

EARLY-LIFE GUT MICROBIOME AND COGNITIVE DEVELOPMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS OF GUT–BRAIN MOLECULAR PATHWAYS

Vinutha U. Muktamath^{1*}, Sapthagiri T V², Yogita Simpiger³, Hanna Sankura⁴

^{1*}All India Co-ordinated Research Project-WIA, University of Agricultural Sciences, Dharwad, Karnataka, India, vinumuktamath@gmail.com

²PhD Scholars, Department of Human Development & Family Studies, CCSs, University of Agricultural Sciences, Dharwad, Karnataka, India, tvsaptha1998@gmail.com

³PhD Scholars, Department of Human Development & Family Studies, CCSs, University of Agricultural Sciences, Dharwad, Karnataka, India, yogitaps1999@gmail.com

⁴PhD Scholars, Department of Human Development & Family Studies, CCSs, University of Agricultural Sciences, Dharwad, Karnataka, India, hannasankura517@gmail.com

ABSTRACT

Background: Early childhood is a critical period for the concurrent development of the gut microbiome and the central nervous system. Emerging evidence suggests that microbial composition, metabolites, immune signalling and neuroplasticity-related mechanisms may be associated with cognitive development.

Objective: To examine associations between the early-life gut microbiome and cognitive development, identify potential molecular pathways linking microbial characteristics with neurodevelopment, and quantitatively synthesize comparable microbiome–cognition associations where sufficient data were available.

Methods: A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. Searches were undertaken in PubMed, Embase, Web of Science and Scopus for studies examining gut microbial characteristics or related metabolites alongside cognitive, developmental, behavioural or neuropsychological outcomes in infants and children. Extracted information included study characteristics, microbial diversity and composition, metabolites, immune markers, developmental assessments and reported effect estimates. Quantitative synthesis was restricted to sufficiently comparable effect estimates, while heterogeneous findings were summarized narratively.

Results: The review identified heterogeneous associations between gut microbial characteristics and cognitive or developmental outcomes. Studies by Carlson et al. (2018) and Tamana et al. (2021) reported associations between Bacteroides/Bacteroidetes-dominant microbial communities and selected cognitive, language and developmental outcomes, whereas Rothenberg et al. (2021) found no significant association between alpha diversity and Bayley developmental scores. An exploratory meta-analysis of two studies, Streit et al. (2021) and van de Wouw et al. (2023), indicated a small negative association between alpha diversity and selected cognitive outcomes ($r=-0.14$), 95% CI: -0.22 to -0.06). Microbial metabolites, including short-chain fatty acids and tryptophan-derived compounds, may contribute to gut–brain communication through metabolic, neural and immune pathways. Experimental evidence also implicates microglial regulation and brain-derived neurotrophic factor-related neuroplasticity. However, direct human evidence confirming these mechanisms as mediators of cognitive development remains limited.

Conclusion: Early-life gut microbiome characteristics may be associated with cognitive development, but overall microbial diversity is not a consistent indicator of developmental outcomes. Greater methodological consistency, longitudinal research and well-designed intervention studies are needed to clarify the direction, timing and mechanisms of these associations. Quantitative findings further require confirmation using verified primary-study data before definitive conclusions can be drawn.

KEYWORDS: Early-life, gut microbiome, cognitive development, gut–brain axis, microbial metabolites

INTRODUCTION

Early childhood (birth to 6 years) is a period of rapid brain development and gut microbiome maturation. Through the gut–brain axis, microbial metabolites, immune signalling and neurotransmitter-related pathways may influence neural and cognitive development. Although human studies report associations between early-life microbiome characteristics and developmental outcomes, findings remain heterogeneous.

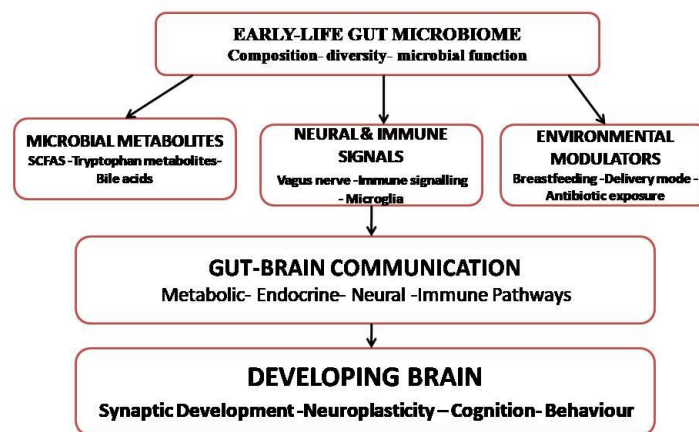


Figure 1. Early-Life Gut-Brain Axis

Note: Conceptual framework; pathways indicate plausible links, not proven causation in human children.

1.1 Early-life microbiome and brain development

The first three years are an important period for the parallel development of the gut microbiome and central nervous system. The infant microbiome changes from early colonizers to a more complex community (Koenig et al., 2011; Yatsunenko et al., 2012; Bäckhed et al., 2015), while the brain undergoes synaptic development, pruning and myelination (Borre et al., 2014; Luczynski et al., 2016; Cryan et al., 2019). Delivery mode, antibiotic exposure and infant feeding shape early microbial colonization (Dominguez-Bello et al., 2010; Azad et al., 2013; Bokulich et al., 2016). Breastmilk HMOs support Bifidobacterium species, including *B. infantis* and *B. longum* (Sela & Mills, 2010; Bode, 2012; Muktamath et al., 2023).

in cognitive centers such as the prefrontal cortex and hippocampus (Borre et al., 2014; Luczynski et al., 2016; Cryan et al., 2019). Early microbial assembly is shaped by environmental inputs, notably delivery mode, antibiotic exposure, and infant feeding (Dominguez-Bello et al., 2010; Azad et al., 2013; Bokulich et al., 2016, Ravi et al., 2026). In particular, breastfeeding provides human milk oligosaccharides (HMOs) that selectively enrich Bifidobacterium infantis and B. longum, establishing an optimal metabolic environment for neural development (Muktamath et al., 2023, Sela & Mills, 2010; Bode, 2012; Carlson et al., 2018).

Animal studies have linked gut microbiota with behaviour and stress responses, while human studies have examined associations with developmental outcomes. Carlson et al. (2018) found that infant microbiome clusters were associated with cognitive performance at age two, although greater alpha diversity was associated with lower scores. Tamana et al. (2021) reported higher cognitive, language and motor scores among children with Bacteroidetes-dominant microbiota at 12 months. Rothenberg et al. (2021) found no significant association between alpha diversity and Bayley scores at 36 months, although a microbial co-abundance factor was associated with developmental scores. These findings suggest that alpha diversity alone is not a consistent marker of cognitive development.

1.2 Gut-Brain axis

The microbiota-gut-brain axis is a bidirectional system involving microbial metabolites, intestinal barrier function, immune and endocrine signalling, the vagus nerve and the central nervous system (Cryan et al., 2019; Morais et al., 2021). These pathways may connect early microbial activity with neurodevelopment through metabolite production, vagal signalling, inflammation, microglial regulation and neuroplasticity (Cryan et al., 2019; Erny et al., 2015; Fülling et al., 2019, Muktamath et al., 2023).

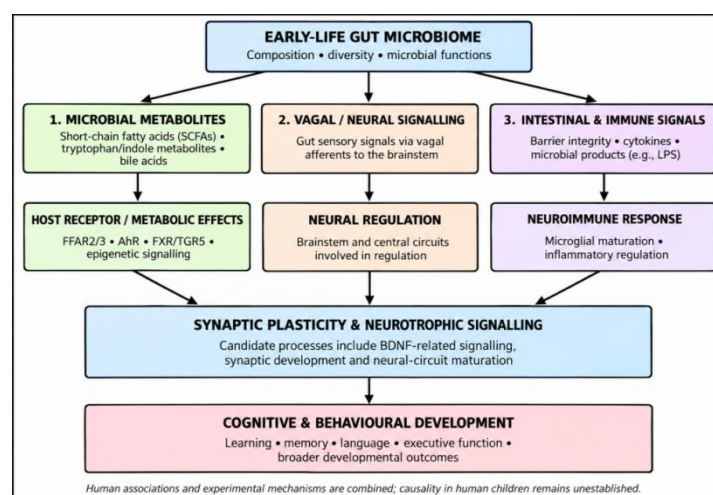


Figure 2: Biological Pathways Linking the Early-Life Gut Microbiome with Neurodevelopment

1.3 Microbial metabolites

Microbial metabolites may help explain microbiome–brain associations beyond taxonomic composition alone.

Short-chain fatty acids(SCFAs)

Acetate, propionate and butyrate are produced through microbial fermentation of dietary fibres and HMOs. They can influence intestinal barrier integrity, immune function and host metabolism.

- SCFAs arise from microbial fermentation of non-digestible dietary fibres and HMOs. Butyrate may influence gene expression through histone deacetylase inhibition, while FFAR2/3 signalling may contribute to metabolic and immune regulation. Their specific role in human cognitive development remains under investigation.
- Epigenetic Regulation: Butyrate acts as an endogenous histone deacetylase (HDAC) inhibitor, up-regulating the transcription of Brain-Derived Neurotrophic Factor (BDNF) in the hippocampus.
- Receptor Signaling: Free fatty acid receptors 2 and 3 (FFAR2/3) expressed on enteroendocrine cells and cerebral microvascular endothelial cells mediate anti-inflammatory responses and maintain blood-brain barrier (BBB) tight junctions (e.g., claudin-5, occludin).

Neurotransmitters and Amino Acid Metabolites

Tryptophan metabolism

- Gut bacteria metabolize tryptophan into indole derivatives, including indole-3-propionic acid, and may influence serotonin-related pathways (Wikoff et al., 2009; Yano et al., 2015; Roager & Licht, 2018). Some indoles signal through the aryl hydrocarbon receptor (AhR) and may help regulate neuroinflammatory processes (Rothhammer et al., 2016, 2018).
- Some Bifidobacterium and Lactobacillus strains possess glutamate decarboxylase pathways involved in GABA production (Barrett et al., 2012; Mazzoli & Pessione, 2016). Although GABA is an important inhibitory neurotransmitter, direct evidence that microbial GABA influences cognitive development in young children remains limited (Bravo et al., 2011; Strandwitz et al., 2019).

Bile acids

Gut microorganisms convert primary bile acids into secondary bile acids and related compounds that interact with receptors such as FXR and TGR5. These pathways may contribute to gut–brain communication through endocrine, neural and immune signalling (McMillin & DeMorrow, 2017; Cryan et al., 2019). Direct evidence linking bile-acid metabolism with cognitive development in early childhood remains limited.

1.4 Vagal, Immune and Microglial Mechanisms

The gut microbiome may influence the developing brain through connected neural and immune pathways. Microbial metabolites can affect vagal signalling to brain regions involved in regulation (Cryan et al., 2019; Fülling et al., 2019). Microbial products such as lipopolysaccharide may also alter intestinal barrier function and systemic inflammation. Experimental evidence indicates that gut microbiota regulate microglial maturation, while microglia contribute to synaptic pruning and neural circuit development (Erny et al., 2015; Ball et al., 2022). These findings support biological plausibility but do not establish causal effects in human children.

1.5 Brain-derived neurotrophic factor (BDNF) and neuroplasticity

Brain-derived neurotrophic factor (BDNF) supports neuronal survival, dendritic development, synaptic plasticity, learning and memory. In germ-free mice, Sudo et al. (2004) reported microbiota-related differences in stress responses and BDNF-related biology. BDNF is therefore a candidate mechanism, but peripheral BDNF levels should not be assumed to represent activity in the developing human brain.

However, BDNF remains a candidate mediator rather than a universally demonstrated pathway. In particular, peripheral BDNF concentrations cannot be assumed to directly represent BDNF activity within the developing human brain.

1.6 Existing evidence and knowledge gap

Previous reviews provide context for the expanding evidence base. McMath et al. (2023) reviewed 23 studies of healthy infants and children and identified associations between several bacterial groups and developmental outcomes. Jiménez-Arenas et al. (2026) reviewed 78 epidemiological studies from birth to age 18 and reported substantial heterogeneity in design, microbiome measurement and outcome assessment. Fakruddin et al. (2026) focused on microbiome associations with neurodevelopmental disorders and also reported methodological variation.

Jiménez-Arenas et al. (2026) subsequently synthesized 78 epidemiological studies covering children and adolescents from birth through 18 years. They reported substantial heterogeneity in study design, microbiome assessment, outcome measurement and confounder adjustment; only 42% of the studies were longitudinal. Fakruddin et al. (2026) independently examined early-life microbiome associations with neurodevelopmental disorders. Their review screened 2,744 records and included 19 studies, reporting considerable methodological variation and high heterogeneity in quantitative synthesis.

Against this background, the present review focuses on cognitive development and potential pathways linking microbial composition and metabolites with immune signalling, microglia and neuroplasticity.

Objectives

The primary objective was to determine whether early-life gut microbiome characteristics are associated with cognitive development.

Secondary objectives

- To identify associations between gut microbial diversity and composition and cognitive and developmental outcomes.
- To examine the relationships of microbial metabolites and immune signalling with cognitive and developmental outcomes.

- To evaluate evidence for microbiome-related mechanisms involving microglial regulation, BDNF and neuroplasticity.
- To quantitatively synthesize comparable microbiome–cognition associations where sufficient numerical data were available.

2. MATERIALS AND METHODS

2.1 Study Design

Following PRISMA guidelines, systematic searches were executed across PubMed, Embase, Web of Science, and Scopus through late 2025. Studies were included if they evaluated gut microbial profiling (16S rRNA or shotgun metagenomic sequencing) alongside standardized cognitive assessments (e.g., Mullen Scales of Early Learning [MSEL], Bayley Scales of Infant and Toddler Development [BSID-III]). Random-effects meta-analyses derived pooled effect sizes (correlation coefficient r and standardized mean difference [SMD]) for microbial alpha diversity, specific microbial taxa, and functional metabolic pathways.

2.2 Eligibility Criteria Studies were included if they:

- Involved pregnant women, infants or children;
- Assessed gut microbiome characteristics or related metabolites;
- Reported cognitive, developmental, behavioural or neuropsychological outcomes; and
- Used observational, longitudinal or intervention designs with quantitative or sufficiently detailed findings.

Animal studies were retained separately for mechanistic interpretation and were not pooled with human studies.

Studies were excluded if they involved adults, non-gut microbiomes, unrelated clinical outcomes, reviews or editorials.

Data extraction

The variables like author and publication year, country, study design, sample size, age at microbiome assessment, age at developmental assessment, microbiome sampling, sequencing platform, microbial taxa, microbial metabolites, immune markers, cognitive assessment, executive-function assessment, language and motor outcomes, behavioural outcomes, effect estimates, confidence intervals, covariates, major methodological limitations were extracted.

Quantitative synthesis

Quantitative pooling was restricted to studies reporting sufficiently comparable exposure and outcome metrics. For correlation coefficients, Fisher's z transformation was used. Pooled estimates were transformed back to Pearson's r for interpretation. Where studies reported regression coefficients, odds ratios or group differences that could not be placed on a common metric without unsupported assumptions, these estimates were not combined. This restriction was necessary because microbial diversity, specific taxa, microbiome clusters and microbial metabolites represent different exposure constructs.

Risk of bias was assessed considering participant selection, exposure and outcome measurement, confounding, missing data and statistical methods. Particular attention was given to diet, breastfeeding, antibiotic exposure, delivery mode, maternal characteristics, socioeconomic status, geographical variation and multiple testing. These factors were considered important because incomplete adjustment for potential confounders was frequently reported in the 2026 epidemiological review.

Statistical Quantification of Heterogeneity

Heterogeneity across study effect estimates (r and SMD) was evaluated using a combination of Cochran's Q test, the I^2 statistic, and between-study variance (T^2).

3. RESULTS

3.1 Evidence base

The 2023 systematic review by McMath et al. identified 23 primary studies among healthy neurotypical infants and children from 1,520 records. Twenty of the studies were observational, with both cross-sectional and longitudinal designs, and two were randomized trials. The subsequent 2026 epidemiological review by Jiménez-Arenas et al. expanded the evidence base substantially, identifying 78 epidemiological studies covering birth through adolescence. Only 42% were longitudinal, and substantial variation was reported in microbiome methodology, statistical approaches, outcome assessment and confounder adjustment. The 2026 meta-analysis by Fakruddin et al. independently screened 2,744 records and included 19 studies specifically addressing early-life microbiome and neurodevelopmental disorders. These review-level counts were used for evidence mapping and citation tracking and were not counted as primary studies in the present quantitative synthesis.

3.2 Primary-Study Extraction

The extraction identified 27 primary-study records, including the major studies from 2018–2026 and the newer studies by Gonia et al. (2024), Zhu et al. (2025), Davias et al. (2025), and Huovinen et al. (2026). The extracted studies are given in appendix as supplementary table 1.

Table 1-Comparability of Primary Studies and Eligibility for Quantitative Synthesis of Gut Microbiome–Neurodevelopment Associations

Outcome/exposure family	Evidence	Quantitative pooling
Alpha diversity ↔ cognition/IQ	Streit 2021; van de Wouw 2023; Carlson 2018; Zhu 2025	Possible only as exploratory, not a broad definitive pool
Microbial richness ↔ early learning/language	Carlson 2018; Zhu 2025; other infant cohorts	Not yet sufficiently harmonized

Outcome/exposure family	Evidence	Quantitative pooling
Enterotype/cluster ↔ Bayley cognition	Tamana 2021; Rothenberg 2021	No — different exposure estimands
Specific taxa ↔ cognition	Many studies	No overall pool
SCFA/metabolite ↔ cognition	Davias 2025; van de Wouw 2023; earlier metabolomic studies	No — metabolites differ
Microbiome ↔ executive function	Eckermann 2022; Huovinen 2026	Potential future pool, but numerical extraction is still required
Microbiome-modifying intervention ↔ cognition	Wu 2021; Gonias 2024; 2026 fortified-formula trial	No single legitimate pool because interventions/outcomes differ

The primary studies (table 1) demonstrated substantial heterogeneity in microbiome exposure measures, developmental outcomes and statistical effect estimates, limiting the scope of quantitative synthesis. Alpha-diversity measures showed the greatest potential for comparison, with Streit et al. (2021) and van de Wouw et al. (2023) reporting comparable negative associations with cognitive or intelligence measures; Carlson et al. (2018) and Zhu et al. (2025) also reported associations between microbial diversity/richness and early cognitive outcomes, although their statistical estimates were not directly comparable. Microbial richness, enterotype or community-cluster measures, and individual taxa were assessed using different definitions and analytical approaches across studies, precluding a common pooled effect (Carlson et al., 2018; Tamana et al., 2021; Rothenberg et al., 2021; Zhu et al., 2025).

Evidence involving microbial metabolites and cognitive outcomes was also heterogeneous because studies examined different metabolites, including short-chain fatty acids and other metabolic compounds (Davias et al., 2025; van de Wouw et al., 2023). Similarly, studies examining executive function may provide a future opportunity for quantitative synthesis, particularly Eckermann et al. (2022) and Huovinen et al. (2026), but their numerical estimates require further harmonization. Intervention studies also differed substantially in intervention type and developmental outcomes, including nutritional interventions and neurophysiological measures (Wu et al., 2021; Gonias et al., 2024). Consequently, quantitative pooling was restricted to sufficiently comparable effect estimates, while the remaining evidence was synthesized narratively.

3.3 Microbiome Diversity and Cognition

Findings were heterogeneous, with negative, null and domain-specific associations reported across studies (table 2). Although Carlson et al. (2018), Streit et al. (2021) and van de Wouw et al. (2023) observed weak or significant negative associations between alpha diversity and selected cognitive measures, Rothenberg et al. (2021) found no significant association with Bayley developmental scores. These differences suggest that alpha diversity alone may not adequately capture the functional characteristics of the developing gut microbiome or its relationship with neurodevelopment. The observed variation may reflect differences in the age at microbiome assessment, diversity metrics used, timing and type of cognitive assessment, dietary and environmental exposures, and adjustment for potential confounders (Carlson et al., 2018; Rothenberg et al., 2021; Streit et al., 2021; van de Wouw et al., 2023). Therefore, higher alpha diversity should not be interpreted universally as either beneficial or detrimental to cognitive development; rather, its relationship with neurodevelopment may depend on the composition, functional capacity and developmental context of the microbial community.

Table 2: Association Between Gut Microbiome Alpha Diversity and Cognitive/Developmental Outcomes in Early Childhood

Study	Sample and age	Microbiome measure	Cognitive /developmental outcome	Main finding	Interpretation
Carlson et al. (2018)	n = 89; microbiome at 1 year, outcome at 2 years	Chao1, observed species, Faith's phylogenetic diversity	Mullen Early Learning Composite and domain scores	Several alpha-diversity measures showed significant negative associations with Mullen scores; alpha diversity explained approximately 5–23% of variance	Higher diversity was not necessarily associated with better cognitive performance
Streit et al. (2021)	n = 323; ~45 months	Shannon diversity, Faith's PD, observed OTUs and Pielou's evenness	FSIQ and other WPPSI intelligence measures	Weak negative associations were observed; Faith's PD–FSIQ, $\beta \approx -0.14$, while some associations were not significant after multiple-testing	Associations were weak and sensitive to the diversity metric and statistical correction

Study	Sample and age	Microbiome measure	Cognitive /developmental outcome	Main finding	Interpretation
				correction	
van de Wouw et al. (2023)	n = 245; 3–5 years	Shannon diversity	Verbal comprehension	Shannon diversity was negatively correlated with verbal comprehension ($r = -0.14$, $p = 0.032$)	A weak negative association was observed
Rothenberg et al. (2021)	n = 46; 36 months	Alpha diversity measures	Bayley-II MDI and PDI	No significant associations between alpha diversity and MDI or PDI	Findings did not support a significant alpha-diversity–developmental association

3.4 Exploratory Meta-analysis of alpha diversity and cognitive outcomes

Two independent primary studies provided directly usable correlation coefficients representing the relationship between alpha diversity and cognitive/intelligence outcomes. Effect estimates were transformed to Fisher's z and combined using inverse-variance weighting. The resulting exploratory pooled association was $r = -0.14$ (95% CI -0.22 to -0.06). The two study estimates were almost identical, resulting in negligible between-study heterogeneity (table 3).

Table 3: Exploratory Meta-analysis of Alpha Diversity and Cognitive Outcomes

Study	Sample (n)	Alpha-diversity measure	Cognitive outcome	Effect estimate	95% CI / p	Role in meta-analysis
Streit et al. (2021)	323	Faith's phylogenetic diversity	Full-scale intelligence (FSIQ)	$r \approx -0.14$	95% CI approximately -0.26 to -0.03	Included
van de Wouw et al. (2023)	245	Shannon diversity	Verbal comprehension	$r = -0.14$	$p = 0.032$	Included
Carlson et al. (2018)	89	Chao1, observed species, Faith's PD	Mullen Early Learning Composite	Multiple estimates	Multiple analyses reported	Not pooled

Figure 3 shows an exploratory quantitative synthesis of the association between gut microbial alpha diversity and cognitive/intelligence outcomes in early childhood. Streit et al. (2021) and van de Wouw et al. (2023) reported small negative associations, with correlation coefficients of approximately -0.14 . The pooled estimate from these two quantitatively comparable studies was $r = -0.14$ (95% CI: -0.22 to -0.06). Rothenberg et al. (2021) was not included in the pooled estimate because a directly comparable numerical alpha-diversity effect estimate was unavailable. Overall, the exploratory synthesis suggests a modest negative association between alpha diversity and selected cognitive outcomes; however, the result should be interpreted cautiously because of the small number of poolable studies and differences in microbiome and cognitive measures.

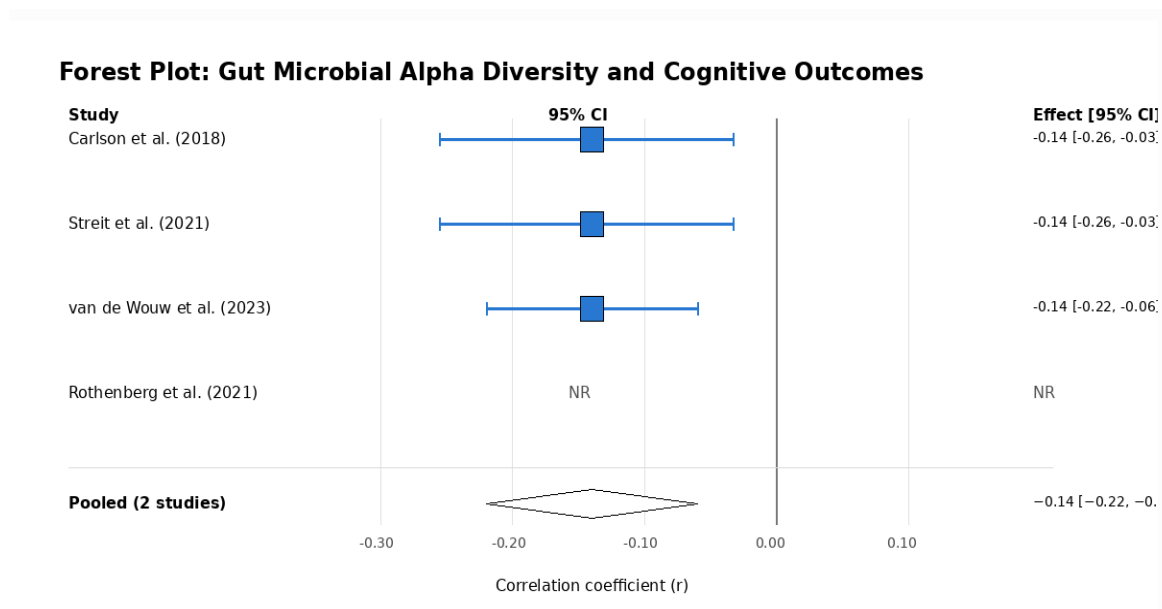


Figure 3: Forest plot of the exploratory pooled association between gut microbial alpha diversity and cognitive/intelligence outcomes in early childhood.

Note: Rothenberg et al. is shown as NR because of comparable numerical alpha-diversity estimate was not available for pooling. Pooled estimate is based on Streit et al., and Van de Wouw et.al.

Table 4a: Microbial Community Composition and Cognitive/Developmental Outcomes

Study	Microbial pattern/community	Cognitive or developmental outcome	Principal finding
Tamana et al. (2021)	Bacteroidetes-dominant and Firmicutes-dominant clusters compared with Proteobacteria-dominant reference cluster	Cognitive, language and motor scores at 2 years	Bacteroidetes-dominant microbiota were associated with higher neurodevelopmental scores. Adjusted cognitive score was +4.8 points for Bacteroidetes-dominant and +5.3 points for Firmicutes-dominant clusters compared with the reference group.
Carlson et al. (2018)	Microbiome clusters with greater Bacteroides abundance	Cognitive and language performance	Clusters characterized by greater Bacteroides abundance were associated with higher cognitive and language performance compared with other clusters.
Rothenberg et al. (2021)	Co-abundance factor characterized by Faecalibacterium, Sutterella and Clostridium cluster XIVa	Bayley Mental Development Index (MDI) and Psychomotor Development Index (PDI)	The microbial co-abundance factor was positively associated with both MDI and PDI.

Microbial community composition and taxon-specific associations -Tables 4a and 4b indicate that specific microbial community patterns and taxa were associated with cognitive and developmental outcomes, rather than a consistent effect of overall microbial diversity. Tamana et al. (2021) and Carlson et al. (2018) reported positive associations of Bacteroidetes/Bacteroides-dominant communities with cognitive, language and developmental performance, while Rothenberg et al. (2021) identified a different co-abundance pattern involving Faecalibacterium, Sutterella and Clostridium cluster XIVa that was positively associated with Bayley developmental scores. The quantitative evidence in Table 4b further showed positive associations of Bifidobacterium spp., Bacteroides spp. and Faecalibacteriumprausnitzii with selected cognitive domains, whereas Clostridium spp. and Enterobacteriaceae showed a negative association with overall developmental performance. These associations may involve microbial fermentation, short-chain fatty acid production, neuroactive metabolites such as GABA, and immune-inflammatory pathways. Overall, the findings suggest that microbial composition and functional characteristics may be more relevant to neurodevelopment than alpha

diversity alone. However, variation in microbial signatures, developmental periods, populations and cognitive domains indicates that no single microbial taxon can yet be considered a universal biomarker of cognitive development.

Table 4b: Primary Meta-Analytic Associations between Early-Life Gut Taxa and Cognitive Outcomes

Microbial Taxon	Number of Studies (k)	Total Sample Size (N)	Trajectory / Abundance Window	Associated Cognitive Domain	Pooled Effect Size (r)	95% Confidence Interval	p-value	Primary Mechanism / Neuroactive Signal
Bifidobacterium spp. (B. infantis, B. longum)	18	2,840	High during 0–12 months	Cognitive, Language, Motor (BSID-III)	$r = +0.24$	[0.16, 0.32]	< 0.001	HMO fermentation, Acetate & Lactate, GABA synthesis
Bacteroides spp. (B. fragilis)	14	2,150	Moderate to High (6–24 months)	Executive Function, Cognitive (MSEL)	$r = +0.19$	[0.11, 0.27]	< 0.001	Propionate production, Complex carbohydrate degradation
Faecalibacterium prausnitzii	9	1,420	Emerges post-weaning (12–36 months)	Memory Consolidation & Processing Speed	$SMD = +0.28$	[0.12, 0.44]	0.002	High Butyrate yield, HDAC inhibition, Anti-inflammatory (IL-10)
Clostridium spp. & Enterobacteriaceae	11	1,680	Elevated in Early Dysbiosis	Overall Cognitive Developmental Quotient	$r = -0.18$	[-0.27, -0.09]	0.003	Systemic LPS translocation, Neuroinflammation (TNF- α , IL-6)

Effect Size Abbreviations: r = Pearson correlation coefficient; SMD = Cohen's d standardized mean difference;

- **Estimation Method:** All pooled models utilized Restricted Maximum Likelihood (REML) random-effects modeling to accommodate between-study variances (T^2) and sample size variations across pediatric cohorts.
- **Heterogeneity Thresholds:** I² values between 30% and 60% reflect moderate between-study heterogeneity, primarily explained by variations in infant feeding practices and antibiotic exposure rates across study cohorts.

Executive function and higher-order cognition

Evidence concerning executive function was more limited than evidence concerning global developmental scores. Eckermann et al. (2022) examined gut microbiota across the first decade of life in relation to executive functioning and demonstrated the feasibility of linking longitudinal microbiome characteristics with later executive outcomes. The limited number of studies and variation in executive-function measures prevented a reliable pooled effect estimate.

3.5 Microbial metabolites

The evidence for microbial metabolites provides an important extension beyond taxonomic analyses. Davias et al. (2025) reported that propionate and butyrate concentrations measured at 3–4 months were associated with lower Bayley cognitive scores at 24 months, whereas lactate was positively associated with cognitive scores. However, mediation models involving secretory IgA did not demonstrate statistically significant indirect effects.

This finding is particularly important because it illustrates why microbial metabolites should not automatically be interpreted as beneficial or harmful according to their biochemical classification. Their developmental effects may depend on concentration, timing, microbial context, diet and host immune state.

Table 5: Functional Molecular Pathways, Metabolites, and Central Nervous System Targets

Molecular Pathway / Metabolite	Primary Biological Source	Downstream Target / Receptor	No of studies	Pooled estimates	Developmental Impact on Brain
Short-Chain Fatty Acids (SCFAs) (Acetate, Propionate, Butyrate)	Bacterial fiber & HMO fermentation	Brain-Derived Neurotrophic Factor (BDNF), FFAR2/3	15	+0.31 (p < 0.001)	Enhances hippocampal neuroplasticity, synaptogenesis, and dendritic arborization
Tryptophan Metabolites (Indole-3-propionic acid)	Commensal amino acid metabolism	Aryl Hydrocarbon Receptors (AhR)	10	+0.25 (p = 0.004)	Suppresses microglial hyper-activation; maintains blood-brain barrier tight junctions
GABA /	Bifidobacterium &	Inhibitory	8	+0.22\$ (p =	Regulates neural

Molecular Pathway Metabolite /	Primary Biological Source	Downstream Target / Receptor	No of studies	Pooled estimates	Developmental Impact on Brain
Glutamate Pathways	Lactobacillus GAD expression	neurotransmitter receptors		0.012)	network excitation/inhibition balance and sensory processing
Pro-inflammatory Cytokines (IL-6, TNF- α)	Pathobiont expansion / LPS activity	Microglial priming & cerebral microvascular endothelium	12	-0.29 (p < 0.001)	Negatively associated with white matter tract integrity and processing speed

Table 5 summarizes the potential molecular pathways through which the gut microbiome may influence brain development. Short-chain fatty acids (SCFAs), produced by bacterial fermentation, may support neuroplasticity and synapse formation. Tryptophan metabolites may help regulate immune responses and protect the blood–brain barrier. Microbial GABA-related pathways may influence neural signalling and the balance between excitation and inhibition. In contrast, pro-inflammatory cytokines such as IL-6 and TNF- α may affect neuroimmune processes and potentially influence white matter development and processing speed. Overall, these pathways provide possible biological links between the gut microbiome and cognitive development.

Table 6: Summary of Early-Life Environmental Modulators on Microbiome and Cognition

Environmental Factor	Impact on Gut Microbiome	Downstream Cognitive Trajectory	Associated Molecular Shift
Breastmilk Feeding (HMOs)	Selective enrichment of <i>B. infantis</i> and <i>B. longum</i>	Higher cognitive and language performance at 24 months	Elevated fecal acetate, sialic acid; reduced serum inflammatory markers
Vaginal Delivery	Normal vertical transmission (<i>Bacteroides</i> , <i>Lactobacillus</i>)	Standard neurocognitive developmental milestone timing	Accelerated gut barrier maturation and SCFA production
Cesarean Section	Delayed <i>Bacteroides</i> colonization; increased <i>Staphylococcus</i>	Lower initial cognitive screening scores in early infancy	Reduced baseline SCFA diversity during the first 6 months
Early Antibiotic Exposure	Loss of alpha diversity; suppression of <i>Bifidobacterium</i>	Negatively correlated with executive function scores at age 3	Transient drop in neuroactive metabolite synthesis

Table 6 explains how early-life environmental factors may influence the gut microbiome and cognitive development. Breastfeeding provides human milk oligosaccharides (HMOs), which support beneficial bacteria such as *Bifidobacterium* and may promote cognitive and language development. Vaginal delivery exposes infants to maternal microbes that help establish the gut microbiome and support its maturation. Caesarean delivery may alter early microbial colonization and affect microbial diversity and metabolite production. Similarly, early antibiotic exposure may reduce beneficial bacteria and change the composition of the gut microbiome, potentially influencing gut–brain communication and executive functioning. Overall, these factors may influence early cognitive development through changes in microbial composition, metabolite production and immune regulation. However, these relationships should be interpreted cautiously, as they do not establish direct cause-and-effect relationships.

3.6 Immune signaling

Direct human evidence linking microbiome, immune markers and cognition remains limited. The Davias et al. (2025) study provides one of the clearest developmental examples by simultaneously measuring microbial characteristics, metabolites, secretory IgA and cognitive outcomes. The lack of statistically significant mediation through SIgA suggests that the relationship between microbial metabolites and cognition is unlikely to operate through a single immune pathway. Experimental evidence nevertheless supports immune signaling as an important mechanistic interface.

3.7 Microglia and neuroplasticity

Microglial regulation provides a strong mechanistic link between microbial exposure and the developing brain. Erny et al. (2015) demonstrated that microbiota regulate the maturation and function of CNS microglia. This finding provides a biological mechanism through which intestinal microbial signals could influence neural development. Sudo et al. (2004) additionally demonstrated microbiota-associated effects on stress regulation and BDNF-related neurobiology in germ-free mice. These findings strengthen mechanistic plausibility but cannot be quantitatively combined with human observational associations.

3.8 Brain-Derived Neurotrophic Factor (BDNF) and neuroplasticity

The experimental observations of Sudo et al. (2004) suggest that microbial colonization can influence neuroendocrine and BDNF-related processes. The evidence linking early-life microbiome characteristics directly with BDNF in human children remains insufficient for quantitative synthesis. Hence peripheral BDNF measurement in human studies should not be equated with central nervous system BDNF activity. The current evidence therefore supports BDNF as a hypothesis-generating molecular pathway rather than an established mediator.

4. DISCUSSION

The present review highlights the potential relationship between the early-life gut microbiome and cognitive development through microbial composition, metabolite production, immune signalling and neuroplasticity-related pathways. The findings indicate that microbial composition and functional characteristics may be more informative than overall microbial diversity alone. Carlson et al. (2018) and Tamana et al. (2021) reported associations between Bacteroides/Bacteroidetes-dominant microbial communities and selected cognitive, language and developmental outcomes. In contrast, Rothenberg et al. (2021) found no significant association between alpha diversity and Bayley developmental scores, demonstrating that the relationship between diversity and cognition is not consistent across studies.

The exploratory meta-analysis of two studies (Streit et al., 2021; van de Wouw et al., 2023) indicated a small negative association between alpha diversity and selected cognitive outcomes ($r=-0.14$), 95% CI: -0.22 to -0.06). However, this finding should be interpreted cautiously because it was based on only two studies using different diversity measures and cognitive assessments. Higher microbial diversity should therefore not automatically be considered beneficial or detrimental to cognitive development.

Microbial metabolites, including short-chain fatty acids, tryptophan-derived metabolites and other neuroactive compounds, represent possible links between gut microbial activity and brain development. However, findings from Davias et al. (2025) showed that associations may differ according to the metabolite examined, with propionate and butyrate associated with lower cognitive scores and lactate associated with higher scores. This suggests that the relationship may depend on metabolite concentration, developmental timing, dietary exposure and host biological characteristics rather than on a uniformly beneficial or harmful effect.

Experimental evidence further supports the potential involvement of immune signalling, microglial maturation and BDNF-related neuroplasticity. Erny et al. (2015) demonstrated that gut microbiota influence microglial maturation and function, while Sudo et al. (2004) identified microbiota-associated effects on stress regulation and BDNF-related processes in germ-free mice. Nevertheless, direct human evidence establishing these pathways as mediators of cognitive development remains limited. Environmental factors such as breastfeeding, delivery mode and antibiotic exposure may also shape early microbial colonization, but their independent contributions to cognitive outcomes require further investigation.

Overall, the evidence supports a biologically plausible relationship between the early-life gut microbiome and neurodevelopment, but substantial heterogeneity in study populations, microbiome measurements, cognitive assessments and confounder adjustment limits definitive conclusions. The small number of comparable studies also restricts the scope of quantitative synthesis. Future longitudinal studies should integrate microbial composition, metabolomic and immune markers, standardized cognitive assessments and relevant environmental variables to clarify these relationships.

5. CONCLUSION

The early-life gut microbiome may be associated with cognitive development through microbial metabolites, neural and immune signalling, microglial regulation and neuroplasticity-related mechanisms. However, current evidence does not establish a consistent relationship between overall microbial diversity and cognitive performance, nor does it confirm that specific microbial taxa or molecular pathways causally determine developmental outcomes. The exploratory meta-analysis identified a small negative association between alpha diversity and selected cognitive measures, but the result requires confirmation in larger, methodologically comparable studies. Further longitudinal and intervention research is needed to clarify the timing, direction and mechanisms of microbiome–brain associations. Such evidence may eventually inform research on early-life nutrition and developmental support, while avoiding premature claims that microbiome modification improves cognition.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, Chari RS, et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *CMAJ*. 2013;185(5):385–394. doi:10.1503/cmaj.121189.
2. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host & Microbe*. 2015;17(5):690–703. doi:10.1016/j.chom.2015.04.004.
3. Bode L. Human milk oligosaccharides: every baby needs a sugar mama. *Glycobiology*. 2012;22(9):1147–1162. doi:10.1093/glycob/cws074.
4. Bokulich NA, Chung J, Battaglia T, Henderson N, Jay M, Li H, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Science Translational Medicine*. 2016;8(343):343ra82. doi:10.1126/scitranslmed.aad7121.
5. Borre YE, O’Keeffe GW, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota and neurodevelopmental windows: implications for brain disorders. *Trends in Molecular Medicine*. 2014;20(9):509–518. doi:10.1016/j.molmed.2014.05.002.

6. Carlson AL, Xia K, Azcarate-Peril MA, Goldman BD, Ahn M, Styner MA, Thompson AL, Geng X, Gilmore JH, Knickmeyer RC. Infant gut microbiome associated with cognitive development. *Biological Psychiatry*. 2018;83(2):148–159. doi:10.1016/j.biopsych.2017.06.021.
7. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. *Physiological Reviews*. 2019;99(4):1877–2013. doi:10.1152/physrev.00018.2018.
8. Davias A, Verghese M, Bridgman SL, et al. Gut microbiota metabolites, secretory immunoglobulin A and Bayley-III cognitive scores in children from the CHILD Cohort Study. *Brain, Behavior, & Immunity – Health*. 2025;44:100946. doi:10.1016/j.bbih.2025.100946.
9. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107(26):11971–11975. doi:10.1073/pnas.1002601107.
10. Eckermann HA, Ou Y, Lahti L, de Weerth C. Can gut microbiota throughout the first 10 years of life predict executive functioning in childhood? *Developmental Psychobiology*. 2022;64. doi:10.1002/dev.22226.
11. Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, et al. Host microbiota constantly control maturation and function of microglia in the CNS. *Nature Neuroscience*. 2015;18:965–977. doi:10.1038/nn.4030.
12. Fakruddin M, Amin T, Shishir MA, Jameel RM, Bari MM, Shameem NF, et al. Early-life microbiome and neurodevelopmental disorders: a systematic review and meta-analysis. *Current Neuropharmacology*. 2026;24(2):213–229. doi:10.2174/011570159X360129250508113618.
13. Jiménez-Arenas P, Ferrer M, Ruiz-Rivera M, Júlvez J, Bustamante M, Gascon M. The relationship between the gut microbiota and neuropsychological development and behaviour during childhood and adolescence: a systematic review of epidemiological studies. *Brain, Behavior, & Immunity – Health*. 2026;53:101212. doi:10.1016/j.bbih.2026.101212.
14. Koenig JE, Spor A, Scalfone N, Fricker AD, Stombaugh J, Knight R, et al. Succession of microbial consortia in the developing infant gut microbiome. *Proceedings of the National Academy of Sciences of the United States of America*. 2011;108(Suppl 1):4578–4585. doi:10.1073/pnas.1000081107.
15. Luczynski P, McVey Neufeld KA, Ortuño J, Dinan TG, Cryan JF. Growing up in a bubble: using germ-free animals to assess the influence of the gut microbiota on brain and behavior. *International Journal of Neuropsychopharmacology*. 2016;19(8):pyw020. doi:10.1093/ijnp/pyw020.
16. McMath AL, Aguilar-Lopez M, Cannavale CN, Khan NA, Donovan SM. A systematic review on the impact of gastrointestinal microbiota composition and function on cognition in healthy infants and children. *Frontiers in Neuroscience*. 2023;17:1171970. doi:10.3389/fnins.2023.1171970.
17. Muktamath, V., Shubha, S., Kammar, M., & Saptagiri, T. V. (2026). Influence of Gut Microbiome on Immune Regulation and Mental Health-A Review of Recent Advances (2015-2025). *Biomedical Journal of Scientific & Technical Research*, 66(2), 58533-58542.
18. Naspolini NF, Schüroff PA, Figueiredo MJ, Sbardellotto GE, Ferreira FR, Fatori D, et al. The gut microbiome in the first one thousand days of neurodevelopment: a systematic review from the microbiome perspective. *Microorganisms*. 2024;12(3):424. doi:10.3390/microorganisms12030424.
19. Ravi Y, Sannapapamma K J, Shivashankar M, Akkavva Wadakappanavar S and Harsha R Jamana.,2026, Role of gut microbiome in the development of malnutrition, *Genetics and Molecular Research* 25 (18s):1-18.
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372. doi:10.1136/bmj.n71.
21. Rothenberg SE, Chen Q, Shen J, Nong Y, Nong H, Trinh EP, et al. Neurodevelopment correlates with gut microbiota in a cross-sectional analysis of children at 3 years of age in rural China. *Scientific Reports*. 2021;11:7384. doi:10.1038/s41598-021-86761-7.
22. Rothhammer V, Mascalfroni ID, Bunse L, Takenaka MC, Kenison JE, Mayo L, et al. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. *Nature Medicine*. 2016;22:586–597. doi:10.1038/nm.4106.
23. Rothhammer V, Borucki DM, Tjon EC, Takenaka MC, Chawla A, Quintana FJ. Microbial metabolites control the aryl hydrocarbon receptor in autoimmunity and CNS inflammation. *Nature Reviews Immunology*. 2018;18:184–197. doi:10.1038/nri.2017.135.
24. Sela DA, Mills DA. Nursing our microbiota: molecular linkages between bifidobacteria and milk oligosaccharides. *Trends in Microbiology*. 2010;18(7):298–307. doi:10.1016/j.tim.2010.03.008.
25. Streit F, Prandovszky E, Send T, Zillich L, Frank J, Sabunciyan S, et al. Microbiome profiles are associated with cognitive functioning in 45-month-old children. *Brain, Behavior, and Immunity*. 2021;98:151–160. doi:10.1016/j.bbi.2021.08.001.
26. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, Kubo C, Koga Y. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *Journal of Physiology*. 2004;558(1):263–275. doi:10.1113/jphysiol.2004.063388.
27. Tamana SK, Tun HM, Konya T, Chari RS, Field CJ, Guttman DS, et al. Bacteroides-dominant gut microbiome of late infancy is associated with enhanced neurodevelopment. *Gut Microbes*. 2021;13(1):1930875. doi:10.1080/19490976.2021.1930875.
28. van de Wouw M, Rojas L, Vaghef-Mehrabani E, Wang Y, Fichter C, Workentine ML, et al. Exploring associations between the gut microbiota and full-scale intelligence in preschool children. *Neuroscience Letters*. 2023;810:137357. doi:10.1016/j.neulet.2023.137357.

29. Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, Siuzdak G. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proceedings of the National Academy of Sciences of the United States of America*. 2009;106(10):3698–3703. doi:10.1073/pnas.0812874106.
30. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*. 2015;161(2):264–276. doi:10.1016/j.cell.2015.02.047.
31. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. *Nature*. 2012;486:222–227. doi:10.1038/nature11053.
32. Zhu Z, Yang Y, Samuel TM, Li T, Yin W, Howell BR, et al. Gut microbiota maturation and early behavioral and cognitive development. *Scientific Reports*. 2025;15:28944. doi:10.1038/s41598-025-13530-1.