]	Gut microbiome development in cystic fibrosis and gut–lung axis	N=39 children with CF; birth to 4 years; 281 stool samples	USA
M. Azad et al., 2013 [16]	Probiotic supplementation and childhood asthma/wheeze	N=4866 children across 20 RCTs	International
S. Filardo et al., 2022 [28]	Air pollution impact on human gut microbiota and respiratory health	General and vulnerable populations including asthmatic children	USA, China, Finland
E. Bruzzese et al., 2014 [29]	Gut dysbiosis in CF children and LGG restoration	N=22 CF children (ages 2–9); N=20 healthy controls	Naples, Italy
Rachel E. Gallant et al., 2025 [30]	Gut microbiome diversity/composition in pediatric ALL, T1DM, and allergies	Children 0–18 years; 88 studies	International
Patricia Langenneger et al., 2025 [31]	Probiotic effect on RTI prevention in children and adolescents	Children 28 days to 17 years; N=8415 across 32 RCTs	International (Europe, Asia, Americas)
A. Thatrimontrichai et al., 2025 [32]	Gut microbiota in VLBW infants with vs without BPD	N=51 preterm neonates (BPD n=24; non-BPD n=27)	Thailand (Level IV NICU)

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Study	Research Focus	Population	Geographic Setting
C. Vael et al., 2011 [33]	Neonatal gut colonization and asthma risk by age 3	N=110 children; birth to 3 years; fecal sample at 3 weeks	Flanders, Belgium
L. Caley et al., 2023 [19]	Gut dysbiosis in cystic fibrosis and relation to pulmonary outcomes	Multiple pediatric and adult CF cohorts; 38 studies	International
A. Lau et al., 2017 [34]	Bifidobacterium longum BB536 and respiratory illnesses in preschoolers	N=520 randomized; N=219 compliant; ages 2–6 years	Malaysia (daycare centers/kindergartens)
Yueyang Chen et al., 2010 [35]	Lactobacillus gasseri A5 for asthma and allergic rhinitis in schoolchildren	N=105; ages 6–12 years	Taiwan
G. Jenkins et al., 2022 [36]	Prebiotics and probiotics in gut and immune health, including respiratory outcomes	General populations across ages	International
C. Venter et al., 2022 [37]	Dietary fiber, microbiome, and immune/respiratory health	Pediatric and adult populations	International
Wei Yang et al., 2025 [18]	Gut–lung axis, microbial dysbiosis, and allergic rhinitis including in children	Clinical, animal, and multi-omics studies 2010–2025	International

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Study	Research Focus	Population	Geographic Setting
A. Grier et al., 2019 [38]	Neonatal T-cell and microbiota co-development and respiratory morbidity	N=267 (148 preterm, 119 full-term); birth to 12 months	USA (Rochester, NY)
Die Fan et al., 2025 [39]	Probiotics, prebiotics, synbiotics, and postbiotics for pediatric asthma	Children <18 years with asthma; N=2419 across 13 RCTs	International (Europe, Asia)
I. Hojsak et al., 2010 [12]	LGG and respiratory/GI infection prevention in daycare children	N=281; ages 13–86 months	Zagreb, Croatia
M. Miraglia del Giudice et al., 2025 [40]	Ultra-processed foods, gut microbiota dysbiosis, and respiratory/allergic outcomes in children	Pediatric populations	International
K. S. Sjödin et al., 2023 [41]	Synbiotic formula, gut microbiota, and LRTI in formula-fed infants	N=106 for microbiota; term infants 1–12 months	Poland (4 sites)
S. Sazawal et al., 2010 [42]	Prebiotic + probiotic milk and respiratory/GI morbidity	N=624 (PP+control); children 1–3 years	New Delhi, India (peri-urban)
Rong Li et al., 2023 [4]	Causal relationships between gut microbiota and asthma phenotypes	Genome-wide data; childhood-onset asthma defined as onset ≤12 years	European-ancestry GWAS datasets

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Study	Research Focus	Population	Geographic Setting
Kamil Rashidi et al., 2021 [43]	Probiotic fermented dairy products and RTI risk	N=10,190 across 22 RCTs including children and adults	International
T. Abrahamsson et al., 2013 [44]	L. reuteri supplementation and respiratory allergies at age 7	N=188 infants; birth to 7-year follow-up	Sweden
Zheng Liu et al., 2026 [14]	Multi-strain probiotic adjunct therapy in pediatric refractory asthma	N=88; ages 4–8 years	Jiangxi, China
Kathryn J. Ray et al., 2022 [8]	LGG and gut microbiota in children with cystic fibrosis	N=50 with baseline fecal samples; ages 2–16; 12-month follow-up	Italy (3 CF centers)
P. Lif Holgerson et al., 2022 [45]	Breast milk and GI microbiota and disease outcomes in preschool children	N=210; birth to 5 years	Sweden
Yu Liu et al., 2023 [9]	Delivery mode, feeding, gut microbiota, and respiratory infection in infants	N=139 at 6 weeks; N=101 at 6 months	Beijing, China
K. Vidal et al., 2019 [46]	Gut and respiratory microbiota and respiratory/diarrheal infections	N=267; birth to 24 months	Dhaka, Bangladesh (peri-urban)

Study	Research Focus	Population	Geographic Setting
Hugues Piloquet et al., 2024 [47]	Synbiotic infant formula and respiratory/GI infection incidence	N=460 randomized (plus N=80 breastfed reference); 1–12 months	France and Belgium (41 sites)
A. Ouwehand et al., 2009 [48]	L. acidophilus NCFM + B. lactis Bl-04 and allergic rhinitis during pollen season	N=47 children with birch pollen allergy; ~age 9 years	Turku, Finland
G. Milani et al., 2024 [49]	Nutritional and dietary interventions for acute respiratory infection in children	Children <18 years; N=16,342 across 50 studies	International (predominantly Asia and LMICs)
Yang Liu et al., 2025 [13]	Probiotics for pediatric asthma	N=902 across 8 RCTs; ages 0–18 years	International (China, Italy, Brazil, Iran, Taiwan, Poland)
G. Ranucci et al., 2018 [50]	GOS/PDX prebiotic formula, gut microbiota, and respiratory infections in high-atopy-risk infants	N=400 randomized; birth to 96 weeks	Padua/Veneto, Italy
M. Hjelmsø et al., 2020 [51]	Prenatal n-3 LCPUFA/vitamin D supplements and infant airway/fecal microbiota	N=695 (n-3 trial); N=581 (vitamin D trial); birth to 1 year	Denmark (COPSAC2010)

Study	Research Focus	Population	Geographic Setting
Atieh Darbandi et al., 2021 [52]	Probiotics and respiratory tract infections 2010–2020	Children and adults; 27 RCTs (N=9433)	International
Courtney E. Price et al., 2022 [53]	Gut microbiome development in CF early life	N=39 CF children; birth to 4 years; 281 stool samples	USA
N. Rutten et al., 2015 [54]	Perinatal probiotics, gut microbiota, and atopic disease in high-risk children	N=99 children with fecal samples; birth to 6 years	Netherlands
S. Soldi et al., 2019 [55]	Prebiotic inulin-type fructans, gut microbiota, and febrile illness in kindergarten children	N=258; ages 3–6 years; 24-week winter study	Kindergarten setting (location not specified)
R. Berni Canani et al., 2017 [56]	Fermented milk with L. paracasei CBA L74, gut microbiota, and immune biomarkers	N=20 healthy children; ages 12–48 months	Naples, Italy
N. Elazab et al., 2013 [57]	Probiotics, atopic sensitization, and asthma/wheeze in children	Multiple pediatric RCTs	International

Study	Research Focus	Population	Geographic Setting
Zhenjie Zhang et al., 2022 [58]	Gut microbiota and cytokines in preterm infants with vs without BPD	N=38 preterm neonates (BPD n=18; non-BPD n=20); GA ≤30 weeks	Beijing, China
C. Duvallet et al., 2018 [59]	Aerodigestive microbiome exchange and aspiration in children	N=220; ages 1–18 years	Boston, USA (tertiary aerodigestive center)
M. N. Zuhair et al., 2025 [60]	LGG for prevention and treatment of respiratory diseases	Children and adults; 13 RCTs	International
Yanglong Guo et al., 2025 [61]	Microbiota dysbiosis in obstructive sleep apnea (including pediatric subgroup)	N=1381 OSA patients, N=692 controls (166 pediatric OSA)	International
Jiayi Hong et al., 2025 [62]	Gut, nasal, and skin microbiota in children with allergic rhinitis ± atopic dermatitis	N=36 children; ages 3–12 years	Shanghai, China
B. Hu et al., 2021 [63]	Gut microbiota and GI peptides in pediatric allergic rhinitis; probiotic + glutamine intervention	N=130 (80 cases, 50 healthy); ages ≤3 years	Hunan, China

Study	Research Focus	Population	Geographic Setting
Yuchen Hu et al., 2024 [64]	Gut and nasal microbiota and allergic rhinitis	17 studies; 1044 AR patients, 954 controls	International
Mengyao Li et al., 2025 [65]	Gut microbiota and allergic rhinitis (case-control)	Case-control studies; N=935 total across studies	China, Australia, Japan
Yongcheng Fu et al., 2025 [66]	Gut microbiota in neonatal RDS and probiotic restoration	N=81 preterm neonates (NRDS=55; non-NRDS=26); NICU	Zhengzhou, China
Miaojun Mo et al., 2022 [67]	Gut microbiota composition and immune function in asthmatic children by control level	N=58 (asthma n=48; healthy n=10); ages 3–14 years	China (hospital outpatient)
Lydia M Nashed et al., 2022 [68]	Gut microbiota in asymptomatic infants with SARS-CoV-2	N=595 infants; 13 SARS-CoV-2 positive; ages 0–24 months	Virginia, USA
Jun-Song Lin et al., 2009 [69]	Probiotic strains and RTI prevention in preschoolers	N=986; ages ~4–5 years	Taiwan (daycare centers)
S. Uwaezuoke et al., 2022 [70]	Postnatal probiotic supplementation and childhood asthma/atopic disorders	N=1320 across 6 RCTs	International (USA, Denmark, Italy, Poland, Taiwan)

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Study	Research Focus	Population	Geographic Setting
Rocky Vester Richmond et al., 2025 [71]	B. longum subsp. infantis B8762 and respiratory/GI health in infants	N=115; ages 6–12 months	Malaysia (3 tertiary centers)
S. Rautava et al., 2008 [72]	LGG + B. lactis Bb-12 and acute infections in early infancy	N=72; enrolled before age 2 months; followed to 12 months	Turku, Finland (community well-baby clinics)
C. Venter et al., 2021 [73]	Dietary fiber, immune health, and respiratory outcomes in children	Pediatric populations across cohorts and trials	International
T. T. Flygel et al., 2025 [74]	Long-term azithromycin effects on gut microbiota in HIV-associated chronic lung disease	N=346; ages 6–19 years; HIV-infected; 48-week treatment + 6-month follow-up	Zimbabwe and Malawi
D. Paganini et al., 2017 [75]	Prebiotic GOS mitigation of iron-induced gut microbiome changes and RTI in Kenyan infants	N=155; ages 6.5–9.5 months; 4-month follow-up	Coastal Kenya (community)
Chian-Feng Huang et al., 2018 [76]	Lactobacillus paracasei and L. fermentum for asthma in school-age children	N=152; ages 6–18 years; 3-month intervention	Taiwan (Taipei Hospital)
R. Das et al., 2013 [77]	Probiotics as adjunct therapy for allergic airway diseases	N=995 across multiple pediatric and adult RCTs	International

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Study	Research Focus	Population	Geographic Setting
L. Drago et al., 2022 [78]	L. salivarius LS01 + B. breve B632 and asthma exacerbations in children (PROPAM)	N=422 per-protocol; ages 3–14 years; 16 weeks	South Italy (primary care)
I. Garaiova et al., 2014 [79]	Lab4 probiotic + vitamin C and respiratory infection prevention in preschoolers	N=69; ages 3–6 years; 6-month study	Slovakia
R. Nocerino et al., 2017 [80]	Fermented cow's milk or rice (L. paracasei CBA L74 postbiotic) and respiratory infections in daycare children	N=377 completed; ages 12–48 months; 3 months	Italy (Naples area daycare)

Thematic Analysis

Theme 1: Early-Life Gut Microbiota Composition and Diversity Are Associated with Childhood Respiratory Disease Risk

The most consistent finding across observational studies is that specific perturbations in the early-life gut microbiota—particularly during the first three to twelve months of life—are associated with elevated risk of childhood respiratory diseases, with asthma and wheezing receiving the most attention.

The landmark CHILD cohort study by Arrieta et al. found that infants at highest risk of asthma (those with atopy and wheeze by 1 year and clinician-diagnosed asthma by age 3) showed a transient gut microbial dysbiosis during the first 100 days of life, characterized by significantly lower relative abundance of the four genera Lachnospira, Veillonella, Faecalibacterium, and Rothia (collectively termed FLVR) [1]. These differences were confirmed by qPCR, with p-values of 0.0001–0.0002 for three of the four genera at 3 months [1], and were accompanied by lower fecal acetate levels (p=0.03)

and altered enterohepatic metabolites [1]. Crucially, by 12 months these differences had largely resolved, underscoring the first 100 days as a critical window [1]. The García-Mauriño Alcazar systematic review of 11 cohorts corroborated this picture, finding consistent evidence that lower relative abundance of Bifidobacterium, Faecalibacterium, Ruminococcus, and Roseburia in infancy is associated with childhood respiratory diseases, though results were inconsistent across studies and no pooled effect sizes were calculable [2].

The German longitudinal cohort by Galazzo et al. extended these findings to school-age outcomes, demonstrating that Lachnobacterium, Lachnospira, and Dialister were significantly enriched in healthy children compared with those who later developed asthma at ages 6–11 years, with effects surviving adjustment for confounders (FDR-adjusted $p < 0.05$) [3]. Higher gut microbial diversity (Shannon index) at 31 weeks of age was associated with lower risk of allergic sensitization at school age (adjusted OR 0.19; $p=7.33\times10^{-3}$), whereas early microbial maturity (higher MAZ) at 5 weeks was paradoxically associated with higher risk of both sensitization and asthma (adjusted OR ~1.43–1.46; $p < 0.01$) [3].

From a diagnostic microbiota perspective, the early Belgian birth cohort by Vael et al. showed that fecal colonization at age 3 weeks with either a Bacteroides fragilis subgroup or a Clostridium coccoides XIVa species was an early indicator of later asthma risk, with odds ratios of 9.8 (95% CI 1.6–59.3) and 3.4 (95% CI 1.2–9.7), respectively, and a DGGE model correctly classifying 73% of cases [33]. The cross-sectional Pakistani study by Nasir and Gul found that asthmatic children aged 1–12 years had significantly lower gut microbial alpha diversity (Shannon index 2.9 vs 3.5 in controls; $p<0.001$) and that low Faecalibacterium prausnitzii abundance was independently associated with asthma (OR 3.7; 95% CI 1.8–7.6) [26].

In contrast to asthma studies where diversity reduction is consistently implicated, the neonatal RDS study by Fu et al. found the opposite pattern: preterm infants with NRDS had significantly greater gut alpha diversity than those without NRDS ($p<0.001$), with robust beta-diversity separation (Adonis $R^2=0.2866$, $p=0.001$) [66]. This counterintuitive finding likely reflects the pathological enrichment of opportunistic taxa (Muribaculaceae Incertae Sedis, Rhodococcus, Corynebacterium)

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rather than a healthy diverse community, and highlights that alpha diversity is an imperfect summary measure whose interpretation depends on which taxa are driving it.

The New Hampshire Birth Cohort Study by Moroishi et al. introduced an intriguing finding: higher gut alpha diversity at 6 weeks was associated with increased—not decreased—risk of subsequent upper RTIs (RR 1.40; 95% CI 1.12–1.76) and wheezing requiring prescription treatment (RR 2.00 among vaginally delivered infants; 95% CI 1.16–3.45) [22]. This apparent contradiction with the asthma literature may reflect different disease mechanisms and the fact that respiratory infections in infancy are partly dependent on pathogen exposure and immune naivety rather than immune dysregulation driven by specific taxa deficits [22]. The species-level associations in that study pointed to Veillonella and Haemophilus influenzae as taxa positively associated with infection risk, and Clostridium butyricum as negatively associated, consistent with the mechanistic literature on SCFA production and immune tolerance [22].

The Mendelian randomization study by Li et al. provided causal evidence for two taxa in childhood-onset asthma: higher genetically predicted abundance of Collinsella (OR 1.404; 95% CI 1.102–1.790; $p=6.04\times10^{-3}$) and Ruminococcaceae UCG014 (OR 1.291; 95% CI 1.063–1.568; $p=1.01\times10^{-2}$) were causally associated with higher childhood-onset asthma risk, whereas Candidatus Soleaferrea was negatively associated with overall asthma risk [4]. These effects were confirmed by multiple sensitivity methods and showed no evidence of pleiotropy, lending stronger causal inference than observational studies can provide [4].

Theme 2: Specific Gut Taxa and Metabolites Mediate Gut–Lung Axis Immunomodulation

The gut–lung axis represents the central mechanistic framework linking microbiota composition to respiratory health. Across studies, short-chain fatty acids (SCFAs)—especially acetate, propionate, and butyrate—emerge as the most consistently implicated mediators.

Arrieta et al. demonstrated lower fecal acetate in high-risk infants at 3 months ($p=0.03$), accompanying reduced FLVR taxa [1]. In germ-free mouse experiments from the same study, inoculation with FLVR taxa significantly reduced bronchoalveolar lavage total cells ($p<0.05$), neutrophils and lymphocytes ($p<0.0001$), histopathology scores ($p<0.01$), and pro-inflammatory cytokines including IFN-γ, TNF, IL-17A, and IL-6 ($p<0.01$ to $p<0.0001$), with Lachnospira

abundance strongly negatively correlated with BAL total cells ($r=-0.82$; $p=0.009$) [1]. This constitutes one of the strongest experimental demonstrations of a causal gut–respiratory pathway in the pediatric literature.

The Berni Canani study demonstrated that fermented milk with L. paracasei CBA L74 significantly increased butyrate-producing taxa including Oscillospira, Faecalibacterium, Roseburia, and Blautia, and elevated fecal butyrate to approximately 45–50 mmol/kg versus ~10 mmol/kg in controls ($p<0.05$) [56], with correlative evidence linking these taxa to elevated innate immunity markers (defensins, LL-37, secretory IgA) [56]. Wei Yang et al. reported that patients with allergic rhinitis show approximately 30–40% lower fecal butyrate and a 1.5-fold higher kynurenine/tryptophan ratio ($p<0.05$), with Mendelian randomization evidence that reduced F. prausnitzii causally increases AR risk (OR 1.32; $p<0.05$) [18]. In pediatric asthma, Mo et al. found that poorer asthma control was significantly associated with lower gut Bifidobacterium, Megasphaera, and Ruminococcaceae, and these taxa were positively correlated with CD3+ T-cell proportions and negatively correlated with CD4+ and CD4+/CD3+ ratios (all $p<0.05$) [67], providing a direct immunological link.

The proposed mechanism—supported across multiple reviews including Druszczyńska et al. [21], Venter et al. [37], and Yang et al. [18] —involves SCFAs signaling through GPR43, GPR109A, and GPR41 on intestinal epithelial and immune cells, inhibiting HDACs, stabilizing Foxp3+ regulatory T cells, reducing Th2 cytokine production (IL-4, IL-5, IL-13), and diminishing IgE responses. LPS from gut dysbiosis-associated gram-negative overgrowth and the consequent increased intestinal permeability are proposed to amplify systemic and airway inflammation [18]. Tryptophan metabolism via the aryl hydrocarbon receptor (AhR) pathway, involving a 1.5-fold elevated kynurenine/tryptophan ratio in allergic rhinitis patients, constitutes an additional SCFA-independent immunomodulatory axis [18].

The CF literature provides a disease-specific window onto these mechanisms. Children with CF exhibit profound gut dysbiosis characterized by reduced Bacteroides, Bifidobacterium, Eubacterium rectale, and F. prausnitzii, and elevated E. coli, Fusobacteria, and Veillonella [19]. Caley et al.'s systematic review found that CF gut dysbiosis is associated with reduced butyrate production

(healthy children have higher acetate, butyrate, and propionate in fecal samples), increased LPS-producing gram-negatives, and heightened intestinal permeability [19]. In the CF RCT by Ray et al., children whose gut microbiota became Bifidobacterium-dominated (more likely after LGG supplementation) had significantly fewer pulmonary exacerbations (IRR 0.55; 95% CI 0.25–0.82; p=0.01), 20 percentage points higher FEV1 (95% CI 8.05–31.92; p=0.001), and lower intestinal inflammation (calprotectin coefficient −16.53 μg/g; p=0.002) compared to those with Bacteroides-dominated microbiota [8]. Beta diversity at 12 months explained 18% of variance in exacerbation rate (R^2=0.18; p=0.003) and 19% in antibiotic days (R^2=0.19; p=0.001) [8].

In the BPD literature, Thatrimontrichai et al. found that in VLBW infants, butyrate-producing taxa (Faecalibacterium, Roseburia, Clostridium, Eubacterium, Coprococcus) were significantly enriched in non-BPD versus BPD infants by LEfSe analysis (LDA score >4), while BPD was associated with higher Enterococcus (11.9% vs 4.4%), Acinetobacter (7.7% vs 0.4%), and Elizabethkingia (6.6% vs 0%) [32]. Zhang et al.'s companion BPD cohort corroborated this: lower gut Shannon diversity was significantly associated with BPD at both days 3–7 (median 3.41 vs 4.38; p=0.00) and days 14–28 (median 3.71 vs 4.58; p=0.00), and BPD was marked by increasing Proteobacteria (53.9% to 80.1% over time; p=0.032) and decreasing Firmicutes (45.0% to 16.7%; p=0.021) within the BPD group, alongside elevated pro-inflammatory cytokines (IL-1β, IL-4, IL-6, IL-8, TNF-α) and reduced IL-10 [58].

Theme 3: RSV and Other Respiratory Infections Are Bidirectionally Associated with Gut Microbiota Alterations

Several studies examined the relationship between RSV infection and gut microbiota, consistently finding that RSV-associated bronchiolitis is accompanied by gut dysbiosis, though the directionality—whether dysbiosis predisposes to or results from infection—remains unclear.

Cabrera-Rubio et al., comparing infants hospitalized for bronchiolitis with healthy controls, found significantly lower gut microbial richness and diversity in bronchiolitis cases (each p=0.001), with the gut community differing significantly from controls (PERMANOVA R^2=0.026; p=0.001) [5]. RSV status was the dominant driver: gut richness differed more between healthy controls and RSV bronchiolitis (p=0.001) than between healthy controls and non-RSV bronchiolitis (p=0.01) [5].

Crucially, reduced gut richness during acute bronchiolitis predicted outcomes at 12-month follow-up: beta diversity explained 1.83% of variance in any recurrent wheezing (p=0.048) and 4.0% of variance in ≥3 wheezing episodes (p=0.020) [5]. A random forest model using gut genera achieved AUC=0.9773 for distinguishing bronchiolitis from controls, with Faecalibacterium, Akkermansia, and Veillonella enriched in controls, and Streptococcus and Klebsiella associated with severe disease and recurrent wheezing in redundancy analysis (p=0.03) [5].

The Yagi systematic review of 12 studies confirmed that RSV infection is associated with altered gut microbiota composition, with increased S24-7/Muribaculaceae, Odoribacteraceae, and Clostridiales and decreased Moraxellaceae and Prevotella in RSV-infected infants relative to healthy controls, alongside significant beta-diversity separation [7]. The Woodall systematic review, spanning multiple RTI pathogens, found a pooled Shannon diversity reduction of 1.45 units (95% CI 0.15–2.50; p<0.0001) in RTI patients versus controls, accompanied by consistent depletion of Lachnospiraceae (6/6 studies), Ruminococcaceae (5/5), and Ruminococcus (6/6), and enrichment of Enterococcus (5/5 studies) [6]. In pediatric-specific CAP, Ruminococcus, Faecalibacterium, Lachnospira, Anaerostipes, and Dorea were depleted, while Streptococcus, Actinomyces, Enterococcus, and Escherichia were enriched [6].

The Sjödin synbiotic RCT provided mechanistic evidence linking specific gut bacteria to LRTI. Infants who developed physician-diagnosed LRTI had higher abundance of Klebsiella species (p=0.06) and higher reads of K. pneumoniae antimicrobial resistance genes compared with matched controls, while synbiotic-fed infants showed lower Klebsiella longitudinally (p=0.01), higher Bifidobacterium breve (p=0.002), and increased antimicrobial d-3-phenyllactic acid over time (interaction p=0.04) [41]. The Moroishi cohort similarly found that higher gut Haemophilus influenzae at 6 weeks was associated with more respiratory infections in cesarean-delivered infants [22], and the Liu delivery-mode cohort found that CSD-associated gut Klebsiella enrichment was significantly associated with respiratory infection risk (p<0.001), while vaginally delivered-associated Escherichia-Shigella enrichment was associated with lower risk (p<0.0001) [9].

The Nashed et al. study of asymptomatic SARS-CoV-2 in infants found decreased Bifidobacterium bifidum (log2 FC approximately −4.8), Akkermansia muciniphila (log2 FC

approximately −2.2), and Veillonella dispar in COVID-positive stool samples versus matched controls (all adjusted $p<0.05$), without any difference in alpha or beta diversity—consistent with a more subtle dysbiosis than is seen in symptomatic adult COVID-19 [68].

Theme 4: Mode of Delivery, Infant Feeding, and Antibiotic Exposure Modify Gut Microbiota and Downstream Respiratory Risk

Early-life exposures that shape gut colonization are consistently identified as moderators of microbiota–respiratory disease associations.

Mode of delivery exerts a pronounced effect on early colonization, with cesarean section (CSD) reducing Bacteroides and increasing Klebsiella, Veillonella, and Enterococcus relative to vaginal delivery (VD) [9]. In the Liu et al. cohort, CSD infants had a 33.3% respiratory infection incidence over the first 6 months compared with 12.7% in VD infants ($p=0.02$), and this difference was abolished by exclusive breastfeeding: the gut microbiota of exclusively breastfed CSD infants was indistinguishable from that of VD infants by 6 months (Adonis $P=0.57$) but remained distinct in mixed-fed infants (Adonis $P<0.001$, $R^2=0.11$) [9]. Galazzo et al. confirmed that vaginal delivery was the strongest predictor of Bacteroides enrichment, with effects persisting to 31 weeks [3], while Grier et al. found that birth mode significantly modified the immune-microbiota co-development trajectory and was adjusted for in all models predicting persistent respiratory disease [38].

Breastfeeding duration and cessation are among the most important dietary modulators of infant gut microbiota. In the Galazzo cohort, cessation of breastfeeding—rather than solid food introduction—drove the most dramatic microbiota shifts, including decreases in Bifidobacteria and increases in Lachnospiraceae [3]. Lif Holgerson et al. found that the 3-month fecal microbiota accounted for the strongest association with later allergic disease (PLS $R^2=0.55$; $Q^2=0.26$) [45], and taxa including Bacteroides, which is associated with immune education, were underrepresented in infants later diagnosed with allergic disease (LDA>2; $p<0.05$) [45].

Antibiotic exposure is the most consistently documented disruptor of gut colonization linked to respiratory allergy risk. Sameeha et al.'s systematic review of 1.5 million children found that antibiotic exposure during the first 6 months of life was associated with asthma (HR 1.21; 95% CI 1.18–1.25) and allergic rhinitis (HR 1.14; 95% CI 1.11–1.18), with macrolides showing stronger

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effects (OR ~1.4–1.7) than β-lactams (OR ~1.2–1.3) [10]. The mechanism involves depletion of Bifidobacterium and SCFA-producing bacteria, with corresponding reductions in Treg differentiation capacity and barrier integrity [10]. Durack et al. demonstrated that early antibiotic exposure had long-term effects on gut community structure in high-risk infants, and the related CF study by Price et al. showed that antibiotic exposure before 6 months persistently elevated Veillonella and Prevotella ASVs and reduced Bifidobacterium at ages 2–4 years [27].

Environmental factors including urban residence, air pollution, and pet exposure have been documented as additional modulators. Zheng et al. demonstrated that short-term air pollution episodes significantly altered gut microbiota in asthmatic children (PERMANOVA p=0.03), with decreases in Firmicutes associated with higher SO_2 (β=−0.0316; p=0.019) and NO_2 (β=−0.0095; p=0.029), and increases in Proteobacteria and Bacteroides [20]. The Filardo systematic review found similar cross-sectional associations between air pollutant exposure and gut dysbiosis, including reduced Clostridia in asthmatic children linked to higher asthma attack frequency [28]. Galazzo et al. showed that having older siblings and pet exposure modestly increased gut microbial diversity, a potentially protective factor [3].

Theme 5: Probiotic, Prebiotic, and Synbiotic Interventions Show Moderate and Strain-Specific Effects on Pediatric Respiratory Outcomes

A substantial portion of the included literature concerns microbiota-targeted interventions, and the overall picture is one of moderate, strain-specific, and dose-dependent efficacy, with clearest evidence for RTI prevention and modest evidence for asthma control.

Respiratory tract infection prevention. The Langenneger systematic review of 32 pediatric RCTs found that 78.1% reported a positive effect of probiotics on RTI incidence, with the mean RTI prevalence of 42% in probiotic groups versus 59% in controls [31]. The Liu meta-analysis of LGG specifically showed significant reductions in acute otitis media (RR 0.76; 95% CI 0.64–0.91; NNT 17), upper respiratory infections in one RCT (RR 0.62; 95% CI 0.50–0.78; NNT 4), and antibiotic treatments (RR 0.80; 95% CI 0.71–0.91) [11]. Hojsak et al.'s placebo-controlled trial in daycare children found that LGG (10^9 CFU/day for 3 months) reduced overall RTIs (RR 0.63; 95% CI 0.51–0.79; NNT 5), upper RTIs (RR 0.66; 95% CI 0.52–0.82), and RTIs lasting >3 days (RR 0.57; 95% CI

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0.41–0.78), with significantly fewer symptom days ($p<0.001$) [12]. Rautava et al. found that LGG + B. lactis Bb-12 (each 10^{10} CFU/day) from before age 2 months reduced early AOM (RR 0.44; 95% CI 0.21–0.90; p=0.014) and recurrent respiratory infections across the first year (RR 0.51; 95% CI 0.27–0.95; p=0.022) [72]. The Rashidi meta-analysis of probiotic fermented dairy products found protective effects in children (RR 0.82; 95% CI 0.73–0.93) with greater effects from Lactobacillus strains than Bifidobacterium strains [43].

Beyond lactobacilli, Bifidobacterium longum BB536 in a 10-month Malaysian trial reduced the mean number of respiratory illness episodes and significantly shortened sore throat duration by 46% (p=0.018), with an associated increase in fecal Faecalibacterium in the BB536 group (p=0.032) [34]. Rocky Vester Richmond et al.'s RCT of B. longum subsp. infantis B8762 in infants aged 6–12 months found significant within-group reductions in fever (p=0.001), cough (p=0.016), nasal congestion (p=0.001), and wheezing (p=0.011) at 4 weeks, alongside lower TNF-α in the probiotic group (p=0.033) [71]. Nocerino et al. demonstrated that fermented milk or rice containing heat-killed L. paracasei CBA L74 (a postbiotic approach) reduced the proportion of daycare children experiencing at least one URTI (48.2% group A vs 70.5% placebo; ARD −22%; $p<0.001$), with elevated fecal defensins and secretory IgA [80].

Prebiotic and synbiotic approaches also showed respiratory benefits. The Ranucci prebiotic formula (GOS/PDX 4 g/L) trial in high-atopy-risk infants found that infants without respiratory infections at 9–12 months had significantly higher fecal Bifidobacteria than those with infections ($p<0.001$), and the prebiotic formula reduced the proportion of infants with any RI by 48 weeks (33% vs 48%; p=0.023), recurrent RIs by 96 weeks (20% vs 32%; p=0.039), and wheezy lower RIs (33% vs 46%; p=0.046) [50]. Sazawal et al.'s community RCT of prebiotic oligosaccharide + B. lactis HN019 in children aged 1–4 years found borderline significant reductions in pneumonia (RR 0.76; 95% CI 0.58–1.00; p=0.05) and severe ALRI (RR 0.65; 95% CI 0.42–1.00; p=0.05), with a significant reduction in days with severe illness (OR 0.84; p=0.004) [42]. The Piloquet synbiotic formula RCT (GOS + L. fermentum CECT5716) found lower LRTI incidence in the synbiotic group (IRR 0.77; 95% CI 0.60–1.00; p=0.049), with higher fecal secretory IgA at 12 months (p=0.015) and lower fecal pH at 4 months ($p<0.0001$) [47]. Lin et al.'s four-arm RCT in Taiwanese preschoolers found that only

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L. casei rhamnosus significantly reduced doctor-diagnosed respiratory infectious diseases (short-term mean difference −0.352 episodes/person-month; p<0.001; long-term −0.309; p<0.001), while the multispecies product and L. rhamnosus T cell-1 did not [69], underscoring the strain-specificity of respiratory benefits.

Asthma outcomes. The Yang Liu et al. meta-analysis of 8 pediatric asthma RCTs found that probiotics significantly reduced acute asthma exacerbations (RR 0.38; 95% CI 0.26–0.56; p<0.00001) and improved FEV1/FVC ratio (MD 5.70 percentage points; 95% CI 1.93–9.47; p=0.003), though FEV1 alone did not significantly improve [13]. The Fan et al. systematic review found that probiotic interventions reduced exacerbations in 5 of 7 studies in pediatric asthma (exemplar: 9% vs 23.8% exacerbation rate; OR 3.17; p<0.001) [39], and that postbiotic bacterial lysates (OM-85 BV, PMBL®) reduced wheezing episodes by 37.9% (p<0.001), respiratory infections by 31.4% (p<0.001), and improved pulmonary function (FEV1, PEF, FVC; all p<0.001 vs conventional therapy) [39]. The PROPAM RCT of L. salivarius LS01 + B. breve B632 in 422 asthmatic children aged 3–14 years found that ≥1 exacerbation occurred in 9.0% of the probiotic group versus 23.8% of placebo (OR 3.17; 95% CI 1.8–5.6; p<0.001), with the number with two exacerbations less than a third in the active group (OR 3.65; p=0.013) [78].

The Chinese RCT of multi-strain probiotic adjunct in pediatric refractory asthma demonstrated that 4 months of supplementation (Bifidobacterium longum BL999, L. acidophilus La-14, S. thermophilus ST-21) achieved complete asthma control in 68.2% versus 36.4% with conventional therapy alone (p<0.05), with significantly higher ACT scores (22.45±1.20 vs 19.78±1.45; p<0.001), superior FEV1 (2.65±0.10 vs 2.30±0.08 L; p<0.001), and faster resolution of cough (5.60±1.50 vs 10.45±2.30 days; p<0.001) [14], accompanied by increases in Shannon diversity and Bifidobacterium (25.00% vs 0.98%; p<0.001) and reductions in Bacteroides and Fusobacteria [14].

Prebiotic dietary fiber. The Venter et al. position paper summarized the evidence that higher maternal resistant starch intake was associated with lower odds of infant doctor-diagnosed wheeze (adjusted OR 0.68; 95% CI 0.49–0.95; p=0.02) [37], and that a high-fiber nutritional supplement bar in pediatric asthma showed no overall pulmonary function benefit except in a compliant subgroup

with noneosinophilic asthma [37]. Soldi et al. demonstrated that prebiotic inulin-type fructans (6 g/day for 24 weeks) in kindergarten children selectively increased fecal Bifidobacterium ($p<0.001$ vs placebo) and attenuated antibiotic-induced depletion of Bifidobacterium at days 1, 7, 14, and end of study (all $p<0.05$) [55], consistent with a mechanism by which prebiotics might protect against respiratory illness by preserving beneficial colonization.

The Paganini RCT in Kenyan infants (6.5–9.5 months) provided a unique environmental context: iron fortification alone decreased Bifidobacterium and Lactobacillus and increased Clostridiales, and was associated with more infants treated for RTI (87% vs 75% in control; $p=0.024$). Adding GOS prebiotic (7.5 g/day) mitigated these adverse microbiota effects and was associated with a significant decrease in RTIs over the 4-month period ($p=0.013$) [75], demonstrating that dietary modulation of gut microbiota through prebiotic supplementation can reduce respiratory morbidity even in high-burden, low-resource settings.

Theme 6: Gut–Lung Axis Communication Pathways and Microbiota in Airway and CF-Specific Disease

Beyond the general asthma and RTI literature, several studies examined disease-specific gut–lung axis relationships, including cystic fibrosis and the aerodigestive microbiome in swallowing dysfunction.

The CF literature is particularly instructive because CFTR dysfunction simultaneously disrupts both gut and lung physiology, creating a natural experiment for studying gut–lung interactions. Price et al.'s two longitudinal cohort reports (2022 and 2023) documented that CF lung-associated genera including Streptococcus, Veillonella, Staphylococcus, Haemophilus, and Prevotella are detectable in the CF gut throughout early childhood, with Veillonella gut abundance decreasing significantly with age ($p=1.09\times10^{-6}$), raising the possibility that the gut serves as a reservoir seeding the lung [27, 53]. The Caley systematic review confirmed CF-related gut dysbiosis characterized by reduced diversity and depletion of Bifidobacterium, Akkermansia muciniphila, F. prausnitzii, Roseburia, and Ruminococcaceae, with elevated Enterobacteriaceae, Lactobacillus, Streptococcus, and Veillonella [19], and identified that SCFA depletion (lower acetate, butyrate, propionate in CF versus non-CF children) and increased LPS from gram-negative overgrowth are

candidate mediators of local and systemic inflammatory tone that may exacerbate lung disease [19]. The Bruzzese RCT showed that 4 weeks of LGG (6×10^9 CFU/day) in CF children reduced fecal calprotectin ($p<0.05$) and partially restored gut microbiota, particularly Bacteroides counts [29], while Ray et al.'s 12-month LGG trial linked LGG-associated Bifidobacterium-dominated microbiota to substantially better pulmonary outcomes (IRR for exacerbations 0.55; FEV1 +20 percentage points) [8].

The Duvallet aerodigestive cohort study found that in children undergoing simultaneous bronchoscopy and upper endoscopy, lung and gastric communities showed high individual-level similarity (median JSD 0.56 for both pairs), but in aspirating children, the lung microbiome became significantly more similar to oropharyngeal communities rather than gastric communities ($p=0.04$ and $p=4\times10^{-5}$), with higher co-occurrence of Veillonella, Prevotella, Fusobacterium, Rothia, and Streptococcus between lung and oropharynx [59]. This finding challenges the assumption that gastric-to-lung microaspiration is the primary driver of lung dysbiosis in children with swallowing dysfunction, and highlights the oropharyngeal-to-lung route as more important [59].

The Hjelmsø RCT of prenatal n-3 LCPUFA and vitamin D supplementation found that prenatal supplements affected infant airway—but not gut—microbiota at 1 month, with significant beta-diversity shifts (PERMANOVA $F=3.74–4.23$; $p=0.004–0.005$) driven by decreases in Gemella and Veillonella and changes in Streptococcus [51]. The mediation of the known protective effect of these supplements on childhood asthma through airway microbiota was estimated at 9% for n-3 LCPUFA ($p=0.11$) and 5.5% for vitamin D ($p=0.39$), which were not statistically significant, suggesting that the airway microbiota represents a minor—rather than central—mediating pathway for these interventions [51].

The Flygel et al. BREATHE RCT examined the gut microbiota consequences of 48 weeks of once-weekly azithromycin in HIV-infected children with chronic lung disease. While azithromycin reduced acute respiratory exacerbations, it significantly lowered gut alpha diversity (observed ASVs coefficient −23.98; $p<0.001$; Shannon −0.21; $p=0.004$), depleted Campylobacter (effect size 0.77; $p<0.001$), Sutterella, and other genera, and disrupted genus–genus interaction networks at 48 weeks; Campylobacter depletion persisted 6 months after cessation [74]. This study illustrates that

respiratory-disease-targeted antibiotic therapy carries collateral gut microbiota consequences that may have downstream immunological implications, and that macrolide-induced gut dysbiosis may partly explain the well-documented increased risk of allergic disease following macrolide use in children [10].

Synthesis

Apparent Contradiction: Is High or Low Gut Diversity Protective for Respiratory Health?

The most striking apparent contradiction in this literature is that across different respiratory outcomes, the direction of the gut diversity–disease association is inconsistent. For asthma and atopic wheeze, lower gut microbial diversity in infancy is the predominant finding across multiple cohorts [2, 3, 26, 67]. For acute respiratory infections in infancy, Moroishi et al. found the opposite: higher alpha diversity at 6 weeks was associated with more infections and wheezing [22]. For neonatal RDS, Fu et al. found greater diversity in NRDS versus non-NRDS preterm infants [66].

These apparent contradictions resolve when the nature of the diversity change is considered. In the context of asthma, low diversity reflects depletion of specific protective commensals (Faecalibacterium, Roseburia, Bifidobacterium, Lachnospiraceae members) that produce SCFAs critical for immune tolerance [1, 3, 18]. In the context of neonatal RDS, the increased diversity in NRDS reflects pathological enrichment of taxa such as Rhodococcus, Corynebacterium, and Muribaculaceae Incertae Sedis that are inversely correlated with Apgar scores and oxygenation indices [66]. In the context of early-life RTI, the positive association of diversity with infection risk in the Moroishi cohort is likely explained by the co-occurrence of pathogenic or conditionally pathogenic taxa (Veillonella, H. influenzae) within a diverse community, particularly in cesarean-delivered infants whose microbial communities differ qualitatively from vaginally delivered infants [22, 22]. The moderating effect of delivery mode is critical here: the alpha-diversity–RTI association was pronounced in vaginally delivered infants (RR ~1.62–2.00) but absent in cesarean-delivered infants, where specific taxa rather than overall richness drove risk [22]. Both findings are likely correct within their respective contexts: diversity per se is not inherently protective or harmful; what matters is community composition, specifically the presence of SCFA-producing, immunomodulatory taxa versus pathobionts.

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Prevention Versus Treatment: Different Mechanisms, Different Responses to Probiotics

The systematic null results for probiotic primary prevention of asthma [15–17, 44] stand in contrast to the significant benefits in treating established asthma [13, 14, 76, 78] and preventing RTIs [11, 12, 31, 72]. This pattern is mechanistically coherent. Asthma development involves complex early-life immune programming during the first 100 days [1], during which the microbiota–immune interface shapes tolerogenic versus Th2-polarizing trajectories. Probiotic strains administered in the perinatal period may lack the specific taxa (notably Lachnospira, Faecalibacterium, Rothia, and Veillonella in combination [1]) required for this programming window, especially given that intervention formulations have typically consisted of Lactobacillus or Bifidobacterium strains rather than the precise taxa implicated. Once asthma is established, the gut–immune axis continues to influence airway inflammation through ongoing SCFA production, Treg maintenance, and mucosal IgA levels, mechanisms accessible to probiotic intervention even after the critical early window has passed. For RTI prevention, the mechanism is more proximate—competition for mucosal niches, enhancement of mucosal IgA and innate immune defenses, and modulation of cytokine balance—and these do not require a specific early developmental window, explaining consistent benefits across diverse age groups.

Disease-Specific Contexts: The CF Gut–Lung Axis as a High-Resolution Model

The CF literature is the most methodologically mature in demonstrating direct functional consequences of gut dysbiosis on lung outcomes. In this disease, CFTR dysfunction creates an obligate experiment: the same genetic mutation disrupts both gut physiology and lung ion transport, enabling study of their interaction without the confounding of selective survival or reverse causality that complicates other settings. The Ray et al. finding that Bifidobacterium-dominated gut microbiota (achievable through LGG supplementation) is associated with 45% fewer pulmonary exacerbations (IRR 0.55; p=0.01) and 20 percentage-point higher FEV1 (p=0.001) [8], alongside the Caley review evidence that SCFA depletion and LPS-driven inflammation correlate with lung function [19], provide the strongest causal chain in the pediatric gut–lung axis literature. The mechanism—gut-derived butyrate and propionate suppressing systemic inflammation and maintaining regulatory T-cell populations—has cross-disease validity: identical taxa (F. prausnitzii, Roseburia,

Bifidobacterium, Lachnospiraceae) are associated with protection in asthma [1, 3, 18], BPD [32, 58], bronchiolitis [5], and allergic rhinitis [18, 64].

Timing: The First 100 Days as a Dominant Critical Window

Across the observational literature, associations between gut microbiota and respiratory outcomes are consistently strongest when the microbiota is measured during the first 3 months of life and outcomes are assessed later in childhood, rather than when both are measured simultaneously [1, 2, 24]. By contrast, among intervention trials that show effects, both preventive RTI trials and therapeutic asthma trials can work beyond this early window [14, 78]. The critical window concept for asthma specifically reflects the timing of immune education in the lamina propria, where dendritic cells are programmed by microbial ligands and metabolites to produce tolerogenic or inflammatory responses—a process that is most influential before the immune system is fully mature, typically in the first 100 days [1, 24, 38]. Within this window, the absence of specific taxa (FLVR) predicts asthma at 3 years with considerable predictive power (OR 13.5–21.5) [1], while experimental supplementation with those taxa ameliorates murine airway inflammation [1]. The practical implication is that preventive interventions for asthma would need to deliver specifically the taxa that are depleted during this early window, not simply any probiotic, a condition not met by current commercially available probiotic products.

DISCUSSION

This systematic review synthesizes evidence from 80 studies to provide a comprehensive analysis of associations between gut microbiota and pediatric respiratory diseases, spanning asthma, allergic rhinitis, RTIs, RSV bronchiolitis, BPD, CF, NRDS, and other conditions. The findings confirm that early-life gut dysbiosis is consistently associated with increased respiratory disease risk, but they also reveal important nuances regarding the direction of diversity–disease associations, the distinction between prevention and treatment effects of probiotics, the primacy of the first 100 days as a critical window, and disease-specific mechanisms (Arrieta et al., 2015; Galazzo et al., 2020; Moroishi et al., 2022; Ray et al., 2022).

1. Early-Life Gut Microbiota Composition and Respiratory Outcomes: The Critical Window of the First 100 Days

The most consistent finding across observational studies is that gut microbiota measurements during the first 3 months of life show stronger associations with later respiratory outcomes than measurements taken later in infancy or childhood (Arrieta et al., 2015; Alcazar et al., 2022; Galazzo et al., 2020). The landmark CHILD cohort study by Arrieta and colleagues demonstrated that infants at highest risk of asthma exhibited transient dysbiosis within the first 100 days, characterized by reduced relative abundance of *Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia* (the FLVR taxa), with this signature predicting asthma at age 3 years with high odds ratios (13.5–21.5) (Arrieta et al., 2015). Importantly, these differences resolved by 12 months, underscoring the first 100 days as a discrete developmental window for immune programming (Arrieta et al., 2015). This finding has been corroborated by the García-Mauriño Alcazar systematic review of 11 cohorts, which found consistent evidence that lower relative abundance of *Bifidobacterium*, *Faecalibacterium*, *Ruminococcus*, and *Roseburia* in infancy is associated with childhood respiratory diseases, though effect sizes could not be pooled due to heterogeneity (Alcazar et al., 2022).

The German longitudinal cohort by Galazzo et al. (2020) extended these observations to school-age outcomes (6–11 years), demonstrating that *Lachnobacterium*, *Lachnospira*, and *Dialister* were significantly enriched in healthy children compared with those who later developed asthma, with effects surviving adjustment for confounders (FDR-adjusted $p < 0.05$). Furthermore, higher gut microbial diversity (Shannon index) at 31 weeks was associated with lower risk of allergic sensitization (adjusted OR 0.19), whereas paradoxically, higher microbial maturity at 5 weeks was associated with higher risk of asthma (Galazzo et al., 2020). This paradox highlights that microbial maturity per se is not protective if the community composition is skewed toward pro-inflammatory taxa (Galazzo et al., 2020).

The mechanistic underpinning of this critical window involves the education of mucosal immune cells by microbial ligands and metabolites. During the first months of life, the intestinal lamina propria contains a high proportion of Treg precursors that require SCFA signaling (particularly

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butyrate and propionate) to mature into functional Foxp3+ Tregs capable of suppressing Th2 responses (Yang et al., 2025; Druszczyńska et al., 2024). Arrieta et al. (2015) demonstrated that infants with FLVR depletion had significantly lower fecal acetate levels ($p=0.03$), and in germ-free mouse experiments, inoculation with FLVR taxa reduced bronchoalveolar lavage inflammatory cells, histopathology scores, and pro-inflammatory cytokines (IFN-γ, TNF, IL-17A, IL-6). This constitutes one of the strongest experimental demonstrations of a causal gut–lung pathway in the pediatric literature (Arrieta et al., 2015).

From a diagnostic perspective, Vael et al. (2011) showed that fecal colonization at age 3 weeks with *Bacteroides fragilis* subgroup or *Clostridium coccoides* XIVa species predicted asthma at age 3 years with odds ratios of 9.8 and 3.4, respectively, and a DGGE model correctly classified 73% of cases. Similarly, the cross-sectional Pakistani study by Nasir and Gul (2025) found that asthmatic children had significantly lower gut alpha diversity (Shannon index 2.9 vs 3.5 in controls; $p<0.001$) and that low *Faecalibacterium prausnitzii* abundance was independently associated with asthma (OR 3.7). These findings collectively support the hypothesis that the first 100 days represent a dominant critical window during which gut microbiota composition programs long-term respiratory immune set points (Arrieta et al., 2015; Durack et al., 2018; Grier et al., 2019).

2. Resolving the Apparent Contradiction: Is High or Low Gut Diversity Protective?

One of the most striking apparent contradictions in this literature is that lower gut diversity is associated with asthma and atopy (Alcazar et al., 2022; Galazzo et al., 2020; Nasir & Gul, 2025), whereas higher diversity is associated with increased RTI risk in some cohorts (Moroishi et al., 2022) and greater diversity is also seen in NRDS compared to non-NRDS preterm infants (Fu et al., 2025). This review proposes that these contradictions resolve when the *composition* of the diverse community is considered, rather than diversity as an abstract metric.

In the context of asthma, low diversity reflects the specific depletion of protective SCFA-producing commensals — *Faecalibacterium*, *Roseburia*, *Bifidobacterium*, *Lachnospiraceae* members —that are essential for Treg maintenance and Th2 suppression (Arrieta et al., 2015; Yang et al., 2025). Conversely, in the Moroishi et al. (2022) cohort of newborns, higher alpha diversity at 6 weeks was associated with

increased risk of upper RTIs (RR 1.40) and wheezing (RR 2.00 in vaginally delivered infants). Detailed taxonomic analysis revealed that this increased diversity included pathogenic or conditionally pathogenic taxa such as *Veillonella* and *Haemophilus influenzae*, while protective taxa such as *Clostridium butyricum* were reduced (Moroishi et al., 2022). Thus, the adverse association was not driven by diversity per se but by the presence of specific pathobionts within a diverse community. Importantly, the association was modified by delivery mode: it was pronounced in vaginally delivered infants (where diversity likely reflects environmental microbial exposures) but absent in cesarean-delivered infants, where specific taxa rather than overall richness drove risk (Moroishi et al., 2022).

In the neonatal NRDS study by Fu et al. (2025), preterm infants with NRDS had significantly *greater* gut alpha diversity than those without NRDS ($p<0.001$), with robust beta-diversity separation (Adonis $R^2=0.2866$, $p=0.001$). However, this increased diversity was driven by pathological enrichment of opportunistic taxa—*Muribaculaceae Incertae Sedis*, *Rhodococcus*, *Corynebacterium*—that were inversely correlated with Apgar scores and oxygenation indices (Fu et al., 2025). Therefore, the interpretation of alpha diversity as a health metric is critically dependent on which taxa are driving the diversity. In healthy development, high diversity with abundant SCFA producers is protective; in pathological contexts, high diversity driven by pathobionts reflects dysbiosis (Arrieta et al., 2015; Moroishi et al., 2022; Fu et al., 2025). This insight has important implications for clinical trial design: interventions should aim not merely to increase diversity but to specifically enrich protective commensals and suppress pathobionts (Galazzo et al., 2020; Ray et al., 2022).

3. Specific Taxa and Metabolites: SCFAs as Central Immunomodulators

Across all pediatric respiratory conditions examined, SCFAs—particularly acetate, propionate, and butyrate—emerge as the most consistently implicated mechanistic mediators of gut–lung axis communication (Arrieta et al., 2015; Yang et al., 2025; Druszczyńska et al., 2024; Canani et al., 2017). Arrieta et al. (2015) demonstrated lower fecal acetate in high-risk infants at 3 months ($p=0.03$). Canani et al. (2017) showed that fermented milk with *Lactobacillus paracasei* CBA L74 significantly increased butyrate-producing taxa (*Oscillospira*, *Faecalibacterium*, *Roseburia*, *Blautia*)

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and elevated fecal butyrate to approximately 45–50 mmol/kg versus ~10 mmol/kg in controls ($p<0.05$), with correlative evidence linking these taxa to elevated innate immunity markers (defensins, LL-37, secretory IgA). In allergic rhinitis, Yang et al. (2025) reported approximately 30–40% lower fecal butyrate and a 1.5-fold higher kynurenine/tryptophan ratio ($p<0.05$), with Mendelian randomization evidence that reduced *F. prausnitzii* causally increases allergic rhinitis risk (OR 1.32; $p<0.05$). The kynurenine/tryptophan pathway, involving the aryl hydrocarbon receptor (AhR), constitutes an SCFA-independent immunomodulatory axis that may be particularly relevant in allergic disease (Yang et al., 2025).

In pediatric asthma, Mo et al. (2022) found that poorer asthma control was significantly associated with lower gut *Bifidobacterium*, *Megasphaera*, and *Ruminococcaceae*, and these taxa were positively correlated with CD3+ T-cell proportions and negatively correlated with CD4+ and CD4+/CD3+ ratios (all $p<0.05$), providing a direct immunological link between gut dysbiosis and altered systemic T-cell profiles. The proposed mechanism—supported across multiple reviews (Druszczyńska et al., 2024; Yang et al., 2025; Venter et al., 2022)—involves SCFA signaling through GPR43, GPR109A, and GPR41 on intestinal epithelial cells and immune cells, inhibiting histone deacetylases (HDACs), stabilizing Foxp3+ Tregs, reducing Th2 cytokine production (IL-4, IL-5, IL-13), and diminishing IgE responses. Additionally, LPS from gram-negative pathobionts (e.g., *Escherichia coli*, *Klebsiella*) can increase intestinal permeability and propagate systemic inflammation that reaches the lung (Caley et al., 2023; Woodall et al., 2022).

The CF literature provides a disease-specific validation of these mechanisms. Children with CF exhibit profound gut dysbiosis with reduced *Bacteroides*, *Bifidobacterium*, *Eubacterium rectale*, and *F. prausnitzii*, and elevated *E. coli*, *Fusobacteria*, and *Veillonella* (Caley et al., 2023). The Caley systematic review found that CF gut dysbiosis is associated with reduced butyrate production, increased LPS-producing gram-negatives, and heightened intestinal permeability (Caley et al., 2023). In the RCT by Ray et al. (2022), children whose gut microbiota became *Bifidobacterium*-dominated (more likely after LGG supplementation) had significantly fewer pulmonary exacerbations (IRR 0.55; 95% CI 0.25–0.82; $p=0.01$), 20 percentage points higher FEV1 (95% CI 8.05–31.92; $p=0.001$), and lower intestinal inflammation (calprotectin coefficient −16.53 µg/g; $p=0.002$) compared to those

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with *Bacteroides*-dominated microbiota. Beta diversity at 12 months explained 18% of variance in exacerbation rate (R^2=0.18; p=0.003) (Ray et al., 2022). This constitutes the strongest causal chain in the pediatric gut–lung axis literature, linking a specific microbial intervention, through changes in gut community structure, to clinically meaningful improvements in lung function and exacerbation frequency (Ray et al., 2022).

4. RSV and Respiratory Infections: Bidirectional Associations

Respiratory syncytial virus (RSV) infection and other RTIs show bidirectional associations with gut microbiota: gut dysbiosis may predispose to severe infection, and infection itself may alter gut microbial composition (Cabrera-Rubio et al., 2024; Yagi et al., 2024; Woodall et al., 2022). Cabrera-Rubio et al. (2024) found that infants hospitalized for bronchiolitis had significantly lower gut microbial richness and diversity compared to healthy controls (each p=0.001), with RSV status as the dominant driver. Reduced gut richness during acute bronchiolitis predicted outcomes at 12-month follow-up: beta diversity explained 1.83% of variance in any recurrent wheezing (p=0.048) and 4.0% of variance in ≥3 wheezing episodes (p=0.020) (Cabrera-Rubio et al., 2024). A random forest model using gut genera achieved AUC=0.9773 for distinguishing bronchiolitis from controls, with *Faecalibacterium*, *Akkermansia*, and *Veillonella* enriched in controls, and *Streptococcus* and *Klebsiella* associated with severe disease and recurrent wheezing (Cabrera-Rubio et al., 2024).

The Yagi systematic review of 12 studies confirmed that RSV infection is associated with altered gut microbiota composition, with increased S24-7/Muribaculaceae, *Odoribacteraceae*, and *Clostridiales* and decreased *Moraxellaceae* and *Prevotella* in RSV-infected infants, alongside significant beta-diversity separation (Yagi et al., 2024). The Woodall systematic review, spanning multiple RTI pathogens, found a pooled Shannon diversity reduction of 1.45 units (95% CI 0.15–2.50; p<0.0001) in RTI patients versus controls, accompanied by consistent depletion of *Lachnospiraceae* (6/6 studies), *Ruminococcaceae* (5/5), and *Ruminococcus* (6/6), and enrichment of *Enterococcus* (5/5 studies) (Woodall et al., 2022). In pediatric-specific community-acquired pneumonia (CAP) , *Ruminococcus* , *Faecalibacterium* , *Lachnospira* , *Anaerostipes*, and *Dorea* were depleted, while *Streptococcus*, *Actinomyces*, *Enterococcus*, and *Escherichia* were enriched (Woodall

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et al., 2022). These findings are consistent with the SCFA-mediated protection framework: depletion of butyrate-producing taxa reduces immune tolerance and may increase susceptibility to severe RTI and post-bronchiolitis wheezing (Cabrera-Rubio et al., 2024; Woodall et al., 2022).

The Nashed et al. (2022) study of asymptomatic SARS-CoV-2 in infants found decreased *Bifidobacterium bifidum* (log2 FC approximately −4.8), *Akkermansia muciniphila* (log2 FC approximately −2.2), and *Veillonella dispar* in COVID-positive stool samples versus matched controls (all adjusted $p<0.05$), without any difference in alpha or beta diversity—consistent with a more subtle dysbiosis than is seen in symptomatic adult COVID-19. This suggests that even mild or asymptomatic respiratory viral infections in young children can perturb gut microbiota composition, potentially affecting long-term immune maturation (Nashed et al., 2022).

5. Moderating Factors: Delivery Mode, Breastfeeding, Antibiotics, and Environment

Early-life exposures that shape gut colonization are consistently identified as moderators of microbiota–respiratory disease associations (Liu et al., 2023; Sameeha et al., 2025; Galazzo et al., 2020; Zheng et al., 2019). Mode of delivery exerts a pronounced effect: cesarean section (CSD) reduces *Bacteroides* and increases *Klebsiella*, *Veillonella*, and *Enterococcus* relative to vaginal delivery (VD) (Liu et al., 2023). In the Liu et al. cohort, CSD infants had a 33.3% respiratory infection incidence over the first 6 months compared with 12.7% in VD infants ($p=0.02$), and this difference was abolished by exclusive breastfeeding: the gut microbiota of exclusively breastfed CSD infants was indistinguishable from that of VD infants by 6 months (Adonis $P=0.57$) but remained distinct in mixed-fed infants (Adonis $P<0.001$, $R^2=0.11$) (Liu et al., 2023). This finding has major public health implications: exclusive breastfeeding may restore CSD-associated gut dysbiosis and reduce respiratory infection risk, providing a modifiable intervention for CSD-born infants (Liu et al., 2023). Galazzo et al. (2020) confirmed that vaginal delivery was the strongest predictor of *Bacteroides* enrichment, with effects persisting to 31 weeks, and Grier et al. (2019) found that birth mode significantly modified immune–microbiota co-development trajectories.

Breastfeeding duration and cessation are among the most important dietary modulators of infant gut microbiota (Holgerson et al., 2022; Galazzo et al., 2020). In the Galazzo cohort, cessation of breastfeeding—rather than solid food introduction—drove the most dramatic microbiota shifts,

including decreases in *Bifidobacteria* and increases in *Lachnospiraceae* (Galazzo et al., 2020). Holgerson et al. (2022) found that the 3-month fecal microbiota accounted for the strongest association with later allergic disease (PLS R^2=0.55; Q^2=0.26), and taxa including *Bacteroides*, which is associated with immune education, were underrepresented in infants later diagnosed with allergic disease (LDA>2; $p<0.05$). These findings support current WHO recommendations for exclusive breastfeeding through 6 months, and suggest that even partial breastfeeding may confer respiratory benefits through microbiota-dependent mechanisms (Holgerson et al., 2022; Liu et al., 2023).

Antibiotic exposure is the most consistently documented disruptor of gut colonization linked to respiratory allergy risk (Sameeha et al., 2025). Sameeha et al.'s systematic review of 1.5 million children found that antibiotic exposure during the first 6 months of life was associated with asthma (HR 1.21; 95% CI 1.18–1.25) and allergic rhinitis (HR 1.14; 95% CI 1.11–1.18), with macrolides showing stronger effects (OR ~1.4–1.7) than β-lactams (OR ~1.2–1.3) (Sameeha et al., 2025). The mechanism involves depletion of *Bifidobacterium* and SCFA-producing bacteria, with corresponding reductions in Treg differentiation capacity and barrier integrity (Sameeha et al., 2025). Durack et al. (2018) demonstrated that early antibiotic exposure had long-term effects on gut community structure in high-risk infants, and the related CF study by Price et al. (2023) showed that antibiotic exposure before 6 months persistently elevated *Veillonella* and *Prevotella* ASVs and reduced *Bifidobacterium* at ages 2–4 years. These findings underscore the importance of antibiotic stewardship in infancy, particularly restricting macrolide use unless clearly indicated (Sameeha et al., 2025).

Environmental factors including air pollution and pet exposure have been documented as additional modulators (Zheng et al., 2019; Filardo et al., 2022). Zheng et al. (2019) demonstrated that short-term air pollution episodes significantly altered gut microbiota in asthmatic children (PERMANOVA $p=0.03$), with decreases in *Firmicutes* associated with higher SO_2 ($\beta=-0.0316$; $p=0.019$) and NO_2 ($\beta=-0.0095$; $p=0.029$), and increases in *Proteobacteria* and *Bacteroides*. The Filardo systematic review found similar cross-sectional associations between air pollutant exposure and gut dysbiosis, including reduced *Clostridia* in asthmatic children linked to higher asthma attack frequency (Filardo et al., 2022). Galazzo et al. (2020) showed that having older siblings and pet

exposure modestly increased gut microbial diversity, a potentially protective factor, consistent with the hygiene hypothesis.

6. Probiotic, Prebiotic, and Synbiotic Interventions: Prevention Versus Treatment

A substantial portion of the included literature concerns microbiota-targeted interventions, and the overall picture is one of moderate, strain-specific, and dose-dependent efficacy, with clearest evidence for RTI prevention and modest evidence for asthma control—but notably, systematic null results for primary asthma prevention (Zuccotti et al., 2015; Azad et al., 2013; Abrahamsson et al., 2013).

Respiratory tract infection prevention: The Langenneger systematic review of 32 pediatric RCTs found that 78.1% reported a positive effect of probiotics on RTI incidence, with mean RTI prevalence of 42% in probiotic groups versus 59% in controls (Langenneger et al., 2025). The Liu meta-analysis of LGG specifically showed significant reductions in acute otitis media (RR 0.76; NNT 17), upper RTIs (RR 0.62; NNT 4), and antibiotic treatments (RR 0.80) (Liu et al., 2013). Hojsak et al.'s placebo-controlled trial in daycare children found that LGG (10^9 CFU/day for 3 months) reduced overall RTIs (RR 0.63; NNT 5), upper RTIs (RR 0.66), and RTIs lasting >3 days (RR 0.57), with significantly fewer symptom days ($p<0.001$) (Hojsak et al., 2010). Rautava et al. (2008) found that LGG + *B. lactis* Bb-12 from before age 2 months reduced early acute otitis media (RR 0.44) and recurrent RTIs across the first year (RR 0.51). The Rashidi meta-analysis of probiotic fermented dairy products found protective effects in children (RR 0.82) with greater effects from *Lactobacillus* than *Bifidobacterium* strains (Rashidi et al., 2021). Beyond lactobacilli, *Bifidobacterium longum* BB536 reduced respiratory illness episodes and shortened sore throat duration by 46% ($p=0.018$), with increased fecal *Faecalibacterium* (Lau et al., 2017). *B. longum* subsp. *infantis* B8762 reduced fever, cough, nasal congestion, and wheezing at 4 weeks, alongside lower TNF-α (Richmond et al., 2025). Nocerino et al. (2017) demonstrated that heat-killed *L. paracasei* CBA L74 (postbiotic) reduced URTI proportion (48.2% vs 70.5% placebo; ARD −22%; $p<0.001$), with elevated fecal defensins and secretory IgA.

Prebiotic and synbiotic approaches also showed benefits. Ranucci et al. (2018) found that GOS/PDX prebiotic formula reduced the proportion of infants with any RTI by 48 weeks (33% vs

48%; p=0.023), recurrent RTIs (20% vs 32%; p=0.039), and wheezy lower RTIs (33% vs 46%; p=0.046). Sazawal et al. (2010) found borderline significant reductions in pneumonia (RR 0.76; p=0.05) and severe ALRI (RR 0.65; p=0.05) with prebiotic + *B. lactis* HN019. The Piloquet synbiotic formula RCT (GOS + *L. fermentum* CECT5716) found lower LRTI incidence (IRR 0.77; p=0.049) with higher fecal secretory IgA (p=0.015) (Piloquet et al., 2024). Lin et al. (2009) demonstrated strain-specificity: only *L. casei rhamnosus* significantly reduced doctor-diagnosed respiratory infectious diseases, while multispecies product and *L. rhamnosus* T cell-1 did not.

Asthma outcomes: In striking contrast to the RTI prevention data, systematic reviews of perinatal probiotic administration for primary asthma prevention have shown no benefit (Zuccotti et al., 2015; Azad et al., 2013; Abrahamsson et al., 2013). The Abrahamsson et al. (2013) seven-year follow-up of *L. reuteri* supplementation in infancy found no effect on respiratory allergies. However, probiotics show significant benefits in treating established asthma. The Yang Liu et al. (2025) meta-analysis of 8 pediatric asthma RCTs found that probiotics significantly reduced acute asthma exacerbations (RR 0.38; 95% CI 0.26–0.56; p<0.00001) and improved FEV1/FVC ratio (MD 5.70 percentage points; p=0.003). The Fan et al. (2025) systematic review found that probiotic interventions reduced exacerbations in 5 of 7 studies, and postbiotic bacterial lysates (OM-85 BV, PMBL®) reduced wheezing episodes by 37.9% (p<0.001) and RTIs by 31.4% (p<0.001). The PROPAM RCT of *L. salivarius* LS01 + *B. breve* B632 in 422 asthmatic children found that ≥1 exacerbation occurred in 9.0% of probiotic group versus 23.8% of placebo (OR 3.17; p<0.001) (Drago et al., 2022). The Chinese RCT of multi-strain probiotic adjunct in pediatric refractory asthma demonstrated that 4 months of supplementation achieved complete asthma control in 68.2% versus 36.4% with conventional therapy alone (p<0.05), with significantly higher ACT scores, FEV1, and faster cough resolution, accompanied by increased Shannon diversity and *Bifidobacterium* (25.00% vs 0.98%; p<0.001) and reductions in *Bacteroides* and *Fusobacteria* (Liu et al., 2026). Huang et al. (2018) found that *Lactobacillus paracasei* and *L. fermentum* improved FEV1 and reduced eosinophil counts in schoolchildren with asthma.

This prevention–treatment discrepancy is mechanistically coherent. Asthma development involves complex early-life immune programming during the first 100 days, when the microbiota–

immune interface shapes tolerogenic versus Th2-polarizing trajectories (Arrieta et al., 2015). Probiotic strains administered perinatally may lack the specific taxa (notably the FLVR consortium: *Lachnospira*, *Veillonella*, *Faecalibacterium*, *Rothia*) required for this programming window, especially given that intervention formulations have typically consisted of *Lactobacillus* or *Bifidobacterium* strains rather than the precise taxa implicated (Arrieta et al., 2015). Once asthma is established, the gut–immune axis continues to influence airway inflammation through ongoing SCFA production, Treg maintenance, and mucosal IgA levels, mechanisms accessible to probiotic intervention even after the critical early window has passed (Fan et al., 2025; Liu et al., 2025). For RTI prevention, the mechanism is more proximate—competition for mucosal niches, enhancement of mucosal IgA and innate immune defenses, and modulation of cytokine balance—and does not require a specific early developmental window, explaining consistent benefits across diverse age groups (Langenneger et al., 2025; Hojsak et al., 2010).

7. Disease-Specific Contexts: Cystic Fibrosis, BPD, and the Aerodigestive Microbiome

Beyond general asthma and RTI literature, several studies examined disease-specific gut–lung axis relationships. The CF literature is particularly instructive because CFTR dysfunction simultaneously disrupts both gut and lung physiology, creating a natural experiment for studying gut–lung interactions (Caley et al., 2023; Ray et al., 2022; Price et al., 2023). Price et al. (2023) documented that CF lung-associated genera including *Streptococcus* , *Veillonella* , *Staphylococcus* , *Haemophilus* , and *Prevotella* are detectable in the CF gut throughout early childhood, raising the possibility that the gut serves as a reservoir seeding the lung. The Caley systematic review confirmed CF-related gut dysbiosis with reduced diversity, depletion of *Bifidobacterium*, *Akkermansia muciniphila*, *F. prausnitzii*, *Roseburia*, and *Ruminococcaceae*, and elevated *Enterobacteriaceae*, *Lactobacillus*, *Streptococcus*, and *Veillonella* (Caley et al., 2023). The Ray et al. (2022) finding that *Bifidobacterium*-dominated gut microbiota (achievable through LGG supplementation) is associated with 45% fewer pulmonary exacerbations and 20 percentage-point higher FEV1 provides the strongest causal chain in the pediatric gut–lung axis literature.

In BPD, two studies found consistent patterns: lower gut Shannon diversity and depletion of butyrate-producing taxa (*Faecalibacterium* , *Roseburia* , *Clostridium* , *Eubacterium* , *Coprococcus*)

in BPD infants versus non-BPD controls, while BPD was associated with higher *Enterococcus*, *Acinetobacter*, and *Elizabethkingia* (Thatrimontrichai et al., 2025; Zhang et al., 2022). Zhang et al. (2022) also found that BPD was marked by increasing *Proteobacteria* (53.9% to 80.1% over time; p=0.032) and decreasing *Firmicutes* (45.0% to 16.7%; p=0.021), alongside elevated pro-inflammatory cytokines (IL-1β, IL-4, IL-6, IL-8, TNF-α) and reduced IL-10. These findings suggest that gut dysbiosis may contribute to BPD pathogenesis, potentially through systemic inflammation (Thatrimontrichai et al., 2025; Zhang et al., 2022).

The Duvallet aerodigestive cohort study challenged assumptions about microbial exchange routes: in children undergoing simultaneous bronchoscopy and upper endoscopy, lung and gastric communities showed high individual-level similarity, but in aspirating children, the lung microbiome became significantly more similar to oropharyngeal rather than gastric communities (p=0.04), with higher co-occurrence of *Veillonella* , *Prevotella* , *Fusobacterium* , *Rothia* , and *Streptococcus* between lung and oropharynx (Duvallet et al., 2018). This finding suggests that the oropharyngeal-to-lung route, rather than gastric-to-lung microaspiration, is the primary driver of lung dysbiosis in children with swallowing dysfunction (Duvallet et al., 2018).

8. Clinical and Research Implications

Clinically, the consistent association between early-life antibiotic exposure and increased respiratory allergy risk supports antibiotic stewardship programs targeting unnecessary prescriptions in infancy (Sameeha et al., 2025). The finding that exclusive breastfeeding can restore CSD-associated gut dysbiosis and reduce RTI risk supports proactive lactation support for mothers delivering by cesarean section (Liu et al., 2023). For pediatric asthma patients with poor control despite standard therapy, probiotic supplementation (particularly strains with demonstrated efficacy, such as *L. salivarius* LS01 + *B. breve* B632 or multi-strain formulations) may be considered as adjunctive therapy, although larger confirmatory trials are needed (Drago et al., 2022; Liu et al., 2026). For CF patients, LGG supplementation to achieve *Bifidobacterium*-dominant gut microbiota is associated with improved lung function and fewer exacerbations, suggesting that gut microbiota monitoring could become part of CF clinical management (Ray et al., 2022; Bruzzese et al., 2014).

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For researchers, the priority is to conduct randomized controlled trials delivering precisely the taxa depleted during the first 100 days (the FLVR consortium: *Lachnospira* , *Veillonella* , *Faecalibacterium*, *Rothia*) for primary asthma prevention in high-risk infants (Arrieta et al., 2015). Such trials would test the causal hypothesis more definitively than standard probiotic strains. Additionally, mechanistic studies should quantify SCFA flux and immune cell trafficking in humans using stable isotope tracers and advanced flow cytometry, and integrate multi-omics (metagenomics, metabolomics, proteomics) to identify novel mediators. Standardization of probiotic strains, dosages, and delivery vehicles is urgently needed to enable meta-analysis and guideline development (Langenneger et al., 2025). Finally, integration of gut microbiota profiling (e.g., 16S rRNA sequencing of stool samples at age 3–6 months) into pediatric respiratory risk stratification should be evaluated in prospective cohort studies with cost-effectiveness analyses.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review demonstrates that gut microbiota composition in early life—particularly during the first 100 days—is consistently and causally associated with pediatric respiratory disease risk, including asthma, allergic rhinitis, RTIs, RSV bronchiolitis, BPD, and CF-related lung disease. The protective effect of specific commensals (*Faecalibacterium* , *Roseburia* , *Bifidobacterium*, *Lachnospiraceae*) is mediated largely through SCFA production (acetate, butyrate, propionate), which promotes Treg differentiation, suppresses Th2 inflammation, and enhances mucosal IgA responses. Apparent contradictions in the literature—such as whether high or low gut diversity is protective—resolve when considering microbial community composition: diversity driven by SCFA producers protects against asthma, whereas diversity driven by pathobionts may increase RTI risk or reflect NRDS pathology.

Probiotic, prebiotic, and synbiotic interventions show moderate, strain-specific efficacy for RTI prevention and established asthma treatment but not for primary asthma prevention. This pattern is mechanistically coherent: asthma prevention requires delivery of specific taxa (FLVR consortium) during the first 100-day critical window, whereas RTI prevention and asthma treatment target

ongoing immune and mucosal defense mechanisms accessible later in childhood. Moderating factors—cesarean delivery (increases risk), exclusive breastfeeding (reduces risk), antibiotic exposure (increases risk, especially macrolides), and air pollution (exacerbates dysbiosis)—are actionable targets for public health intervention.

Recommendations :

1. **For clinical practice:** Promote exclusive breastfeeding through 6 months, particularly for cesarean-delivered infants; implement antibiotic stewardship in infancy; consider probiotic adjuncts for pediatric asthma refractory to standard therapy (strains with RCT evidence); monitor gut microbiota in CF patients as part of comprehensive care.

2. **For research:** Prioritize RCTs delivering the FLVR consortium for primary asthma prevention; conduct mechanistic human studies quantifying SCFA flux and immune cell trafficking; standardize probiotic strains and dosages; integrate gut microbiota profiling into pediatric respiratory risk stratification with cost-effectiveness analysis.

3. **For policy:** Support public health campaigns promoting vaginal delivery when safe, exclusive breastfeeding, and reduced unnecessary antibiotic use; fund research on gut microbiota-targeted interventions in low- and middle-income countries; develop regulatory frameworks for probiotic products with health claims for pediatric respiratory outcomes.

REFERENCES

1. Arrieta M, Stiemsma LT, Dimitriu P, et al (2015) Early infancy microbial and metabolic alterations affect risk of childhood asthma. Science Translational Medicine. https://doi.org/10.1126/scitranslmed.aab2271

2. Alcazar CG, Paes VM, Shao Y, et al (2022) The association between early-life gut microbiota and childhood respiratory diseases: a systematic review. The Lancet Microbe. https://doi.org/10.1016/S2666-5247(22)00184-7

3. Galazzo G, Best N van, Bervoets L, et al (2020) Development of the Microbiota and Associations With Birth Mode, Diet, and Atopic Disorders in a Longitudinal Analysis of Stool

© The Indonesian Journal of General Medicine

Samples, Collected From Infancy Through Early Childhood. Gastroenterology. https://doi.org/10.1053/j.gastro.2020.01.024

4. Li R, Guo Q, Zhao J, et al (2023) Assessing causal relationships between gut microbiota and asthma: evidence from two sample Mendelian randomization analysis. Frontiers in Immunology. https://doi.org/10.3389/fimmu.2023.1148684

5. Cabrera-Rubio R, Calvo C, Alcolea S, et al (2024) Gut and respiratory tract microbiota in children younger than 12 months hospitalized for bronchiolitis compared with healthy children: can we predict the severity and medium-term respiratory outcome? Microbiology spectrum. https://doi.org/10.1128/spectrum.02556-23

6. Woodall C, McGeoch L, Hay A, Hammond A (2022) Respiratory tract infections and gut microbiome modifications: A systematic review. PLoS ONE. https://doi.org/10.1371/journal.pone.0262057

7. Yagi K, Lukacs NW, Huffnagle GB, et al (2024) Respiratory and Gut Microbiome Modification during Respiratory Syncytial Virus Infection: A Systematic Review. Viruses. https://doi.org/10.3390/v16020220

8. Ray KJ, Santee C, McCauley K, et al (2022) Gut Bifidobacteria enrichment following oral Lactobacillus-supplementation is associated with clinical improvements in children with cystic fibrosis. BMC Pulmonary Medicine. https://doi.org/10.1186/s12890-022-02078-9

9. Liu Y, Ma J, Zhu B, et al (2023) A health-promoting role of exclusive breastfeeding on infants through restoring delivery mode-induced gut microbiota perturbations. Frontiers in Microbiology. https://doi.org/10.3389/fmicb.2023.1163269

10. Sameeha F, Riaz S, Aslam M, Perveen A (2025) Association between early-life antibiotic exposure and gut microbiome alterations linked to allergic diseases in children: a systematic review. European Journal of Medical Research. https://doi.org/10.1186/s40001-025-03685-y

11. Liu S, Hu P, Du X, et al (2013) Lactobacillus rhamnosus GG supplementation for preventing respiratory infections in children: A Meta-analysis of Randomized, Placebo-controlled Trials. Indian Pediatrics. https://doi.org/10.1007/s13312-013-0123-z

© The Indonesian Journal of General Medicine

12. Hojsak I, Snovak N, Abdovic S, et al (2010) Lactobacillus GG in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: a randomized, double-blind, placebo-controlled trial. Clinical Nutrition. https://doi.org/10.1016/j.clnu.2009.09.008
13. Liu Y, Zhang Y, Li Y, et al (2025) Probiotics for children with asthma: a systematic review and meta-analysis. Frontiers in Pediatrics. https://doi.org/10.3389/fped.2025.1577152
14. Liu Z, Deng W, Xu W, et al (2026) Probiotic supplementation modulates the gut microbiome and improves clinical outcomes in pediatric refractory asthma. Frontiers in Microbiology. https://doi.org/10.3389/fmicb.2026.1756436
15. Zuccotti G, Meneghin F, Aceti A, et al (2015) Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. Allergy European Journal of Allergy and Clinical Immunology. https://doi.org/10.1111/all.12700
16. Azad M, Coneys JG, Kozyrskyj A, et al (2013) Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: systematic review and meta-analysis. British medical journal. https://doi.org/10.1136/bmj.f6471
17. Zhao R (2026) The association between early-life respiratory infections and childhood asthma: a meta-analytic perspective. Frontiers in Medicine. https://doi.org/10.3389/fmed.2026.1751843
18. Yang W, Wu H, Li X, et al (2025) Gut–lung axis in allergic rhinitis: microbial dysbiosis and therapeutic strategies. Frontiers in Microbiology. https://doi.org/10.3389/fmicb.2025.1654997
19. Caley L, White H, Goffau MD de, et al (2023) Cystic Fibrosis-Related Gut Dysbiosis: A Systematic Review. Digestive Diseases and Sciences. https://doi.org/10.1007/s10620-022-07812-1
20. Zheng P, Zhang B, Zhang K, et al (2019) The Impact of Air Pollution on Intestinal Microbiome of Asthmatic Children: A Panel Study. BioMed Research International. https://doi.org/10.1155/2020/5753427
21. Druszczyńska M, Sadowska B, Kulesza J, et al (2024) The Intriguing Connection Between the Gut and Lung Microbiomes. Pathogens. https://doi.org/10.3390/pathogens13111005

22. Moroishi Y, Gui J, Hoen A, et al (2022) The relationship between the gut microbiome and the risk of respiratory infections among newborns. Communications Medicine. https://doi.org/10.1038/s43856-022-00152-1

23. Aldriwesh M, Al-Mutairi AM, Alharbi A, et al (2023) Paediatric Asthma and the Microbiome: A Systematic Review. Microorganisms. https://doi.org/10.3390/microorganisms11040939

24. Durack J, Kimes NE, Lin D, et al (2018) Delayed gut microbiota development in high-risk for asthma infants is temporarily modifiable by Lactobacillus supplementation. Nature Communications. https://doi.org/10.1038/s41467-018-03157-4

25. Esposito S, Ballarini S, Argentiero A, et al (2022) Microbiota profiles in pre-school children with respiratory infections: Modifications induced by the oral bacterial lysate OM-85. Frontiers in Cellular and Infection Microbiology. https://doi.org/10.3389/fcimb.2022.789436

26. Nasir F, Gul S (2025) Microbial Signatures of Pediatric Disease: Investigating the Gut Microbiome in Asthma and Eczema. Indus Journal of Bioscience Research. https://doi.org/10.70749/ijbr.v3i6.1576

27. Price CE, Hampton T, Valls R, et al (2023) Development of the intestinal microbiome in cystic fibrosis in early life. Msphere. https://doi.org/10.1128/msphere.00046-23

28. Filardo S, Pietro MD, Protano C, et al (2022) Impact of Air Pollution on the Composition and Diversity of Human Gut Microbiota in General and Vulnerable Populations: A Systematic Review. Toxics. https://doi.org/10.3390/toxics10100579

29. Bruzzese E, Callegari M, Raia V, et al (2014) Disrupted Intestinal Microbiota and Intestinal Inflammation in Children with Cystic Fibrosis and Its Restoration with Lactobacillus GG: A Randomised Clinical Trial. PLoS ONE. https://doi.org/10.1371/journal.pone.0087796

30. Gallant RE, Reza S, Wiemels JL, Greaves M (2025) Microbiome and pediatric leukemia, diabetes, and allergies: Systematic review and meta-analysis. PLoS ONE. https://doi.org/10.1371/journal.pone.0324167

31. Langenneger P, List SR, Rivas ASP, et al (2025) The Effect of Probiotics on Prevention of Respiratory Tract Infections in Children and Adolescents: A systematic Review. Principles and Practice of Clinical Research Journal. https://doi.org/10.21801/ppcrj.2024.104.3

© The Indonesian Journal of General Medicine

32. Thatrimontrichai A, Praditaukrit M, Maneenil G, et al (2025) Characterization of gut microbiota in very low birth weight infants with versus without bronchopulmonary dysplasia. Clinical and experimental pediatrics. https://doi.org/10.3345/cep.2024.01718

33. Vael C, Vanheirstraeten L, Desager K, Goossens H (2011) Denaturing gradient gel electrophoresis of neonatal intestinal microbiota in relation to the development of asthma. BMC Microbiology. https://doi.org/10.1186/1471-2180-11-68

34. Lau A, Yanagisawa N, Hor Y, et al (2017) Bifidobacterium longum BB536 alleviated upper respiratory illnesses and modulated gut microbiota profiles in Malaysian pre-school children. Beneficial Microbes. https://doi.org/10.3920/BM2017.0063

35. Chen Y, Lin Y-L, Jan R-L, et al (2010) Randomized placebo-controlled trial of lactobacillus on asthmatic children with allergic rhinitis. Pediatric Pulmonology. https://doi.org/10.1002/ppul.21296

36. Jenkins G, Mason P, Researcher BU (2022) The Role of Prebiotics and Probiotics in Human Health: A Systematic Review with a Focus on Gut and Immune Health. Food & Nutrition Journal. https://doi.org/10.29011/2575-7091.100245

37. Venter C, Meyer R, Greenhawt M, et al (2022) Role of dietary fiber in promoting immune health—An EAACI position paper. Allergy European Journal of Allergy and Clinical Immunology. https://doi.org/10.1111/all.15430

38. Grier A, Laniewski N, Gill A, et al (2019) Aberrant newborn T cell and microbiota developmental trajectories predict respiratory compromise during infancy. iScience. https://doi.org/10.1016/j.isci.2022.104007

39. Fan D, Hu J, Lin N (2025) Effects of probiotics, prebiotics, synbiotics and postbiotics on pediatric asthma: a systematic review. Frontiers in Nutrition. https://doi.org/10.3389/fnut.2025.1586129

40. Giudice MM del, Dinardo G, Grella C, et al (2025) Ultra-Processed Foods and Respiratory and Allergic Diseases in Childhood: Epidemiological Evidence and Mechanistic Insights. Nutrients. https://doi.org/10.3390/nu17203269

© The Indonesian Journal of General Medicine

41. Sjödin KS, Sjödin A, Ruszczyński M, et al (2023) Targeting the gut-lung axis by synbiotic feeding to infants in a randomized controlled trial. BMC Biology. https://doi.org/10.1186/s12915-023-01531-3

42. Sazawal S, Dhingra U, Hiremath G, et al (2010) Prebiotic and Probiotic Fortified Milk in Prevention of Morbidities among Children: Community-Based, Randomized, Double-Blind, Controlled Trial. PLoS ONE. https://doi.org/10.1371/journal.pone.0012164

43. Rashidi K, Razi B, Darand M, et al (2021) Effect of probiotic fermented dairy products on incidence of respiratory tract infections: a systematic review and meta-analysis of randomized clinical trials. Nutrix Journal. https://doi.org/10.1186/s12937-021-00718-0

44. Abrahamsson T, Jakobsson T, Björkstén B, et al (2013) No effect of probiotics on respiratory allergies: a seven-year follow-up of a randomized controlled trial in infancy. Pediatric Allergy and Immunology. https://doi.org/10.1111/pai.12104

45. Holgerson PL, Esberg A, West C, Johansson I (2022) The breast milk and childhood gastrointestinal microbiotas and disease outcomes: a longitudinal study. Pediatric Research. https://doi.org/10.1038/s41390-022-02328-w

46. Vidal K, Sultana S, Patron A, et al (2019) Microbiota and Health Study: a prospective cohort of respiratory and diarrheal infections and associated risk factors in Bangladeshi infants under two years. medRxiv. https://doi.org/10.1101/19000505

47. Piloquet H, Vrignaud B, Gillaizeau F, et al (2024) Efficacy and safety of a synbiotic infant formula for the prevention of respiratory and gastrointestinal infections: A randomized controlled trial. American Journal of Clinical Nutrition. https://doi.org/10.1016/j.ajcnut.2024.03.005

48. Ouwehand A, Nermes M, Collado M, et al (2009) Specific probiotics alleviate allergic rhinitis during the birch pollen season. World Journal of Gastroenterology. https://doi.org/10.3748/WJG.15.3261

49. Milani G, Alberti I, Abodi M, et al (2024) A systematic review and meta-analysis on nutritional and dietary interventions for the treatment of acute respiratory infection in pediatric patients: An EAACI taskforce. Allergy European Journal of Allergy and Clinical Immunology. https://doi.org/10.1111/all.15997

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50. Ranucci G, Buccigrossi V, Borgia E, et al (2018) Galacto-Oligosaccharide/Polidextrose Enriched Formula Protects against Respiratory Infections in Infants at High Risk of Atopy: A Randomized Clinical Trial. Nutrients. https://doi.org/10.3390/nu10030286

51. Hjelmsø M, Shah SA, Thorsen J, et al (2020) Prenatal dietary supplements influence the infant airway microbiota in a randomized factorial clinical trial. Nature Communications. https://doi.org/10.1038/s41467-020-14308-x

52. Darbandi A, Asadi A, Ghanavati R, et al (2021) The effect of probiotics on respiratory tract infection with special emphasis on COVID-19: Systemic review 2010–20. International Journal of Infectious Diseases. https://doi.org/10.1016/j.ijid.2021.02.011

53. Price CE, Hampton T, Valls R, et al (2022) Development of the Intestinal Microbiome in Cystic Fibrosis in Early Life. bioRxiv. https://doi.org/10.1101/2022.05.27.493808

54. Rutten N, Gorissen D, Eck A, et al (2015) Long Term Development of Gut Microbiota Composition in Atopic Children: Impact of Probiotics. PLoS ONE. https://doi.org/10.1371/journal.pone.0137681

55. Soldi S, Vasileiadis S, Lohner S, et al (2019) Prebiotic supplementation over a cold season and during antibiotic treatment specifically modulates the gut microbiota composition of 3-6 year-old children. Beneficial Microbes. https://doi.org/10.3920/BM2018.0116

56. Canani RB, Filippis FD, Nocerino R, et al (2017) Specific Signatures of the Gut Microbiota and Increased Levels of Butyrate in Children Treated with Fermented Cow's Milk Containing Heat-Killed Lactobacillus paracasei CBA L74. Applied and Environmental Microbiology. https://doi.org/10.1128/AEM.01206-17

57. Elazab N, Mendy A, Gasana J, et al (2013) Probiotic Administration in Early Life, Atopy, and Asthma: A Meta-analysis of Clinical Trials. Pediatrics. https://doi.org/10.1542/peds.2013-0246

58. Zhang Z, Jiang J, Li Z, Wan W (2022) The Change of Cytokines and Gut Microbiome in Preterm Infants for Bronchopulmonary Dysplasia. Frontiers in Microbiology. https://doi.org/10.3389/fmicb.2022.804887

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59. Duvallet C, Larson K, Snapper S, et al (2018) Aerodigestive sampling reveals altered microbial exchange between lung, oropharyngeal, and gastric microbiomes in children with impaired swallow function. bioRxiv. https://doi.org/10.1101/476580

60. Zuhair MN, Wiriansya EP, Masyhuri I, et al (2025) Role of Lacticaseibacillus rhamnosus GG in the Management of Respiratory Diseases: A Systematic Review and Meta-Analysis. Preventive Nutrition and Food Science. https://doi.org/10.3746/pnf.2025.30.3.222

61. Guo Y, Sun S, Wang Y, et al (2025) Microbial dysbiosis in obstructive sleep apnea: a systematic review and meta-analysis. Frontiers in Microbiology. https://doi.org/10.3389/fmicb.2025.1572637

62. Hong J, Tang Z, Zhang D, et al (2025) Profiling of the gut, skin and nasal microbiotas revealed clinically relevant microbial taxa from children with allergies: a pilot study. Frontiers in Allergy. https://doi.org/10.3389/falgy.2025.1497914

63. Hu B, Kuang Y, Jing Y, et al (2021) Pediatric allergic rhinitis with functional gastrointestinal disease: Associations with the intestinal microbiota and gastrointestinal peptides and therapeutic effects of interventions. Human and Experimental Toxicology. https://doi.org/10.1177/09603271211017325

64. Hu Y, Zhang R, Li J, et al (2024) Association Between Gut and Nasal Microbiota and Allergic Rhinitis: A Systematic Review. Journal of Asthma and Allergy. https://doi.org/10.2147/JAA.S472632

65. Li M, Wang Q, Wang R, et al (2025) Association between gut microbiota and allergic rhinitis: a systematic review and meta-analysis. PeerJ. https://doi.org/10.7717/peerj.19441

66. Fu Y, Wang X, Nie L, et al (2025) Gut microbiota characteristics in neonatal respiratory distress syndrome and the therapeutic potential of probiotics in recovery. Frontiers in Microbiology. https://doi.org/10.3389/fmicb.2025.1544055

67. Mo M, Wang J, Gu H, et al (2022) Intestinal Microbes-based Analysis of Immune Mechanism of Childhood Asthma. Cellular and Molecular Biology. https://doi.org/10.14715/cmb/2022.68.2.11

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68. Nashed LM, Mani J, Hazrati S, et al (2022) Gut microbiota changes are detected in asymptomatic very young children with SARS-CoV-2 infection. Gut. https://doi.org/10.1136/gutjnl-2021-326599

69. Lin J-S, Chiu Y, Lin N-T, et al (2009) Different effects of probiotic species/strains on infections in preschool children: A double-blind, randomized, controlled study. Vaccine. https://doi.org/10.1016/j.vaccine.2008.11.114

70. Uwaezuoke S, Ayuk A, Eze J, et al (2022) Postnatal probiotic supplementation can prevent and optimize treatment of childhood asthma and atopic disorders: A systematic review of randomized controlled trials. Frontiers in Pediatrics. https://doi.org/10.3389/fped.2022.956141

71. Richmond RV, Mageswary U, Ali A, et al (2025) Therapeutic Potential of Bifidobacterium longum subsp. infantis B8762 on Gut and Respiratory Health in Infant. International Journal of Molecular Sciences. https://doi.org/10.3390/ijms26031323

72. Rautava S, Salminen S, Isolauri E (2008) Specific probiotics in reducing the risk of acute infections in infancy – a randomised, double-blind, placebo-controlled study. British Journal of Nutrition. https://doi.org/10.1017/S0007114508116282

73. Venter C, Meyer R, Greenhawt M, et al (2021) Role of Dietary Fiber in Promoting Immune Health -- An EAACI Position Paper. https://doi.org/10.22541/au.163807080.07633496/v1

74. Flygel TT, Bargheet A, Abotsi R, et al (2025) Effect of long-term azithromycin treatment on gut microbial diversity in children and adolescents with HIV-associated chronic lung disease. EBioMedicine. https://doi.org/10.1016/j.ebiom.2025.105832

75. Paganini D, Uyoga MA, Kortman G, et al (2017) Prebiotic galacto-oligosaccharides mitigate the adverse effects of iron fortification on the gut microbiome: a randomised controlled study in Kenyan infants. Gut. https://doi.org/10.1136/gutjnl-2017-314418

76. Huang C-F, Chie W, Wang I (2018) Efficacy of Lactobacillus Administration in School-Age Children with Asthma: A Randomized, Placebo-Controlled Trial. Nutrients. https://doi.org/10.3390/nu10111678

77. Das R, Naik S, Singh M (2013) Probiotics as Additives on Therapy in Allergic Airway Diseases: A Systematic Review of Benefits and Risks. BioMed Research International. https://doi.org/10.1155/2013/231979

78. Drago L, Cioffi L, Giuliano M, et al (2022) The Probiotics in Pediatric Asthma Management (PROPAM) Study in the Primary Care Setting: A Randomized, Controlled, Double-Blind Trial with Ligilactobacillus salivarius LS01 (DSM 22775) and Bifidobacterium breve B632 (DSM 24706). Journal of Immunological Research. https://doi.org/10.1155/2022/3837418

79. Garaiova I, Muchová J, Nagyová Z, et al (2014) Probiotics and vitamin C for the prevention of respiratory tract infections in children attending preschool: a randomised controlled pilot study. European Journal of Clinical Nutrition. https://doi.org/10.1038/ejcn.2014.174

80. Nocerino R, Paparo L, Terrin G, et al (2017) Cow's milk and rice fermented with Lactobacillus paracasei CBA L74 prevent infectious diseases in children: A randomized controlled trial. Clinical Nutrition. https://doi.org/10.1016/j.clnu.2015.12.004

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