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AGE-DEPENDENT DISRUPTION OF GUT MICROBIOME MATURATION IN INFANTS AND YOUNG CHILDREN WITH CONGENITAL HEART DISEASE: A WHOLE-GENOME SHOTGUN METAGENOMIC SEQUENCING STUDY

Faniya R. Babadjanova[1]*, Shoira A. Agzamova[2], Zarina R. Khaybullina[3]

[1]Urgench State Medical Institute, Urgench, Uzbekistan
[2]Tashkent State Medical University, Tashkent, Uzbekistan
[3]Republican Specialized Scientific and Practical Medical Center of Surgery named after Academician V. Vakhidov, Tashkent, Uzbekistan
***Corresponding author:** Faniya R. Babadjanova; E-mail: babadjanovafaniya@gmail.com; ORCID: 0009-0001-0210-1951

ABSTRACT

Congenital heart disease (CHD) may disturb intestinal perfusion, feeding, and early microbial succession, yet age-resolved microbiome data from Central Asian children remain limited. We compared fecal bacterial communities in 73 children with CHD and 36 age-matched healthy controls aged 0-3 years. Participants were stratified into 0-6 months (CHD, n=18; control, n=12), 6-12 months (CHD, n=24; control, n=12), and 1-3 years (CHD, n=31; control, n=12). Bacterial community structure was characterized by whole-genome shotgun metagenomic sequencing. Alpha diversity, phylum-level composition, genus-level relative abundance, and the Firmicutes/Bacteroidota ratio were evaluated. Across all age strata, CHD was associated with reduced microbial richness and evenness. In infants aged 0-6 months, Shannon diversity was 1.49±0.09 in CHD versus 2.27±0.24 in controls, Pielou evenness was 0.52±0.02 versus 0.63±0.04, and the mean number of detected genera was 20.5±2.6 versus 40.4±5.9 ($p<0.05$). The divergence persisted at 1-3 years, when Shannon diversity was 2.22±0.07 versus 2.87±0.09 and Pielou evenness was 0.513±0.016 versus 0.69±0.03. CHD samples showed persistent enrichment of Proteobacteria and depletion of age-associated saccharolytic and butyrate-producing taxa. During the first 6 months, Escherichia/Shigella (21.7±6.9%), Enterococcus (10.5±4.0%), Enterobacter (9.2±3.0%), and Veillonella (12.8±2.0%) were increased, whereas Bifidobacterium (18.1±3.9% vs 50.4±11.2%) and Faecalibacterium (0.021±0.004% vs 1.02±0.04%) were reduced. Older children with CHD remained deficient in Agathobacter, Faecalibacterium, Roseburia, Lachnospira, and Subdoligranulum. These findings indicate delayed and incomplete microbiome maturation in young children with CHD, characterized by reduced ecological stability, expansion of facultative anaerobes, and loss of short-chain-fatty-acid-producing capacity. Longitudinal studies integrating feeding, medication exposure, cardiac phenotype, and metabolomics are warranted.

KEYWORDS: congenital heart disease; gut microbiome; whole-genome shotgun metagenomic sequencing; microbial maturation; alpha diversity; Proteobacteria; butyrate-producing bacteria

INTRODUCTION

The first three years of life are a critical period for the assembly of the intestinal microbiome [1-7]. Delivery mode, breastfeeding, complementary feeding, antibiotic exposure, geography, and host physiology jointly shape the transition from a low-diversity infant community toward a more complex anaerobe-rich ecosystem. This maturation supports epithelial barrier integrity, immune education, energy harvest, and the production of short-chain fatty acids (SCFAs), particularly butyrate [11,12]. Disruption during this developmental window may have consequences that extend beyond the gastrointestinal tract.

Congenital heart disease is the most common major congenital anomaly and encompasses a heterogeneous group of structural defects. Infants with CHD frequently experience impaired systemic or mesenteric perfusion, hypoxemia, venous congestion, feeding difficulties, recurrent hospitalization, exposure to antibiotics, and nutritional insufficiency. Each of these factors may alter the intestinal ecological niche. In severe disease, intestinal hypoperfusion and mucosal barrier dysfunction may favor facultative anaerobes while suppressing obligate anaerobic fermenters. The resulting microbial configuration could reinforce inflammation, malabsorption, and poor growth, forming a clinically relevant heart-gut axis.Previous studies in pediatric cardiac populations have predominantly examined perioperative cohorts, neonates in intensive care, or small samples at a single developmental stage. Age is, however, a major determinant of early microbial composition; therefore, differences related to CHD should be interpreted against age-specific controls. Data from Central Asia are particularly scarce, despite region-specific dietary and environmental exposures that may influence baseline microbiome development. The present study aimed to characterize age-dependent differences in fecal bacterial diversity and taxonomic composition between children with CHD and healthy controls from the Khorezm region of Uzbekistan. We hypothesized that CHD would be associated with lower alpha diversity, persistent enrichment

of Proteobacteria and facultative anaerobes, delayed acquisition of Bacteroidota, and depletion of butyrate-producing genera across the first three years of life.

MATERIAL AND METHODS

Study design and participants

This age-stratified comparative study included 109 children aged 0-3 years: 73 with a clinically and echocardiographically confirmed CHD and 36 healthy controls. Participants were recruited in the Khorezm region of Uzbekistan during the study period. The microbiome cohort was divided into three developmental strata: 0-6 months (18 CHD and 12 controls), 6-12 months (24 CHD and 12 controls), and 1-3 years (31 CHD and 12 controls). Controls had no known structural heart disease, acute infection, or clinically significant growth deficit at assessment.

Children were eligible for the CHD group when a congenital structural cardiac defect had been documented by pediatric cardiology evaluation. Stool was collected before microbiome-directed treatment. Exclusion criteria and the handling of recent antibiotic or probiotic exposure should be verified against the primary study protocol before submission. Feeding mode was recorded where available; 58.6% of controls were breastfed.

Ethics

The study was approved by the Ethical Committee of the Ministry of Health of the Republic of Uzbekistan (approval number 6/15-2104, date of approval May 24, 2026). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from a parent or legal guardian of each participant.

Stool collection, DNA extraction, and sequencing

Fresh stool samples were collected in sterile containers, transported under controlled conditions, and processed for total microbial DNA extraction. Gut microbial communities were analyzed using whole-genome shotgun metagenomic sequencing rather than 16S rRNA gene amplicon sequencing. This approach involved sequencing total DNA fragments recovered from each stool sample, thereby enabling taxonomic characterization of the microbial community and assessment of its functional genetic potential. Sequencing was performed using a Genoscan nucleic acid sequencing system manufactured by SESANA LLC, Russian Federation, in accordance with Technical Specifications TU 26.51.53-004-95224908-2020. The available Genoscan configurations included the Genoscan 3700, 4000, 5000, and 6000 models. The Genoscan 4000 is registered as a medical device under registration number RZN 2025/24616. The exact instrument model used for the samples included in this study should be confirmed from the laboratory report before submission. Unlike whole-genome shotgun metagenomic sequencing, shotgun metagenomic sequencing does not rely on amplification of a selected 16S variable region or taxon-specific primer pairs. Instead, total microbial DNA is fragmented, sequencing libraries are prepared, and all available DNA fragments are sequenced. This permits taxonomic identification at higher resolution and enables evaluation of microbial genes associated with short-chain fatty acid production, vitamin metabolism, inflammatory potential, detoxification pathways, and other metabolic functions.

The following technical details should be obtained from the sequencing laboratory before submission: the DNA extraction kit and manufacturer, DNA quality-control criteria, library preparation kit, exact Genoscan model, sequencing chemistry, read configuration and read length, average sequencing depth per sample, inclusion of negative controls, and criteria used for excluding low-quality samples. Bioinformatic and taxonomic analysis.

Raw shotgun metagenomic reads were subjected to quality control to remove low-quality sequences, sequencing adapters, and reads of human origin. The remaining microbial reads were analyzed using the laboratory bioinformatic pipeline. Taxonomic classification was performed across multiple hierarchical levels, including phylum, family, genus, and, where sufficient sequence resolution was available, species level. Relative abundance was calculated as the proportion of microbial reads assigned to each taxon.

The functional potential of the gut microbiome was evaluated from microbial gene content, including pathways associated with the production of short-chain fatty acids, particularly butyrate and propionate, as well as vitamin metabolism, inflammatory potential, detoxification, and other biologically relevant microbial functions. Functional results represent the genetic potential of the microbial community and should not be interpreted as direct measurements of metabolite concentrations or gene expression.

Alpha diversity was assessed using the Shannon diversity index, Simpson diversity index, Pielou evenness index, and the number of detected taxa. The Firmicutes/Bacteroidota ratio was calculated from phylum-level relative abundances. Because Bacteroidota abundance was close to zero in some early-life samples, extremely high F/B values were interpreted cautiously.Before submission, the following information must be obtained from the laboratory: bioinformatic software and version, quality-filtering thresholds, human-read removal method and reference genome, taxonomic reference database and version, minimum abundance threshold, functional annotation database, pathway reconstruction method, and normalization procedure. Statistical analysis Continuous variables are presented as mean ± standard error. Statistical comparisons between children with congenital heart disease and age-matched healthy controls were performed separately within the 0–6-month, 6–12-month, and 1–3-year age strata. Comparisons between cyanotic and acyanotic CHD phenotypes were performed where corresponding subgroup data were available. A two-sided p-value of <0.05 was considered statistically significant. The source dataset reported most taxonomic comparisons as $p<0.05$ or $p>0.05$; therefore, these thresholded values were retained, and exact p-values were not estimated retrospectively. Zero relative-

abundance values were retained as reported and were not replaced by arbitrary pseudocounts for descriptive presentation. Given the number of taxonomic comparisons, findings without adjustment for multiple testing should be regarded as exploratory. The statistical software and version, tests used to assess distribution normality, exact between-group tests, and the method of multiple-comparison correction must still be confirmed from the original statistical analysis protocol.

RESULTS

Alpha diversity and microbial maturation

Alpha-diversity indices increased with age in both groups, but the trajectory was consistently attenuated in children with CHD (Table 1). During the first 6 months, the CHD group had markedly lower Shannon diversity, Simpson diversity, Pielou evenness, and detected genera than controls. At 6-12 months, the number of genera remained approximately half that observed in controls (27.5±1.6 vs 55.7±4.0). By 1-3 years, richness increased in the CHD group but remained substantially lower than in controls (76.1±1.8 vs 120±10 genera), while Pielou evenness declined to 0.513±0.016. Thus, increasing age did not normalize community diversity or evenness in CHD.

Table 1. Age-stratified alpha diversity of the gut microbiome

Measure	0-6 mo control n=12	0-6 mo CHD n=18	6-12 mo control n=12	6-12 mo CHD n=24	1-3 y control n=12	1-3 y CHD n=31
Shannon index	2.27±0.24	1.49±0.09*	2.58±0.08	1.90±0.03	2.87±0.09	2.22±0.07
Simpson diversity	0.82±0.03	0.65±0.04*	0.89±0.03	0.81±0.05	0.86±0.02	0.79±0.01
Pielou evenness	0.63±0.04	0.52±0.02*	0.65±0.02	0.580±0.003	0.69±0.03	0.513±0.016
Detected genera	40.4±5.9	20.5±2.6*	55.7±4.0	27.5±1.6	120±10	76.1±1.8

Values are mean±SE. *p<0.05 versus age-matched control as marked in the source dataset. CHD, congenital heart disease.

Phylum-level composition

The principal phyla were Bacillota (Firmicutes), Bacteroidota, Actinobacteriota, Proteobacteria, and Verrucomicrobiota (Table 2). Controls showed the expected age-related decline in Proteobacteria and expansion of Bacteroidota and Bacillota. In contrast, Proteobacteria remained elevated in CHD, reaching 31.3±1.9% at 6-12 months compared with 9.5±4.4% in controls. At 1-3 years, Bacillota accounted for 25.0±2.7% in CHD versus 46.2±3.8% in controls, while Actinobacteriota remained high (33.7±3.4% vs 8.9±1.2%). These patterns suggest delayed transition from an infant-type community to a more diverse anaerobe-dominated configuration.

Table 2. Relative abundance (%) of major bacterial phyla by age

Phylum	0-30 d C	0-30 d CHD	1-6 mo C	1-6 mo CHD	6-12 mo C	6-12 mo CHD	1-3 y C	1-3 y CHD
Bacillota (Firmicutes)	23.4±2.0	29.5±1.9	29.9±4.5	19.9±4.5	30.0±6.8	33.3±3.1	46.2±3.8	25.0±2.7
Bacteroidota	0.0018±0.0001	0.100±0.002	0.131±0.062	20.2±7.4	17.03±2.07	9.8±1.9	31.3±2.7	24.9±3.0
Actinobacteriota	18.2±1.2	14.7±1.1	20.6±4.4	37.9±4.8	12.9±1.9	24.7±5.7	8.9±1.2	33.7±3.4
Proteobacteria	29.0±1.9	41.6±4.0	49.2±6.4	34.4±4.5	9.5±4.4	31.3±1.9	5.2±2.0	11.8±1.7
Verrucomicrobiota	0.060±0.002	0.121±0.002	0.042±0.002	0.505±0.004	0.305±0.004	0.603±0.005	1.40±0.05	2.20±0.03
F/B ratio	13000	295	228	0.96	1.76	3.36	1.49	1.0

Values are mean±SE unless otherwise stated. C, control; CHD, congenital heart disease; F/B, Firmicutes/Bacteroidota ratio. Extreme early-life F/B values reflect near-zero Bacteroidota abundance and should be interpreted cautiously.

Genus-level differences in early infancy

The most pronounced genus-level divergence was observed in the first 6 months (Table 3). CHD was characterized by expansion of Escherichia/Shigella, Veillonella, Enterococcus, Enterobacter, Streptococcus, Eggerthella, Staphylococcus, Klebsiella, and Citrobacter. Conversely, Bifidobacterium, Lactobacillus, Rothia, and

Faecalibacterium were depleted. Escherichia/Shigella was more than twice as abundant in CHD (21.7±6.9% vs 9.8±1.6%), whereas Bifidobacterium was reduced by approximately two-thirds (18.1±3.9% vs 50.4±11.2%). Cyanotic CHD showed particularly high Escherichia/Shigella (37.0±4.0%) and Veillonella (17.0±2.8%) and lower Bifidobacterium (16.9±4.0%) than acyanotic CHD.

Table 3. Selected genus-level relative abundances during the first 6 months of life

Genus	Control (%)	All CHD (%)	p	Acyanotic CHD (%)	Cyanotic CHD (%)	p
Escherichia/Shigella	9.8±1.6	21.7±6.9	<0.05	16.9±2.9	37.0±4.0	<0.05
Bifidobacterium	50.4±11.2	18.1±3.9	<0.05	28.0±3.8	16.9±4.0	<0.05
Lactobacillus	9.3±1.0	1.5±0.3	<0.05	1.6±0.1	1.5±0.2	>0.05
Veillonella	4.2±1.0	12.8±2.0	<0.05	7.6±1.7	17.0±2.8	<0.05
Enterococcus	0.24±0.01	10.5±4.0	<0.05	9.9±1.3	10.9±2.3	>0.05
Enterobacter	0.01±0.003	9.2±3.0	<0.05	8.6±2.9	9.5±3.6	>0.05
Citrobacter	0.100±0.034	2.9±1.2	<0.05	1.3±0.4	5.9±1.3	<0.05
Faecalibacterium	1.02±0.04	0.021±0.004	<0.05	0.020±0.001	0.022±0.006	>0.05

Values are mean±SE. The second p column compares cyanotic and acyanotic CHD groups.

Persistence of dysbiosis after complementary feeding

At 6-12 months, when controls acquired fiber-degrading and SCFA-producing bacteria, children with CHD continued to show enrichment of Escherichia/Shigella (35.8±2.9% vs 5.8±1.1%), Veillonella (16.9±2.0% vs 2.1±0.7%), and several facultative or atypical intestinal taxa. Akkermansia (0.001±0.001% vs 0.440±0.023%), Prevotella (0.44±0.34% vs 5.12±0.87%), Agathobacter (0.031±0.009% vs 3.99±0.98%), Subdoligranulum (0.004±0.001% vs 1.108±0.056%), Faecalibacterium (3.690±0.090% vs 12.65±2.45%), Roseburia, and Lachnospira were reduced or absent (all reported $p<0.05$). These differences indicate impaired acquisition of mucin-associated, complex-carbohydrate-degrading, and butyrate-producing functions.

Among children aged 1-3 years, CHD remained associated with an immature community configuration. The source dataset identified increased Collinsella and Rothia, reduced Odoribacter, and persistent reduction of key butyrate producers. Changes were more pronounced in selected cardiac phenotypes: acyanotic CHD with pulmonary hypertension showed taxa associated with altered bile-acid metabolism, whereas cyanotic CHD showed greater enrichment of taxa linked to barrier dysfunction and lower Akkermansia. Because subgroup sizes and multivariable estimates were not available in the chapter dataset, these phenotype-specific observations should be considered exploratory.

DISCUSSION

This study demonstrates an age-dependent but persistent disturbance of gut microbial maturation in children with CHD from birth to three years of age. Three findings are central. First, CHD was associated with lower richness, diversity, and evenness at every developmental stage. Second, Proteobacteria and multiple facultative anaerobic genera remained prominent after the age at which they normally decline. Third, the acquisition of saccharolytic and butyrate-producing anaerobes was delayed or incomplete, even after complementary feeding and transition to a broader family diet.

The reduction in alpha diversity was not limited to early infancy. Although low diversity can be physiological in breastfed neonates, healthy controls showed the expected age-related increase in detected genera and Shannon diversity. Children with CHD followed a shallower trajectory and retained low evenness at 1-3 years. This pattern is consistent with ecological immaturity: a community containing fewer taxa and dominated by a limited number of genera may be less resilient to nutritional change, infection, hospitalization, and medication exposure. Importantly, diversity alone is not inherently beneficial; its interpretation depends on developmental stage and taxonomic context. Here, the diversity findings were accompanied by coherent compositional changes, strengthening their biological relevance.

The persistent enrichment of Proteobacteria is particularly notable [8-10]. During normal succession, facultative anaerobes consume oxygen and enable later colonization by obligate anaerobes. Failure of this transition may reflect recurrent oxygenation of the intestinal niche, inflammation, altered motility, antibiotic selection, or impaired perfusion. Escherichia/Shigella, Enterobacter, Enterococcus, and Klebsiella can expand under inflammatory or oxygenated conditions and may contribute to a feed-forward cycle of barrier disruption. The cross-sectional design does not establish causality, but the higher Escherichia/Shigella abundance observed in cyanotic CHD supports the plausibility of a relationship with hypoxemia or disease severity.

The marked reduction in Bifidobacterium and Lactobacillus during the first 6 months may also reflect feeding difficulties and lower exposure to human-milk oligosaccharides. Feeding mode is a dominant determinant of the infant microbiome, and only partial feeding information was available in the source dataset. Consequently, the observed CHD-control differences should not be interpreted as effects of cardiac anatomy alone. Future analyses should adjust for exclusive breastfeeding, formula composition, delivery mode, prematurity, antibiotic exposure, hospitalization, oxygen saturation, heart failure, and nutritional status.

After complementary feeding, healthy controls acquired Prevotella and a broader group of butyrate producers, including Agathobacter, Faecalibacterium, Roseburia, Lachnospira, and Subdoligranulum. Their depletion in CHD suggests reduced fermentation of dietary complex carbohydrates and lower capacity for butyrate production. Butyrate supports colonocyte energy metabolism, epithelial tight junctions, and anti-inflammatory immune regulation [11,12]. A reduced butyrogenic guild could therefore provide a mechanistic link between dysbiosis, intestinal barrier dysfunction, malabsorption, and impaired growth in CHD. This functional interpretation remains inferential because microbial metabolites and metagenomic pathways were not directly quantified in the present dataset.

The F/B ratio was highly unstable in the youngest strata because Bacteroidota abundance approached zero [15]. This illustrates why the F/B ratio should not be treated as a universal marker of dysbiosis, especially in infancy. Age-specific taxonomic trajectories and ecologically coherent genus-level patterns are more informative than a single ratio. Likewise, terms such as “pathogenic load” should be used cautiously in amplicon studies because genus-level classification cannot distinguish pathogenic from commensal strains.

This study adds age-resolved evidence from an understudied Central Asian population and includes matched control strata spanning major stages of dietary transition. Nevertheless, several limitations require emphasis. The design was cross-sectional; subgroup sample sizes were modest; sequencing and bioinformatic metadata need full reporting; and the available analysis did not include beta diversity, differential-abundance models with false-discovery-rate correction, or multivariable adjustment for key confounders. Relative abundance is compositional and cannot establish absolute bacterial load [16,17]. Functional capacity was inferred from taxonomy rather than measured by shotgun metagenomics or metabolomics. Finally, phenotype-specific comparisons should be treated as exploratory until replicated in larger cohorts.

Longitudinal sampling before and after cardiac intervention would help determine whether dysbiosis precedes clinical deterioration or reflects treatment exposure. Combining microbiome profiles with fecal SCFAs, inflammatory markers, intestinal permeability indices, oxygen saturation, pulmonary artery pressure, and standardized anthropometry could clarify the clinical significance of microbial immaturity and identify potentially modifiable pathways.

CONCLUSIONS

Children with CHD showed delayed and incomplete maturation of the gut microbiome throughout the first three years of life. The pattern comprised lower alpha diversity and evenness, persistent enrichment of Proteobacteria and facultative anaerobes, and reduced acquisition of Bacteroidota-associated saccharolytic taxa and butyrate-producing genera. These findings support a developmentally informed heart-gut axis in CHD but do not establish causality. Microbiome-directed interventions should not be recommended from these data alone; prospective studies with detailed exposure adjustment and direct functional measurements are needed.

AUTHOR CONTRIBUTIONS

F.R.B.: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, and Writing – Original Draft. S.A.A.: Conceptualization, Supervision, Validation, and Writing – Review & Editing. Z.R.K.: Methodology, Supervision, Validation, Interpretation of Data, and Writing – Review & Editing. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was reviewed and approved by the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan (Approval No. 6/15-2107, dated May 27, 2025). The research was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participating children before enrollment in the study.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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DATA AVAILABILITY
The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request, subject to ethical approval, participant confidentiality requirements, and applicable institutional data-protection policies.

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