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Early-Life Exposure to General Anesthesia and Gut Microbiome Dysbiosis in Children: A Systematic Review

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Abstract

Early-life exposure to general anaesthesia and surgery may alter gastrointestinal microbial development, although the independent effects of anaesthetic agents and the persistence of associated disturbances remain uncertain. This systematic review evaluated changes in gut microbiome composition, microbial diversity, metabolic characteristics, intestinal barrier function, and postoperative recovery among children exposed to general anaesthesia and surgery. PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane CENTRAL were searched from inception to September 26, 2026. Study selection followed PRISMA 2020, risk of bias was assessed using ROBINS-I, evidence certainty was evaluated using GRADE, and findings were synthesised narratively following SWiM guidelines. Thirteen studies involving 523 children from seven countries were included. Compositional alterations involved reduced Bifidobacterium, Bacteroides, and Lactobacillus, alongside increased Enterococcus and Enterobacteriaceae. Six of eight studies reported reduced alpha diversity, while six of seven identified altered beta diversity. Short-chain fatty acid reductions and intestinal barrier disturbances were also reported. Evidence concerning long-term persistence was inconsistent. Ten studies had serious risk of bias, two moderate, and one critical; evidence certainty was low or very low. Perioperative dysbiosis was associated with anaesthesia and surgery, but anaesthesia-specific causality remains unestablished.

Keywords: *cardiopulmonary bypass, dysbiosis, general anesthesia, gut microbiome, systematic review.*

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INTRODUCTION

General anaesthesia constitutes an essential component of paediatric healthcare, enabling surgical and diagnostic interventions during infancy and early childhood, when neurological, immunological, and gastrointestinal systems remain developmentally vulnerable. Contemporary paediatric anaesthetic practice encompasses a broad spectrum of procedures involving neonates, infants, and young children, while continuing scientific debate concerns the biological consequences of exposure during critical developmental periods (Srinivasan et al., 2024; Salaün et al., 2026). Evidence from the General Anaesthesia compared to Spinal Anaesthesia (GAS) trial indicates that a single, relatively brief exposure to sevoflurane-based general anaesthesia during infancy does not produce detectable differences in the neurodevelopmental outcomes evaluated at two and five years, although these findings do not resolve questions concerning repeated exposure or biological effects outside the central nervous system (Davidson et al., 2016; McCann et al., 2019). The gastrointestinal microbiome represents a particularly relevant but comparatively underexamined biological system because microbial colonisation undergoes substantial structural and functional maturation during the first three years of life, influencing mucosal immunity, intestinal barrier development, microbial metabolism, and communication along the microbiota–gut–brain axis (Cryan et al., 2019; Pantazi et al., 2023). Alterations in early microbial colonisation may have developmental implications, as demonstrated by associations between early-life antibiotic exposure and subsequent childhood weight trajectories, although such associations cannot establish comparable effects of anaesthetic exposure (Mbakwa et al., 2016). Microbial disturbances involving facultative organisms and reductions in beneficial anaerobic populations are also relevant to intestinal inflammatory vulnerability in neonates, particularly in relation to necrotising enterocolitis (Neu & Pammi, 2018). Paediatric perioperative care introduces multiple exposures capable of modifying microbial ecology, including anaesthetic agents,

surgical stress, antimicrobial prophylaxis, opioid administration, interrupted enteral nutrition, and postoperative intensive care, with opioid-associated microbial dysbiosis providing an additional mechanistic concern (Thomas et al., 2022). The intersection of developmental microbiology and paediatric anaesthesiology consequently raises a clinically consequential question concerning whether perioperative microbial alterations reflect direct anaesthetic effects, accompanying surgical interventions, or their combined biological influences.

Current knowledge concerning anaesthesia-associated intestinal microbial disturbances derives from two partially overlapping research streams: controlled preclinical investigations and observational clinical studies involving heterogeneous paediatric surgical populations. Experimental evidence demonstrates that general anaesthesia can modify intestinal microbial diversity and composition independently of surgical intervention, while neonatal exposure to isoflurane or repeated sevoflurane has been associated with subsequent dysbiosis and neurobehavioural alterations in animal models (Serbanescu et al., 2019; Wang et al., 2019; Liu et al., 2021). Repeated early-life anaesthesia and surgery have likewise been linked to anxiety-like behaviours and microbial community disturbances in juvenile rats, while experimental manipulation of gut microbiota and supplementation with eicosapentaenoic acid have provided further evidence concerning the potential involvement and modifiability of microbiota-associated neurodevelopmental pathways (Zhou et al., 2023; Chaki et al., 2025; Fan et al., 2025). Clinical investigations, however, predominantly examine microbial changes surrounding complex surgical exposures rather than isolated administration of anaesthetic agents. Research involving paediatric cardiopulmonary bypass has examined intestinal bacterial composition, microbial diversity, gastrointestinal permeability, inflammatory responses, and postoperative physiological disturbances, establishing a substantial observational foundation for evaluating perioperative microbial ecology (Salomon et al., 2021; Jiang et al., 2024; Owens et al., 2024; Zhang et al., 2024; Koc et al., 2025; Agzamova & Babadjanova, 2026). Longitudinal observations have also addressed postoperative microbial trajectories, while investigations involving adenotonsillectomy and palatoplasty extend the clinical evidence beyond cardiac surgery and provide opportunities to consider differences in operative characteristics and follow-up intervals (Vieira et al., 2013; Chuang et al., 2024; Yin et al., 2024). Research on repeated anaesthetic exposure in childhood offers a distinct comparison between previously exposed and never-exposed populations, although interpretation remains dependent on the comparability of their underlying clinical histories (Yang et al., 2023). Perioperative probiotic trials have evaluated the feasibility of modifying intestinal microbial disturbances and associated gastrointestinal outcomes, providing intervention-based evidence without directly randomising anaesthetic exposure (Umenai et al., 2014; Toritsuka et al., 2024; Zhang et al., 2026). Collectively, these research streams support the biological plausibility of perioperative microbiome alterations while demonstrating considerable differences in exposure definition, comparator selection, microbial measurement, and causal interpretability.

A fundamental research gap persists between documenting perioperative microbial alterations and establishing whether general anaesthesia independently contributes to intestinal dysbiosis during early childhood. Most available clinical investigations involve children undergoing surgery and compare microbial measurements obtained before and after the procedure, thereby combining the potential effects of anaesthetic administration with surgical injury, antibiotic prophylaxis, fasting, altered feeding, analgesic exposure, and postoperative clinical management (Salomon et al., 2021; Owens et al., 2024; Koc et al., 2025). This attribution problem is particularly pronounced in congenital heart disease, where intestinal microbial disturbances may already be present before surgical intervention and may be influenced by altered systemic oxygenation, intestinal perfusion, underlying disease severity, and inflammatory physiology (Huang et al., 2022; Renk et al., 2024). Associations between microbial characteristics and postoperative complications, including feeding intolerance, acute lung injury, and neurodevelopmental outcomes, therefore require careful separation of potential causal effects from disease-related confounding and prognostic relationships (Jiang et al., 2024; Fundora et al., 2026). Additional methodological limitations arise from differences in sampling schedules, sequencing approaches, bacterial quantification methods, microbial diversity indices, and the treatment of longitudinal observations, which complicate direct comparisons across studies. Research involving gastrointestinal surgical conditions introduces a separate problem because intestinal resection, diversion, reconstruction, and disease-specific anatomical disturbances can independently alter microbial composition, limiting the relevance of these populations for isolating

perioperative anaesthetic effects (Rao et al., 2020; Lin et al., 2023; Barreiros-Mota et al., 2023; Chantakhow et al., 2026). Investigations restricted to microbial metabolites provide valuable information concerning microbial function but cannot independently establish compositional dysbiosis when direct community measurements are unavailable (Leroue et al., 2025). Human comparisons involving different anaesthetic agents have identified microbiome-related differences in adult intestinal samples and paediatric oral microbial communities, although neither population–measurement combination resolves the effects of anaesthetic techniques on the developing intestinal microbiome of young children (Liu et al., 2022; Xie et al., 2024; Wang et al., 2025). The unresolved questions consequently concern the independence of anaesthetic effects from perioperative co-exposures, the consistency of microbial alterations across measurement methods, and the persistence of changes beyond the immediate postoperative period.

The scientific and clinical significance of these limitations lies in the possibility that transient perioperative disturbances and sustained alterations during early microbial development may have different biological implications, despite appearing similar when assessed through isolated postoperative samples. Microbial community composition, functional metabolites, intestinal epithelial integrity, and systemic inflammatory responses represent related but non-equivalent dimensions of gastrointestinal health, requiring careful interpretation when evaluating potential consequences of early-life perioperative exposure (Cryan et al., 2019; Pantazi et al., 2023; Neu & Pammi, 2018). Clinical associations between dysbiosis, reduced short-chain fatty acids, intestinal barrier dysfunction, and feeding intolerance suggest that microbial measurements may provide information concerning postoperative gastrointestinal vulnerability, particularly among children undergoing complex cardiac procedures (Salomon et al., 2021; Owens et al., 2024; Agzamova & Babadjanova, 2026). The underlying congenital condition and its physiological consequences nevertheless remain major potential determinants of both microbiome characteristics and clinical outcomes, preventing direct interpretation of these associations as evidence of anaesthetic-induced injury (Huang et al., 2022; Renk et al., 2024). Existing evaluations of the interaction between cardiopulmonary bypass, intestinal microbiota, and immune dysregulation highlight the complexity of combining microbial and inflammatory evidence in this population, while broader discussions of postoperative intestinal dysbiosis demonstrate the additional interpretative difficulties introduced by gastrointestinal pathology and surgical anatomical modification (Prout et al., 2025; Vaou et al., 2026). Evidence concerning perioperative probiotic supplementation indicates that some microbial and gastrointestinal outcomes may be responsive to intervention, although variability across clinical populations and treatment protocols limits generalisation and does not establish whether the initiating disturbance originates from anaesthesia itself (Umenai et al., 2014; Toritsuka et al., 2024; Zhang et al., 2026; Alansari et al., 2026). Failure to distinguish these mechanisms risks overstating the biological hazards of necessary paediatric anaesthesia, obscuring modifiable elements of perioperative care, and weakening the interpretation of subsequent developmental outcomes. A rigorous synthesis separating observable microbial disturbances from causal attribution is therefore necessary to establish the evidentiary boundaries of current clinical knowledge and identify which perioperative factors warrant more controlled investigation.

The present systematic review is positioned at the intersection of developmental microbiome research, paediatric perioperative medicine, and evidence-based evaluation of non-randomised clinical exposure studies. Its specific contribution lies in applying an exposure-attribution framework that distinguishes comparisons involving children with and without previous general anaesthesia, cardiac procedures involving cardiopulmonary bypass, and non-cardiac extra-abdominal surgical interventions, rather than treating all postoperative microbial disturbances as equivalent evidence of anaesthetic effects. This approach differs substantively from broader examinations of intestinal dysbiosis following paediatric gastrointestinal surgery and from reviews focused principally on cardiopulmonary bypass-associated inflammatory mechanisms, because it explicitly evaluates whether the available clinical comparisons support inference about anaesthetic exposure rather than the perioperative treatment bundle (Prout et al., 2025; Vaou et al., 2026). Excluding procedures that directly modify gastrointestinal anatomy addresses an important source of conceptual and clinical heterogeneity identified in studies involving neonatal intestinal surgical disorders, enterostomy, and postoperative enterocolitis (Rao et al., 2020; Barreiros-Mota et al., 2023; Chantakhow et al., 2026). The analytical framework also differentiates microbial taxonomic composition, alpha diversity, beta

diversity, short-chain fatty acids, longitudinal persistence, and intestinal barrier or inflammatory markers, recognising that these outcomes capture different biological properties and cannot automatically be combined into a single measure of dysbiosis. Methodological transparency is strengthened through systematic reporting according to PRISMA 2020, structured synthesis without meta-analysis under SWiM, domain-based assessment of bias using ROBINS-I, and outcome-specific evaluation of evidence certainty using GRADE (Page et al., 2021; Campbell et al., 2020; Sterne et al., 2016; Guyatt et al., 2008). The distinction between randomisation of a perioperative intervention and randomisation of the exposure under review is especially relevant when interpreting probiotic trials, because methodological appraisal must correspond to the causal comparison being investigated rather than the nominal study design (Sterne et al., 2019; Toritsuka et al., 2024; Zhang et al., 2026). The proposed contribution is consequently not the introduction of an untested biological mechanism, but a structured and critically appraised synthesis that clarifies the strength, consistency, limitations, and clinical interpretation of existing evidence concerning early-life anaesthesia-associated intestinal microbial disturbances.

This systematic review aims to critically evaluate changes in gut microbiome composition, alpha diversity, and beta diversity associated with exposure to general anaesthesia and surgery during infancy and early childhood, while examining the relationship of these alterations to microbial metabolic characteristics, intestinal barrier integrity, inflammatory responses, and postoperative recovery. The review specifically seeks to determine the consistency and direction of reported microbial changes across clinically distinct exposure groups, assess whether existing comparison designs permit separation of anaesthetic effects from surgical procedures and accompanying perioperative interventions, and evaluate the available evidence concerning persistence or restoration of microbial communities beyond the immediate postoperative period. A further objective is to identify methodological and clinical factors that influence the interpretation of reported outcomes, including the type of surgical procedure, cardiopulmonary bypass exposure, cumulative anaesthetic exposure, microbial measurement methods, and the timing of sample collection. These objectives are addressed through systematic identification and appraisal of eligible clinical investigations, structured narrative synthesis across predefined outcome domains, and explicit assessment of methodological limitations and evidence certainty. The principal scientific contribution is an integrated assessment that distinguishes the observed association between perioperative exposure and intestinal dysbiosis from the unresolved question of whether anaesthetic agents exert independent effects on the developing gut microbiome. The methodological contribution consists of an outcome-specific and exposure-stratified synthesis that preserves important differences between study designs without imposing potentially misleading pooled estimates across incompatible measurements. The anticipated practical contribution is to clarify the evidentiary basis for interpreting perioperative microbiome alterations in paediatric healthcare, identify potentially modifiable elements of perioperative management, and establish research priorities for prospective studies incorporating appropriate anaesthetised comparators, standardised microbial assessments, systematic measurement of co-exposures, and longitudinal follow-up. These contributions are intended to support more precise scientific conclusions and better-informed clinical research without extending causal claims beyond the available evidence.

RESEARCH METHODS

This study employed a systematic review design using a structured narrative synthesis to evaluate associations between exposure to general anaesthesia and surgery during infancy or early childhood and subsequent alterations in the gastrointestinal microbiome. The review followed a protocol established before study screening and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement, with synthesis procedures guided by the Synthesis Without Meta-analysis (SWiM) reporting framework (Page et al., 2021; Campbell et al., 2020). Literature searches were conducted in five electronic databases, comprising PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL), covering database inception through September 26, 2026, without restrictions on publication date or language. The search strategy combined three conceptual domains using the Boolean operator AND: exposure to general anaesthesia, including specific volatile and intravenous anaesthetic agents, surgical procedures, perioperative interventions, and cardiopulmonary

bypass; gastrointestinal microbiome characteristics, including microbiota, dysbiosis, and 16S ribosomal RNA sequencing; and paediatric populations encompassing infancy and early childhood. Controlled vocabulary and synonymous free-text terms were combined using OR within each conceptual domain. Eligible studies included randomised controlled trials, non-randomised comparative investigations, and prospective or retrospective observational cohorts involving children exposed to general anaesthesia for surgical or diagnostic procedures, provided that gastrointestinal or faecal microbiome outcomes were assessed against an unexposed or less-exposed comparison group or the participants' own pre-exposure measurements. Studies involving gastrointestinal resection, diversion, reconstruction, enterostomy, pull-through procedures, or portoenterostomy were excluded because direct anatomical modification could independently influence intestinal microbial composition. Investigations assessing exclusively oral, respiratory, or other non-intestinal microbial communities were excluded, together with animal experiments, literature reviews, study protocols without results, correspondence, case reports, and publications lacking eligible comparative or longitudinal microbiome measurements. Included reports were additionally required to have a resolvable PubMed identifier and to be published in Scopus-indexed journals or by major peer-reviewed publishers. The database searches identified 705 records, comprising 146 from PubMed/MEDLINE, 198 from Embase, 171 from Scopus, 132 from Web of Science, and 58 from CENTRAL. Following removal of 201 duplicate records, 504 records underwent title and abstract screening, of which 414 were excluded. Ninety reports were sought for full-text retrieval; three could not be obtained, leaving 87 reports for eligibility assessment. Seventy-four reports were excluded according to the predefined criteria, resulting in 13 eligible studies involving 523 children from seven countries. Both reviewers independently screened titles and abstracts, assessed retrieved full-text reports, and resolved disagreements through discussion without third-party adjudication. Reference lists of included studies and relevant published reviews were examined for additional eligible publications, while trial registries were consulted for related registrations and ongoing investigations; forward citation searching was not performed.

Data extraction was performed independently by both reviewers using a piloted extraction form, with discrepancies reconciled against the original publications to maintain consistency and traceability. The extracted information included study identification, publication characteristics, country, research design, participant population and age range, sample size and comparison groups, anaesthetic and surgical exposures, number and duration of exposures when reported, comparator characteristics, faecal sampling schedules, microbiome measurement methods, sequencing platforms, hypervariable regions, bioinformatic procedures, microbial diversity indices, reported quantitative outcomes, and methodological characteristics relevant to critical appraisal. Unreported numerical values were recorded as unavailable rather than estimated or reconstructed. The unit of analysis was the individual eligible study, with outcome-specific extraction organised according to reported clinical comparisons and measurement periods. Studies were categorised into three exposure strata: general anaesthesia exposure compared with no previous exposure, cardiac surgery involving cardiopulmonary bypass, and non-cardiac extra-abdominal surgical procedures. Outcomes were classified into six predefined domains: gastrointestinal microbial composition and taxonomic abundance; alpha diversity; beta diversity and microbial community structure; short-chain fatty acid concentrations and associated microbial taxa; persistence and recovery of microbial alterations; and intestinal barrier, inflammatory, and immune markers. Methodological quality was evaluated using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) instrument across seven domains encompassing confounding, participant selection, exposure classification, deviations from intended exposure, missing data, outcome measurement, and selection of reported results (Sterne et al., 2016). ROBINS-I was applied to all included studies because general anaesthesia and surgical exposure were not randomly allocated, including in the three trials in which randomisation concerned perioperative probiotic supplementation rather than the exposure of interest. Overall risk-of-bias judgements were determined by the highest-risk domain, while methodological features of probiotic allocation were described separately to avoid conflating intervention randomisation with anaesthetic exposure assignment. Certainty of evidence was assessed for each outcome domain using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, with non-randomised exposure evidence initially classified as low certainty and evaluated for limitations involving risk of bias, inconsistency, indirectness, imprecision, and publication bias (Guyatt et al.,

2008). Evidence synthesis followed SWiM principles through structured comparisons of the direction, consistency, and clinical interpretation of reported findings across exposure strata, microbiome measurement techniques, diversity metrics, and postoperative sampling intervals. Quantitative meta-analysis was not undertaken because differences in exposure definitions, comparator groups, sequencing approaches, measurement indices, and follow-up schedules prevented the construction of sufficiently comparable pooled effect estimates. Methodological rigour was supported by independent study selection and data extraction, reconciliation against full-text publications, explicit documentation of eligibility decisions, domain-specific risk-of-bias assessment, outcome-level certainty appraisal, and preservation of reported numerical values without imputation. The review analysed previously published aggregate data without direct recruitment of human participants or access to identifiable individual-level information.

RESULTS AND DISCUSSION

Study Selection, Characteristics, and Methodological Distribution of the Evidence

The systematic literature search identified 705 records across five electronic databases, reflecting the multidisciplinary distribution of research concerning paediatric anaesthesia, perioperative gastrointestinal disturbances, and intestinal microbial ecology. Embase contributed the largest number of records (n = 198), followed by Scopus (n = 171), PubMed/MEDLINE (n = 146), Web of Science (n = 132), and Cochrane CENTRAL (n = 58). The distribution indicates that potentially relevant evidence was dispersed across biomedical, clinical, and interdisciplinary indexing systems, supporting the use of multiple databases rather than reliance on a single bibliographic source. The identification and selection procedures were organised according to the PRISMA 2020 reporting framework to distinguish records initially retrieved from reports subsequently assessed for eligibility (Page et al., 2021).

Removal of 201 duplicate records reduced the initial dataset to 504 unique records eligible for title and abstract screening, corresponding to approximately 71.5% of the records originally identified. Screening excluded 414 records that did not satisfy the review criteria, leaving 90 reports requiring full-text retrieval and assessment. Three reports could not be retrieved, and the remaining 87 underwent full-text eligibility evaluation, during which 74 were excluded for predefined methodological or population-related reasons. The final inclusion of 13 studies demonstrates the narrow intersection between early-life general anaesthesia exposure and direct gastrointestinal microbiome measurement, despite the considerably broader literature addressing anaesthesia-associated neurodevelopmental outcomes and postoperative intestinal disturbances (McCann et al., 2019; Prout et al., 2025).

The full-text exclusion pattern provides information about the conceptual boundaries of the available evidence rather than representing only an administrative stage of the review. The most frequent exclusion categories involved the absence of an eligible early-life general anaesthesia exposure (n = 16), the absence of a gastrointestinal microbiome outcome (n = 15), and populations outside the specified paediatric developmental period (n = 10). Nine additional reports were excluded because major co-exposures or direct gastrointestinal surgical modifications prevented an interpretable assessment of the exposure addressed by the review. Studies involving neonatal gastrointestinal abnormalities, intestinal reconstruction, and postoperative enterocolitis illustrate why changes resulting from altered intestinal anatomy cannot be treated as equivalent to microbiome alterations following procedures that preserve gastrointestinal continuity (Rao et al., 2020; Lin et al., 2023; Barreiros-Mota et al., 2023; Chantakhow et al., 2026).

The numerical distribution of screening and eligibility decisions is presented in Table 1, which preserves the original identification, exclusion, and inclusion counts without adjustment. The table distinguishes reports that could not be retrieved from those excluded after full-text assessment, maintaining an important methodological separation between unavailable evidence and studies evaluated against the eligibility criteria. Its exclusion categories also identify recurring limitations concerning exposure classification, microbiome outcome measurement, comparator availability, and extractable information, all of which influence the interpretability of clinical findings. Transparent reporting of these decisions is consistent with the methodological principles of reproducible systematic reviews and structured evidence synthesis without meta-analysis (Page et al., 2021; Campbell et al., 2020).

Table 1. PRISMA 2020 Flow of Study Identification, Screening and Selection.

Stage	Detail	n
Records identified from databases	PubMed/MEDLINE	146
	Embase	198
	Scopus	171
	Web of Science	132
	Cochrane CENTRAL	58
Total records identified		705
Records removed before screening	Duplicate records	201
Records screened	Title and abstract screening	504
Records excluded	Clearly irrelevant on title and abstract	414
Reports sought for retrieval		90
Reports not retrieved	Full text unavailable	3
Reports assessed for eligibility	Full-text assessment	87
Reports excluded at full text	No early-life general anaesthesia exposure	16
	No gut microbiome or microbiota outcome	15
	Population not paediatric or outside the early-life age group	10
	Exposure not separable from surgery, antibiotics or other major co-exposures	9
	Review, protocol, conference abstract, editorial or other non-primary report	8
	No eligible comparator or longitudinal microbiome assessment	7
	Insufficient extractable microbiome or exposure data	5
	Duplicate or overlapping cohort	4
Total full-text reports excluded		74
Studies included in the review		13
Total participants	Children	523
Countries represented		7

The 13 eligible investigations collectively included 523 children from seven countries and were published between 2013 and 2026, providing a geographically distributed but methodologically heterogeneous evidence base. Ten studies examined children undergoing cardiac surgery involving cardiopulmonary bypass, two investigated non-cardiac extra-abdominal procedures, and one compared children with repeated early-life general anaesthesia exposure against never-exposed controls. The predominance of cardiac surgical populations indicates that available knowledge is concentrated among children experiencing substantial cardiovascular and inflammatory disturbances rather than among children undergoing routine elective anaesthesia without major physiological complications. This distribution is consistent with the clinical emphasis of investigations addressing cardiopulmonary bypass-associated microbial changes, intestinal barrier injury, and postoperative gastrointestinal dysfunction (Salomon et al., 2021; Owens et al., 2024; Koc et al., 2025; Agzamova & Babadjanova, 2026).

Differences in comparator selection created distinct levels of interpretative relevance for the review's central research question. The matched cohort involving repeated anaesthetic exposures compared children receiving at least three general anaesthetics before three years of age with children who had never undergone anaesthesia, providing a comparison that directly addressed exposure history but remained vulnerable to differences in underlying surgical indications and clinical characteristics (Yang et al., 2023). The concurrent surgical comparison involving cardiopulmonary bypass and major non-cardiac operations provided a different analytical advantage because both

groups underwent general anaesthesia and surgery, allowing additional examination of disturbances associated with bypass-related physiological stress (Salomon et al., 2021). Neither design independently isolated anaesthetic pharmacological effects, but their contrasting structures demonstrate why comparator characteristics must be evaluated before interpreting postoperative microbial differences as evidence of an anaesthesia-specific association.

The non-cardiac evidence included children undergoing adenotonsillectomy for obstructive sleep apnoea and palatoplasty for cleft palate, introducing surgical populations whose procedures did not directly reconstruct the gastrointestinal tract. These investigations broadened the clinical scope beyond congenital heart disease and provided information from different postoperative observation periods, including early postoperative measurement and follow-up extending to 12 months (Vieira et al., 2013; Chuang et al., 2024). Differences in underlying disease, antimicrobial prophylaxis, nutritional conditions, and postoperative recovery nevertheless complicate comparisons between these populations and children receiving cardiopulmonary bypass. The relevance of disease-related confounding is further supported by evidence that children with congenital heart disease may exhibit intestinal microbial disturbances before surgery, potentially reflecting altered perfusion and oxygenation rather than exposure to anaesthesia itself (Huang et al., 2022; Renk et al., 2024).

Three included investigations incorporated randomised allocation to perioperative probiotic interventions, although randomisation did not concern general anaesthesia or the surgical procedures under examination. Their observational contribution to the review therefore consisted of perioperative microbial measurements and comparisons associated with exposure trajectories, while the randomised treatment contrasts addressed probiotic supplementation and gastrointestinal outcomes (Umenai et al., 2014; Toritsuka et al., 2024; Zhang et al., 2026). Distinguishing these analytical contrasts is necessary because random allocation to a preventive intervention does not remove confounding from an independently occurring anaesthetic or surgical exposure. The decision to assess bias in relation to the non-randomised exposure contrast follows the conceptual basis of ROBINS-I, while recognition of the separate randomised treatment comparison avoids transferring assumptions about treatment allocation to an exposure that was not randomised (Sterne et al., 2016; Sterne et al., 2019).

Microbiome measurement approaches differed substantially across the eligible investigations, limiting the direct comparability of their reported outcomes. Eight studies used 16S ribosomal RNA gene sequencing, four quantified selected bacterial taxa using culture-based or culture-independent approaches, and one did not specify its microbiome profiling platform, while sequencing investigations differed in hypervariable regions, analytical pipelines, and diversity indices. Differences in sampling intervals introduced further heterogeneity because early postoperative observations, measurements at three or twelve months, and assessments at school age represent biologically distinct stages of microbial development and potential recovery. The importance of developmental timing is supported by evidence that intestinal colonisation and microbial community maturation undergo substantial changes throughout early childhood, making age and measurement interval essential considerations when interpreting taxonomic abundance and diversity (Pantazi et al., 2023; Cryan et al., 2019).

The methodological distribution of the included studies establishes a necessary distinction between evidence demonstrating perioperative microbial associations and evidence capable of supporting independent causal attribution to general anaesthesia. The concentration of studies in cardiopulmonary bypass populations, limited availability of appropriately anaesthetised comparators, and variation in microbiome measurement methods indicate that clinical and methodological heterogeneity must inform subsequent interpretation of microbial composition, diversity, and persistence. Structured synthesis across exposure categories and outcome domains is consequently more defensible than treating the available investigations as interchangeable observations or generating pooled estimates from incompatible measurements, consistent with the principles of SWiM reporting (Campbell et al., 2020). These characteristics provide the analytical basis for evaluating the direction and consistency of reported intestinal microbial disturbances while preserving the distinction between anaesthetic exposure, surgical stress, disease-related physiological differences, and other perioperative determinants (Salomon et al., 2021; Yin et al., 2024; Koc et al., 2025).

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Gut Microbiome Composition, Microbial Diversity, and Community Structure Following Early-Life Anaesthesia and Surgery

Alterations in gastrointestinal microbial composition represent the most consistently reported microbiological outcome across the 13 included investigations involving 523 children, although the biological interpretation of these changes varies according to the underlying clinical exposure. The principal compositional pattern involves reductions in bacterial groups commonly associated with early intestinal colonisation, particularly Bifidobacterium, Bacteroides, and Lactobacillus, alongside increased representation of Enterococcus, Escherichia-Shigella, and members of the Enterobacteriaceae family. These alterations are biologically relevant because the establishment of anaerobic microbial populations during infancy contributes to gastrointestinal ecological maturation, microbial metabolic activity, and the development of host–microorganism interactions that regulate intestinal homeostasis (Pantazi et al., 2023; Cryan et al., 2019). The consistency of directional changes across different surgical populations nevertheless requires interpretation as an association with the broader perioperative exposure rather than as evidence that anaesthetic agents independently produce microbial dysbiosis.

Quantitative findings from paediatric cardiopulmonary bypass populations provide a more specific description of these compositional disturbances, particularly concerning the redistribution of dominant intestinal bacterial taxa during the postoperative period. In a cohort of 20 infants undergoing cardiopulmonary bypass, the relative abundance of Enterococcus increased from 37.14% before surgery to 49.63% after surgery, whereas Bifidobacterium decreased from 20.71% to 12.59%, indicating a pronounced shift between facultative bacterial populations and organisms associated with early-life intestinal microbial development (Zhang et al., 2024). Comparable compositional differences were observed in a probiotic intervention trial, where Actinobacteriota declined from 14.46% to 5.08% in the placebo group, while another cardiac surgical cohort reported an increase in Escherichia-Shigella from 31% to 35% and postoperative Enterococcus abundance reaching 11% (Zhang et al., 2026; Koc et al., 2025). These findings demonstrate changes in the relative representation of microbial groups, but their interpretation remains constrained by the compositional nature of sequencing-derived abundance data, which cannot independently establish corresponding increases or decreases in absolute bacterial concentrations.

The biological implications of these taxonomic changes extend beyond identifying bacterial genera that increase or decrease after surgery, particularly when microbial disturbances occur during early intestinal development. Bifidobacterium contributes to the utilisation of substrates available during infancy and participates in establishing microbial metabolic conditions associated with intestinal ecological development, while Bacteroides forms part of the succession towards more complex anaerobic communities (Pantazi et al., 2023). Conversely, increased representation of facultative organisms and Enterobacteriaceae is relevant to clinical observations involving intestinal inflammation and disturbed microbial colonisation among vulnerable neonatal populations, although the presence of these organisms does not independently establish pathological infection or intestinal injury (Neu & Pammi, 2018). The association between congenital heart disease, impaired intestinal perfusion, and preoperative microbial disturbances further indicates that postoperative compositional patterns may reflect an interaction between baseline physiological vulnerability and perioperative treatment rather than a uniform response to general anaesthesia (Huang et al., 2022; Renk et al., 2024).

Variation in microbial measurement methods constitutes an additional interpretative challenge because sequencing-based community profiling and targeted bacterial quantification do not generate equivalent descriptions of gastrointestinal microbial ecology. Eight investigations employed 16S ribosomal RNA gene sequencing, whereas four relied on culture-based or culture-independent quantification of selected bacterial populations, and one did not specify its microbiome profiling platform. Sequencing studies differed in the amplified hypervariable region, analytical workflow, reference database, and diversity index, while targeted assays could quantify predetermined microbial groups without characterising broader community richness or intersample dissimilarity. These distinctions are particularly important when comparing the findings of studies using targeted quantification after palatoplasty or cardiac surgery with investigations examining microbial community structure through sequencing-based approaches (Vieira et al., 2013; Umenai et al., 2014; Chuang et al., 2024). Table 3 presents the original measurement classifications, sampling schedules,

and reported analytical methods, allowing differences in microbiological resolution and observation periods to be evaluated alongside the reported findings.

Table 3. How The Gut Microbiome Was Measured and When it Was Sampled

Study	Measurement class	Sampling schedule	Method as reported
Yang 2023	16S rRNA gene sequencing	One rectal sample per child at 6 to 9 years of age, at least three years after the last exposure	16S rRNA gene sequencing of the V4 to V5 region, Illumina NovaSeq 6000, 250 bp paired-end; alpha diversity in QIIME, weighted UniFrac principal coordinate analysis with ANOSIM and PERMANOVA, LEfSe with an LDA threshold above 3.6
Koc 2025	16S rRNA gene sequencing	Paired faecal samples before surgery and after surgery	16S rRNA gene sequencing, Illumina MiSeq with Reagent Kit v3, DADA2; alpha diversity by Shannon, Simpson and Chao1 with a rank test; beta diversity by Aitchison distance on centred log-ratio counts with PERMANOVA using adonis in vegan
Yin 2024	16S rRNA gene sequencing	Faecal samples before bypass, early after bypass, and one year after bypass	16S rRNA gene sequencing of the V3 to V4 region with primers 338F and 806R, Illumina NovaSeq; alpha diversity by Chao1 and Shannon on the amplicon sequence variant table; beta diversity by weighted UniFrac principal coordinate analysis with PERMANOVA
Owens 2024	Platform not specified in the report	Paired samples before surgery and after surgery	Gut microbiome profiling with plasma barrier markers, faecal and plasma short-chain fatty acids and plasma cytokines; the report does not specify the sequencing platform or the hypervariable region
Agzamova 2026	Culture-based quantification	Stool samples before surgery and during the early postoperative period	Culture-based quantitative microbiology of clinically relevant bacterial groups with faecal short-chain fatty acids by gas chromatography. The authors state that this gives lower taxonomic resolution than 16S rRNA gene sequencing or metagenomics
Jiang 2024	16S rRNA gene sequencing	Faecal samples on admission before surgery, with grouping by the postoperative outcome	16S rRNA gene sequencing of the V3 to V4 region with primers 343F and 798R, Illumina NovaSeq PE250, SILVA v138 at 70% confidence; Sobs and Shannon in Mothur with Wilcoxon rank-sum tests, weighted UniFrac principal coordinate analysis with PERMANOVA, PICRUSt2 functional prediction, random forest and receiver operating characteristic analysis
Salomon 2021	16S rRNA gene sequencing	Paired faecal samples before surgery and after surgery, with barrier	16S rRNA gene sequencing of the V4 region with primers U515F and 806R, Illumina MiSeq, taxonomy by BLAST

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		markers at baseline and at 24 and 48 hours	against SILVA v128; alpha diversity by operational taxonomic unit richness and Shannon index; beta diversity by Bray-Curtis and Jaccard similarity with permutational multivariate analysis of variance
Zhang 2024	16S rRNA gene sequencing	Faecal samples before and after bypass surgery	16S rRNA gene sequencing; the report does not specify the hypervariable region or the platform
Toritsuka 2024	Quantitative panel of named taxa	Serial faecal and blood sampling through the perioperative period to at least postoperative day 7	Microbiota analysis in faeces and blood with organic acid concentrations in faeces, plasma intestinal fatty acid binding protein and immunological assays; four perioperative microbiota clusters were derived
Zhang 2026	16S rRNA gene sequencing	Faecal samples within 24 hours before surgery and after surgery in both arms, giving four groups: control before, control after, treatment before, treatment after	16S rDNA sequencing of the V4 region with primers 515F and 806R, Illumina NovaSeq 6000; alpha diversity by Chao1, Pielou evenness, Shannon and Simpson in QIIME2; beta diversity by Jaccard and Bray-Curtis principal coordinate analysis with PERMANOVA; LEfSe and Metastats for differential taxa
Umenai 2014	Culture-independent quantitative panel	Faecal sampling from one week before surgery to one week after surgery	Culture-independent quantitative analysis of faecal bacterial counts with organic acid measurement; counts reported as log10 cells per gram
Chuang 2024	16S rRNA gene sequencing	Stool samples at baseline and again at 3 and 12 months after surgery, with in-laboratory polysomnography at the same visits	16S rRNA gene sequencing of the V3 to V4 region with primers 341F and 806R, Illumina MiSeq 300 bp paired-end; alpha diversity by Chao1, observed species, Shannon and Simpson; beta diversity by Bray-Curtis dissimilarity; Tax4Fun functional prediction and LEfSe with Benjamini-Hochberg correction
Vieira 2013	Culture-based quantification	Faecal samples before surgery and 24 hours after surgery	Selective culture and quantification of the anaerobes Bacteroides species and Bifidobacterium species and the microaerophile Lactobacillus species

Alpha diversity findings reveal a less uniform pattern than taxonomic composition, illustrating the methodological importance of distinguishing microbial richness from ecological evenness. Six of the eight studies reporting alpha diversity identified a significant reduction in at least one diversity measure following exposure or between comparison groups, whereas two studies found no statistically significant change in their reported indices. In the comparison between children undergoing cardiopulmonary bypass and those receiving major non-cardiac surgery under general anaesthesia, both microbial richness and Shannon diversity were significantly lower in the bypass group, with p-values below 0.001, suggesting that bypass-associated physiological disturbances contributed to differences beyond those associated with general anaesthesia and surgery alone (Salomon et al., 2021). This distinction limits the interpretation of reduced diversity as a direct pharmacological effect of anaesthesia because the more pronounced disturbance occurred in the population exposed to additional cardiovascular and inflammatory stress.

Differences between richness and evenness measures become particularly apparent in studies assessing microbial development beyond the immediate postoperative period. Following adenotonsillectomy, microbial richness measured using Chao1 and observed species indices declined significantly at three and twelve months, whereas Shannon and Simpson indices did not demonstrate corresponding significant alterations, indicating that a reduction in detectable taxa did not necessarily coincide with a comparable redistribution of relative abundance (Chuang et al., 2024). In children assessed at six to nine years of age after repeated early-life anaesthetic exposure, observed species, Chao1, and Shannon indices were not statistically significant, with p-values of 0.11, 0.09, and 0.06, respectively, while Simpson diversity reached statistical significance at $p = 0.024$ (Yang et al., 2023). These divergent results demonstrate that alpha diversity cannot be adequately characterised through a single index without considering the distinct ecological properties represented by richness and evenness measurements.

The absence of statistically significant alpha diversity alterations in selected cardiac surgical cohorts further challenges the assumption that perioperative dysbiosis necessarily produces a measurable reduction in microbial diversity. The GuMiBear investigation found no significant differences in Chao1, Shannon, or Simpson indices between preoperative and postoperative samples, despite reporting compositional characteristics relevant to congenital heart disease and cardiac surgery (Koc et al., 2025). A separate longitudinal investigation similarly found no significant early change in microbial diversity following cardiopulmonary bypass, with reported p-values of at least 0.227, indicating that perioperative taxonomic redistribution may occur without a corresponding reduction in conventional diversity indices (Yin et al., 2024). These findings suggest that microbial community disturbance is a multidimensional phenomenon in which taxonomic abundance, richness, and evenness may respond differently to surgical and physiological exposures.

Beta diversity provides complementary information by evaluating differences in microbial community structure between samples or comparison groups rather than measuring diversity within individual samples. Six of the seven investigations reporting beta diversity identified statistically significant community-level differences, using analytical approaches involving weighted UniFrac, Bray–Curtis, or Jaccard distances and permutation-based multivariate comparisons. The cohort comparing children with repeated early-life anaesthetic exposure against never-exposed peers identified significant differences in community structure through weighted UniFrac analysis, with the first two principal coordinates explaining 29.6% and 28.29% of the observed variability (Yang et al., 2023). The principal exception was the paired cardiopulmonary bypass cohort in which postoperative and preoperative microbial communities did not demonstrate statistically significant separation, indicating that the community-level response was not uniform across clinical populations (Koc et al., 2025).

The greater consistency of reported beta diversity differences relative to alpha diversity findings suggests that changes in microbial community membership and relative abundance may be detectable even when within-sample richness remains comparatively stable. This distinction is compatible with the developmental nature of intestinal microbial ecology, in which transitions between bacterial groups can alter community organisation without producing equivalent changes in the total number or distributional evenness of detected taxa (Pantazi et al., 2023; Cryan et al., 2019). Interpretation nevertheless requires consideration of the distance metric, sequencing methodology, and statistical approach because weighted phylogenetic distances, abundance-based dissimilarities, and presence–absence measures quantify different aspects of microbial community variation. The available evidence therefore supports an association between early-life perioperative exposure and altered gastrointestinal microbial structure, while differences in study design, baseline disease characteristics, and microbial measurement prevent attribution of this association specifically to anaesthetic agents (Salomon et al., 2021; Yin et al., 2024; Yang et al., 2023).

The synthesis of taxonomic composition, alpha diversity, and beta diversity demonstrates that gastrointestinal microbial alterations following paediatric anaesthesia and surgery are more consistently expressed through changes in bacterial abundance and community structure than through a uniform reduction in within-sample diversity. The repeated observation of reduced Bifidobacterium and Bacteroides alongside increased facultative bacterial populations is biologically plausible given the developmental importance of intestinal anaerobic colonisation, but these changes remain strongly influenced by pre-existing disease, surgical stress, antimicrobial exposure, and postoperative care

(Neu & Pammi, 2018; Huang et al., 2022; Salomon et al., 2021). Methodological heterogeneity further restricts direct quantitative comparison because studies differ in microbial detection platforms, sampling intervals, sequencing regions, and diversity metrics, making a pooled effect estimate potentially misleading. The most defensible interpretation is that early-life anaesthesia and surgery are associated with measurable disturbances in intestinal microbial ecology, while the magnitude, ecological significance, and independent contribution of anaesthetic administration remain insufficiently established by the available clinical evidence.

Methodological Risk of Bias, Clinical Consequences, and Certainty of Evidence on Perioperative Gut Microbiome Alterations

The methodological appraisal revealed substantial limitations in the causal interpretability of the available clinical evidence, particularly concerning the independent contribution of general anaesthesia to gastrointestinal microbial disturbances. Among the 13 included investigations, two were classified as having moderate overall risk of bias, ten as serious, and one as critical, indicating that most reported associations were vulnerable to important methodological limitations. Confounding represented the predominant concern because antibiotic prophylaxis, preoperative fasting, surgical injury, postoperative analgesia, and intensive care interventions frequently occurred alongside anaesthetic exposure without adequate separation or adjustment. The importance of these concurrent exposures is supported by evidence concerning opioid-associated microbial dysbiosis and the independent contribution of surgical and cardiovascular physiological disturbances to intestinal microbial alterations (Thomas et al., 2022; Salomon et al., 2021). These limitations restrict causal interpretation even when the direction of microbial change appears consistent across studies.

Variation in study design and participant selection contributed additional uncertainty to the interpretation of postoperative microbial outcomes. The investigation incorporating a concurrent non-cardiac surgical comparator provided a more informative comparison of cardiopulmonary bypass-associated disturbances than studies relying exclusively on preoperative and postoperative samples, although missing data remained an important limitation (Salomon et al., 2021). Other investigations experienced substantial reductions between recruitment and analysis, including cohorts in which 13 of 33 recruited infants and 29 of 86 screened children contributed to the analysed samples, while a probiotic trial retained 44 of 80 randomised participants for microbiome analysis (Koc et al., 2025; Zhang et al., 2026). Such reductions may introduce selection bias when stool availability or participant retention is associated with postoperative illness severity, feeding status, or clinical recovery. The evaluation of these methodological limitations followed the seven-domain structure of ROBINS-I, with overall judgements based on the most severe domain-level assessment rather than an average across domains (Sterne et al., 2016).

The distribution of risk-of-bias judgements is presented in Table 4, preserving the original assessments for each included investigation and methodological domain. Confounding was rated as serious in most observational comparisons, while the study involving palatoplasty received a critical judgement because postoperative microbial measurements followed cefazolin prophylaxis without an adequate means of distinguishing antibiotic effects from surgical or anaesthetic influences (Vieira et al., 2013). The three probiotic investigations required particular methodological consideration because their randomised intervention concerned microbiome modulation rather than allocation to general anaesthesia, making the randomised treatment comparison conceptually different from the exposure association evaluated in this review (Umenai et al., 2014; Toritsuka et al., 2024; Zhang et al., 2026). Applying a risk-of-bias framework to the actual exposure contrast is essential to avoid assigning unwarranted causal strength to observational findings embedded within randomised clinical trials (Sterne et al., 2019).

Table 4. Risk of bias in the included studies, assessed with ROBINS-I.

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Yang 2023	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Koc 2025	Serious	Serious	Low	Moderate	Serious	Moderate	Moderate	Serious

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Yin 2024	Serious	Moderate	Low	Moderate	Moderate	Low	Moderate	Serious
Owens 2024	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Agzamova 2026	Serious	Moderate	Moderate	Serious	Moderate	Serious	Moderate	Serious
Jiang 2024	Serious	Serious	Moderate	Moderate	Moderate	Low	Serious	Serious
Salomon 2021	Moderate	Moderate	Low	Moderate	Serious	Low	Moderate	Serious
Zhang 2024	Serious	Moderate	Low	Moderate	Moderate	Low	Moderate	Serious
Toritsuka 2024	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Zhang 2026	Moderate	Moderate	Low	Low	Serious	Low	Moderate	Serious
Umenai 2014	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Chuang 2024	Serious	Moderate	Low	Serious	Moderate	Low	Moderate	Serious
Vieira 2013	Critical	Moderate	Moderate	Serious	Moderate	Serious	Moderate	Critical

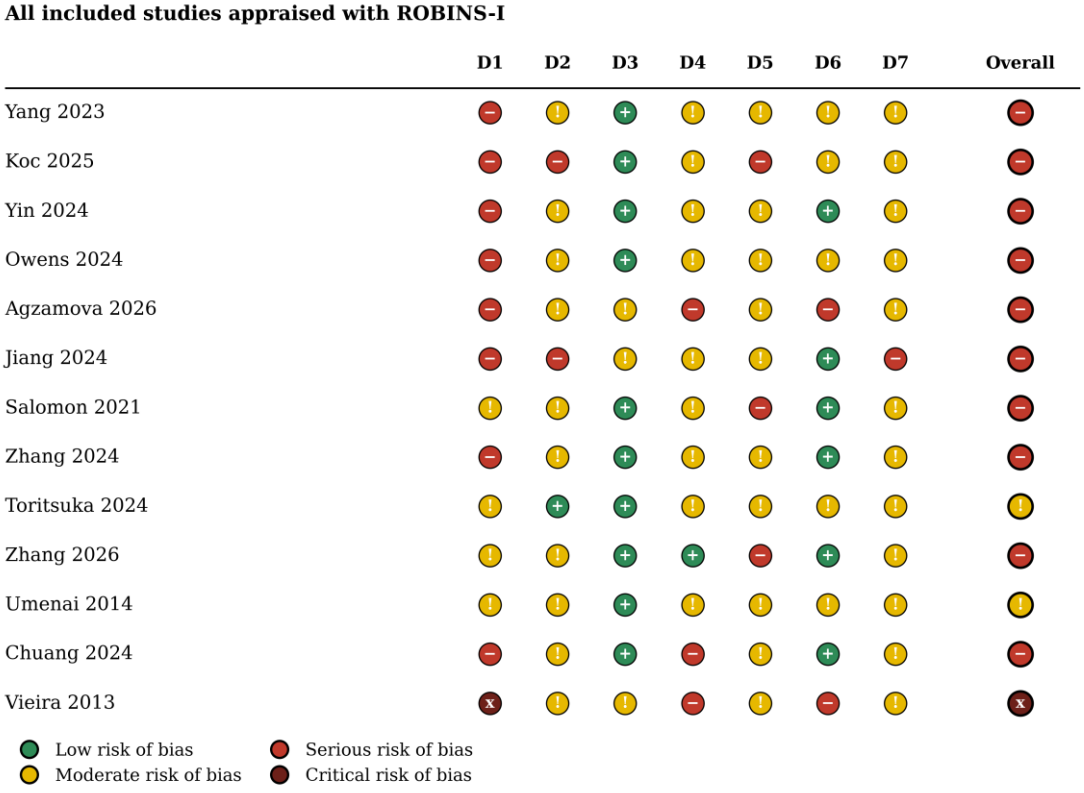


Figure 2. Risk of bias by study and domain.

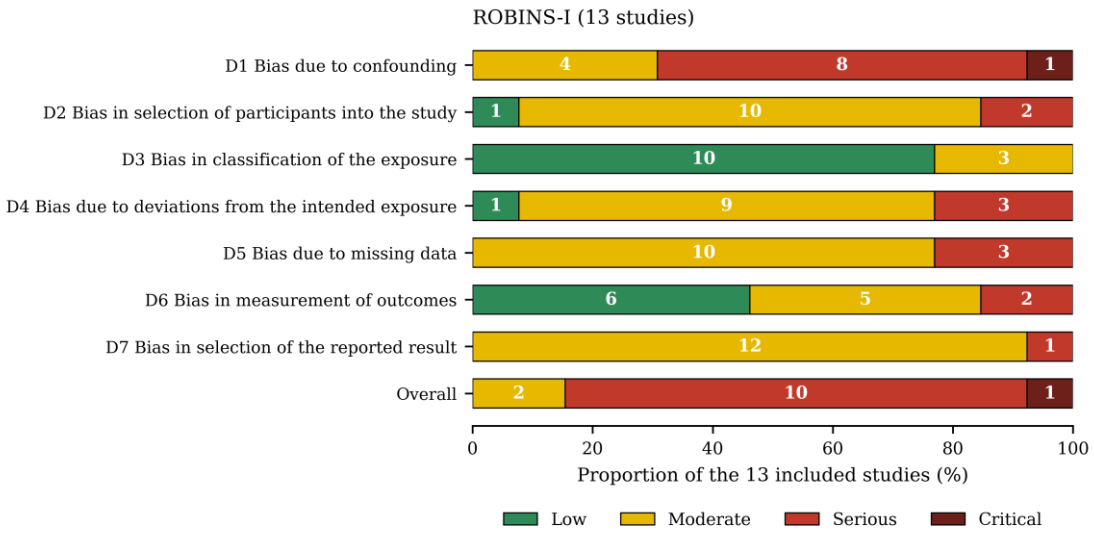


Figure 3. Distribution of risk-of-bias judgements by domain.

The domain-level assessments in Table 4, together with Figures 2 and 3, demonstrate that methodological weaknesses were not distributed uniformly across studies or outcome measurements. Exposure classification was generally less problematic than confounding because surgical and anaesthetic histories could usually be identified, whereas the independent effects of anaesthesia could not be estimated from the available comparison structures. Outcome measurement also varied in reliability according to whether investigations used sequencing-based community profiling, targeted bacterial quantification, or incompletely specified analytical platforms, although measurement quality alone could not compensate for inadequate control of baseline disease characteristics. The methodological distinction between identifying an exposure and estimating its independent effect is central to interpreting observational clinical evidence, particularly when concurrent interventions share plausible biological pathways with the outcome under investigation (Sterne et al., 2016; Salomon et al., 2021). Risk-of-bias judgements therefore indicate limitations in causal attribution rather than establishing that the measured microbial disturbances were absent or biologically irrelevant.

The functional consequences of perioperative microbial alterations were examined through short-chain fatty acid measurements, intestinal permeability indicators, and inflammatory biomarkers, extending the assessment beyond taxonomic composition and diversity. Five investigations addressed short-chain fatty acids or associated microbial populations, although only three directly measured relevant metabolite concentrations rather than inferring metabolic activity from bacterial abundance. Faecal butyrate and propionate concentrations declined following cardiopulmonary bypass in one paediatric cohort, while another investigation associated postoperative feeding intolerance with reduced plasma and faecal short-chain fatty acids and altered gastrointestinal microbial composition (Agzamova & Babadjanova, 2026; Owens et al., 2024). These findings support an association between perioperative microbial disturbance and altered intestinal metabolic characteristics, but they do not establish whether metabolite reductions precede clinical dysfunction or arise secondary to disease severity, nutritional interruption, and postoperative physiological stress.

Evidence concerning intestinal barrier integrity provides an additional biological dimension because circulating markers of epithelial injury may reflect physiological disturbances not fully captured by microbial sequencing. Children undergoing cardiopulmonary bypass demonstrated increased fatty acid binding protein 2 and claudin-3 alongside reduced citrulline compared with non-bypass surgical controls, with significant postoperative differences observed at 24 and 48 hours despite comparable baseline measurements (Salomon et al., 2021). Comparable postoperative increases in intestinal fatty acid binding protein, diamine oxidase, D-lactate, and C-reactive protein were reported in the placebo arm of a probiotic trial, while elevated claudin-related markers accompanied feeding intolerance in another cardiac surgical cohort (Zhang et al., 2026; Owens et al., 2024). Associations between microbial characteristics and inflammatory markers were also observed

among infants developing bypass-associated acute lung injury, including relationships involving interleukin-8, high mobility group box 1, and Enterobacteriaceae (Jiang et al., 2024). The convergence of microbiome and barrier-related findings suggests clinically relevant gastrointestinal disturbances following complex surgery, although their temporal and causal relationships remain unresolved.

The persistence of microbial alterations represents a particularly important uncertainty because short-term postoperative dysbiosis and sustained disturbance during microbial development cannot be assumed to have equivalent biological implications. In a longitudinal cardiac surgical investigation, microbial alpha diversity increased by one year after cardiopulmonary bypass, and microbial communities were no longer statistically distinguishable from those of healthy comparison children, suggesting the possibility of ecological recovery (Yin et al., 2024). Contrasting evidence emerged following adenotonsillectomy, where microbial richness remained reduced at 12 months, while a matched cohort identified community compositional differences at six to nine years of age among children who had undergone repeated general anaesthesia before their third birthday (Chuang et al., 2024; Yang et al., 2023). These differences cannot be interpreted as a simple contradiction in biological recovery because the investigations differed in surgical indication, exposure frequency, comparison groups, sampling intervals, and whether the same participants were followed longitudinally.

The relationship between microbial disturbances and postoperative outcomes also raises the possibility of modifying certain perioperative gastrointestinal consequences without establishing anaesthesia as their independent cause. Probiotic interventions involving Bifidobacterium and other bacterial preparations have been investigated in children undergoing cardiac surgery, with reported differences in microbial composition, intestinal injury markers, organic acid concentrations, and selected feeding-related outcomes (Umenai et al., 2014; Toritsuka et al., 2024; Zhang et al., 2026). A systematic review and meta-analysis examining perioperative probiotic supplementation in paediatric and neonatal gastrointestinal surgery provides additional evidence concerning intervention-related clinical outcomes, although its surgical populations and treatment exposures are not directly equivalent to those examined in the present review (Alansari et al., 2026). The potential responsiveness of microbial and intestinal outcomes to probiotic interventions is therefore relevant to perioperative management, but intervention efficacy cannot retrospectively identify the original cause of dysbiosis. Table 5 presents the original structured synthesis across six outcome domains, distinguishing the consistency of observed associations from the strength of causal attribution.

Table 5. Structured Synthesis of Findings By Outcome Domain, Reported Without Pooling in Accordance with The Swim Guideline.

Outcome domain	Contributing studies	What the studies report	Consistency and attribution
Gut microbiome composition and taxon abundance	13 studies, 523 children	Every study reported a compositional shift. The direction is consistent at genus level across strata and methods: Bifidobacterium, Bacteroides and Lactobacillus fall and Enterococcus, Escherichia-Shigella and Enterobacteriaceae rise. Enterococcus rose from 37.14% to 49.63% and Bifidobacterium fell from 20.71% to 12.59% after bypass in one series; Actinobacteriota fell from 14.46% to 5.08% in the placebo arm of one trial; Escherichia-Shigella rose from 31% to 35% and Enterococcus to 11% in another. Reductions in Lactobacillus, Bacteroides and Bifidobacterium were significant after palatoplasty as well	Consistent in direction across 13 studies, 3 strata and 4 measurement methods; not attributable to anaesthesia alone in any of them

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Alpha diversity	8 studies, 356 children	Six of the eight studies reporting alpha diversity found a significant reduction after exposure or in the exposed group. Richness and Shannon diversity were both lower in children undergoing bypass than in children having non-cardiac surgery under anaesthesia without bypass (both $p < 0.001$). Richness fell after adenotonsillectomy on Chao1 and observed species while Shannon and Simpson did not move. Two studies found no significant change: one paired bypass cohort on Chao1, Shannon and Simpson, and one trajectory cohort between the pre-bypass and early post-bypass samples (all p at or above 0.227)	Directionally consistent where richness indices were used, inconsistent across indices within the same study; the index chosen changes the answer
Beta diversity and community structure	7 studies, 336 children	Six of the seven studies reporting beta diversity found a significant difference in community structure attributable to exposure or exposure status, on weighted UniFrac, Bray-Curtis or Jaccard distances with PERMANOVA. The exception is the paired bypass cohort in which pre-operative and post-operative samples did not cluster beyond sampling variability. In the one study with an unexposed comparison group, PERMANOVA rejected similarity between exposed and never exposed children years after the last anaesthetic	Consistent, and the most robust signal in the review because a community distance is less sensitive than a diversity index to sequencing depth and region
Short-chain fatty acids and SCFA-producing taxa	5 studies, 225 children	Faecal butyrate and propionate fell significantly after bypass in one cohort; plasma and stool short-chain fatty acids were lower in children who developed feeding intolerance, with mediation analysis linking the microbiome shift to reduced butyric and propionic acid; SCFA-producing microbes rose significantly between the early postoperative and the one-year sample. Total organic and acetic acids were higher in the probiotic arm of one pilot trial, while faecal organic acids did not differ between arms in a larger one	Consistent in direction for a short-term fall, and only three studies measured a short-chain fatty acid concentration rather than inferring it from taxa
Persistence and recovery of the microbiome change	5 studies, 278 children	Only three studies looked beyond the postoperative admission. The trajectory cohort found alpha diversity significantly higher one year after bypass than early after it (all p at or below 0.004) and communities no longer distinguishable from controls (all p at or above 0.102). The adenotonsillectomy cohort found	Directly contradictory: recovery by one year in one cohort, persistence at 12 months and at 6 to 9 years in two others. Design, not biology, may explain the difference

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		richness still reduced at 3 and 12 months. The matched cohort found a compositional difference at 6 to 9 years of age, at least three years after the last of three or more anaesthetics	
Intestinal barrier, inflammatory and immune markers	7 studies, 296 children	Fatty acid binding protein 2 and claudin-3 rose and citrulline fell after bypass against non-bypass surgical controls; intestinal fatty acid binding protein, diamine oxidase, D-lactate and C-reactive protein all rose after bypass in a placebo arm; claudin-2, claudin-3 and fatty acid binding protein were higher in children who developed feeding intolerance; interleukin-8 and high mobility group box 1 were higher in children who developed bypass-associated lung injury, with interleukin-8 associated with Enterobacteriaceae	Consistent that barrier permeability rises with the exposure; no study establishes the direction between barrier injury and the compositional change

Certainty-of-evidence assessment was undertaken to distinguish the consistency of observed associations from the confidence that those associations represent reliable and clinically interpretable effects. The GRADE framework classified evidence concerning microbial composition, alpha diversity, short-chain fatty acids, and persistence as very low certainty, whereas evidence concerning beta diversity and intestinal barrier or inflammatory markers was classified as low certainty. These ratings reflect the predominance of non-randomised exposure comparisons, substantial confounding, heterogeneity in outcome measurement, and limited longitudinal evidence, rather than implying that the observed microbial differences were necessarily artefactual (Guyatt et al., 2008). The distinction is important because statistically significant associations and repeated directional findings do not independently establish the certainty of causal interpretation. Table 6 preserves the original outcome-specific certainty judgements and their stated methodological justifications.

Table 6. GRADE Certainty of Evidence for Each Outcome Domain.

Outcome	Evidence	Risk of bias	Inconsistency	Imprecision	Certainty	Basis for the rating
Compositional shift in the gut microbiome after early-life anaesthesia and surgery	13 non-randomised studies	Serious	Not serious	Serious	Very low	Starts low as a body of non-randomised exposure evidence. Downgraded once more for risk of bias, because in twelve of thirteen studies the comparator shares none of the perioperative antibiotic, fasting and intensive care

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						exposures, and once for indirectness, because no study isolates the anaesthetic from the operation
Reduction in alpha diversity	8 non-randomised studies	Serious	Serious	Serious	Very low	Downgraded for risk of bias, for inconsistency because richness and evenness indices disagree within the same studies, and for imprecision because the largest contributing sample is 55 children and several are under 25
Change in beta diversity and community structure	7 non-randomised studies	Serious	Not serious	Not serious	Low	Downgraded once for risk of bias. Not downgraded for inconsistency, since six of seven studies agree, nor for imprecision, since a PERMANOVA on community distance is interpretable in small samples
Reduction in short-chain fatty acids and SCFA-producing taxa	5 non-randomised studies	Serious	Not serious	Serious	Very low	Downgraded for risk of bias and for imprecision: only three studies measured a short-chain fatty acid concentration, in 20, 26 and 21 children
Persistence of the	5 non-randomised	Serious	Very serious	Serious	Very low	Downgraded for risk of bias,

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microbiome change beyond the postoperative admission	studies					twice for inconsistency because the three studies point in opposite directions at one year and beyond, and once for imprecision
Rise in intestinal barrier and inflammatory markers alongside the microbiome change	7 non-randomised studies	Serious	Not serious	Not serious	Low	Downgraded once for risk of bias. The finding is consistent across four independent cohorts and rests on quantitative assays rather than on sequencing, so neither inconsistency nor imprecision was downgraded

The combined methodological and clinical evidence supports a cautious interpretation of perioperative gastrointestinal dysbiosis as a measurable biological association whose independent relationship with anaesthetic exposure remains unresolved. Experimental investigations demonstrate that anaesthetic agents can influence intestinal microbial communities under controlled conditions, including neonatal animal models in which microbial manipulation has been linked to neurobehavioural consequences, but these findings cannot establish equivalent causal pathways in children undergoing clinically necessary surgery (Liu et al., 2021; Zhou et al., 2023; Chaki et al., 2025; Fan et al., 2025). Human investigations comparing different anaesthetic techniques have reported microbiome-related differences in adult intestinal samples and paediatric oral microbial communities, indicating the feasibility of agent-specific comparisons while leaving the developing paediatric gastrointestinal microbiome insufficiently characterised (Liu et al., 2022; Xie et al., 2024). Future investigations should prioritise prospective comparison groups exposed to anaesthesia without major surgical injury where clinically feasible, standardised microbial measurements, systematic documentation of perioperative antibiotics and nutritional exposures, and repeated sampling extending beyond hospital discharge. Such designs would permit more informative differentiation between anaesthetic effects, disease-associated microbial abnormalities, and modifiable perioperative determinants while addressing the limitations identified through the present risk-of-bias and evidence-certainty assessments.

CONCLUSION

This systematic review demonstrates that exposure to general anaesthesia and surgery during infancy and early childhood is associated with alterations in gastrointestinal microbial composition and community structure, although the independent contribution of anaesthetic agents remains undetermined. Evidence from 13 studies involving 523 children across seven countries indicates a recurring reduction in Bifidobacterium, Bacteroides, and Lactobacillus, accompanied by increased

representation of Enterococcus, Escherichia-Shigella, and Enterobacteriaceae. Six of eight studies assessing alpha diversity reported significant reductions, although differences between richness and evenness indices limited the consistency of interpretation, while six of seven investigations examining beta diversity identified significant alterations in microbial community structure. Changes in short-chain fatty acid concentrations, intestinal barrier markers, and inflammatory responses further suggest that perioperative microbial disturbances may coincide with gastrointestinal metabolic and physiological dysfunction, particularly among children undergoing cardiopulmonary bypass. Evidence concerning the persistence of these alterations remains inconclusive, with individual investigations reporting microbial recovery within one year, reduced richness persisting for twelve months, or compositional differences detectable at school age following repeated early-life exposure. Differences in study populations, surgical procedures, comparator characteristics, microbiome measurement techniques, and follow-up intervals prevent these findings from establishing a consistent trajectory of long-term microbial recovery or disturbance.

The principal contribution of this review is the systematic differentiation between observable perioperative gastrointestinal dysbiosis and the unresolved causal effects of general anaesthesia, supported by exposure-stratified synthesis, methodological appraisal, and outcome-specific evaluation of evidence certainty. Risk-of-bias assessment identified two studies at moderate risk, ten at serious risk, and one at critical risk, while GRADE assessments classified the certainty of evidence as low or very low across the six evaluated outcome domains. Confounding from surgical stress, antimicrobial prophylaxis, fasting, analgesic administration, underlying disease, and postoperative intensive care represents the primary limitation preventing independent attribution of microbial changes to anaesthetic exposure. These findings support clinical awareness of gastrointestinal microbial disturbances following early-life surgical interventions without establishing that routine paediatric general anaesthesia independently causes persistent dysbiosis or subsequent developmental harm. The practical implications concern improved characterisation of potentially modifiable perioperative exposures and more cautious interpretation of microbiome-related postoperative outcomes rather than immediate changes to established anaesthetic practice. Future research should prioritise prospective controlled investigations incorporating appropriate anaesthetised comparison groups, standardised microbial diversity and metabolic measurements, comprehensive recording of perioperative co-exposures, and longitudinal assessment extending beyond hospital discharge. Such investigations are necessary to clarify the independent biological contribution of anaesthetic agents, establish the duration and clinical relevance of microbiome alterations, and provide a stronger evidentiary foundation for paediatric perioperative care.

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