Journal of Zhejiang University-SCIENCE B 2025 26(10):995-1014
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Research Article
https://doi.org/10.1631/jzus.B2400330

Check for updates

Pediatric inflammatory bowel disease in mother–child pairs: clinical risk factors and gut microbiota characteristics

Cunzheng ZHANG[1,2*], Ruqiao DUAN[1,2*], Nini DAI[3*], Yuzhu CHEN[1,2], Gaonan LI[1,2], Xiao'ang LI[1,2], Xiaolin JI[1,2], Xuemei ZHONG[4], Zailing LI[3✉], Liping DUAN[1,2✉]

[1]*Department of Gastroenterology, Peking University Third Hospital, Beijing 100191, China*
[2]*Beijing Key Laboratory for Helicobacter Pylori Infection and Upper Gastrointestinal Diseases, Beijing 100191, China*
[3]*Department of Pediatrics, Peking University Third Hospital, Beijing 100191, China*
[4]*Department of Gastroenterology, Children's Hospital Capital Institute of Pediatrics, Beijing 100020, China*

Abstract: Objective: The risk factors and role of mother–child gut microbiota in pediatric inflammatory bowel disease (PIBD) remain unclear. We aimed to explore the clinical risk factors associated with PIBD, analyze the characteristics of gut microbiota of children and their mothers, and examine the correlation of the microbial composition in mother–child pairs. Methods: We conducted a case-control study including children with PIBD and their mothers as the case group, as well as healthy children and their mothers as the control group. Questionnaires were used to collect information such as family illness history and maternal and early-life events. Fecal samples were collected from the children and mothers for microbiota 16S ribosomal RNA (rRNA) sequencing to analyze the composition and its potential association with PIBD. Results: A total of 54 pairs of cases and 122 pairs of controls were recruited. A family history of autoimmune disease and antibiotic use during pregnancy were associated with an increased risk of PIBD, and a higher education level of the father was associated with a decreased risk of PIBD. Children with PIBD and mothers exhibited different gut microbiota compared to healthy children and mothers. Similarities were observed in the gut microbiota of mothers and children in the same groups. Some bacterial biomarkers of mothers discovered in this study had the power to predict PIBD in their offspring. Conclusions: PIBD is influenced by maternal risk factors and has unique gut microbiota characteristics. The mother–child gut microbiota is closely related, suggesting the transmission and influence of the gut microbiota between mothers and children. This study highlights the potential pathogenesis of PIBD and provides a basis for developing targeted interventions.

Key words: Inflammatory bowel disease (IBD); Risk factor; Gut microbiota; Mother–child pair

1 Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract, including two main forms: Crohn's disease (CD) and ulcerative colitis (UC). It is widely recognized that IBD is associated with a complex interplay between genetic susceptibility, environmental factors, and microbial dysbiosis, all of which contribute to dysregulated immune responses (le Berre et al., 2023; Dolinger et al., 2024). IBD can occur at any age, with disease onset under 17 years defined as pediatric IBD (PIBD) (Nameirakpam et al., 2020). Approximately 25% of patients with IBD have PIBD, and its incidence and prevalence continue to increase globally (Nameirakpam et al., 2020; Kuenzig et al., 2022). Studies have shown that patients who develop IBD during childhood have more severe disease courses and a higher risk of complications compared with adult patients (Bouhuys et al., 2023). Therefore, it is imperative to identify the risk factors that may affect PIBD and to explore its pathogenesis.

✉ Liping DUAN, duanlp@bjmu.edu.cn
Zailing LI, topbj163@sina.com
* The three authors contributed equally to this work
Liping DUAN, https://orcid.org/0000-0001-6886-6888
Zailing LI, https://orcid.org/0009-0004-6513-2431
Cunzheng ZHANG, https://orcid.org/0009-0005-6119-574X
Ruqiao DUAN, https://orcid.org/0000-0001-8496-0364
Nini DAI, https://orcid.org/0000-0003-0429-1645

Received June 25, 2024; Revision accepted Aug. 26, 2024;
Crosschecked Sept. 10, 2025; Published online Sept. 26, 2025

Compared with adult IBD, PIBD is thought to be more influenced by maternal and early-life events due to lower cumulative exposure to environmental factors after birth (Jezernik et al., 2020). Various prenatal, perinatal, and postnatal determinants, such as maternal diet, antibiotic exposure, delivery mode, feeding pattern, and weaning time, have been reported to modulate the risk of developing IBD (Piovani et al., 2019; Velosa et al., 2022). However, the specific mechanisms of these associations are still poorly understood, and one hypothesis is that the effects are mediated by alterations in the gut microbiota of both mothers and offspring.

The gut microbiota exerts a significant influence on the occurrence and development of IBD. Multiple studies have reported alterations in the microbial composition and the presence of specific strains in stool and colon samples from patients with IBD (Pittayanon et al., 2020). There are many sources of the gut microbiota, and one important source is the maternal microbiota, which is vertically transmitted to offspring, thus determining the first colonizers in the human digestive system (Wang et al., 2020). Mother-to-infant microbial transmission takes place from the beginning of pregnancy to a very long time after delivery and is influenced by various intrinsic and extrinsic factors, including a set of prenatal, perinatal, and postnatal factors mentioned above (Xiao and Zhao, 2023). Perturbations of a mother's gut microbiota may be associated with poor development of the offspring's immune system, leading to persistent and long-term susceptibility to certain diseases (Koren et al., 2024). However, little is known about whether microbiota-sharing between mothers and offspring persists over much longer periods of time and whether it is associated with disease development. To the best of our knowledge, no studies have investigated the gut microbial compositions of IBD mother–child pairs or evaluated the correlation between them.

Consequently, the present study aimed to investigate the clinical risk factors linked to PIBD and to analyze the gut microbiota profiles of both affected children and their mothers. By adopting a case-control study design, we hoped to unravel the interplay between genetic, environmental, and microbial factors that contribute to the development of PIBD and explore potential microbial biomarkers to predict IBD in children.

2 Methods

2.1 Study design and population

This was a multicenter case-control study. Between July 2022 and December 2023, eligible children with a confirmed diagnosis of PIBD were recruited from pediatric outpatient clinics and wards of Peking University Third Hospital and Children's Hospital Capital Institute of Pediatrics in China. Controls were randomly selected from the same hospitals (individuals without PIBD or other gastrointestinal diseases).

The inclusion criteria were as follows: (1) children under 17 years old; (2) a diagnosis of PIBD confirmed by doctors based on a combination of clinical, endoscopic, radiological, and histopathological criteria; and (3) mothers who cooperated with the questionnaire and signed an informed consent form (children over eight years old also needed to sign an informed consent form). The exclusion criteria were as follows: (1) children with any serious physical or mental illness other than PIBD; (2) mothers with any serious physical or mental illness during the preconception, pregnancy, or lactation period; and (3) mothers or children with a history of antibiotic, probiotic, or prebiotic use within the previous three months.

2.2 Questionnaire and fecal sample collection

The following information was extracted from both the case and control groups using standardized questionnaires administered by trained investigators: demographics such as age, gender, and living environment; family-related factors such as having siblings, passive smoke inhalation, family history of PIBD and autoimmune disease, and parental education level; and specific details related to the mother's preconception, pregnancy, or lactation periods, including medication history and any past illnesses. Additionally, we inquired about the early-life experiences of the children, focusing on feeding patterns and antibiotic use. For the case group, we also collected detailed information on their PIBD.

Fecal samples were collected from both children and their mothers in the case and control groups using stool nucleic acid collection and preservation tubes containing DNA preservation solution (Norgen, ON, Canada) after guidance by trained personnel. Following collection, the samples were immediately stored at −80 °C in a freezer.

2.3 Fecal 16S rRNA amplicon sequencing

After the fecal samples were thawed, we extracted the total microbial DNA using the QIAamp PowerFecal Pro DNA Kit (QIAGEN, NRW, Germany) and measured the DNA concentration. We amplified the V3-V4 hypervariable region of the bacterial 16S ribosomal RNA (rRNA) gene using primers 5'-CCTAYGGGRBGCASCAG-3' (forward) and 5'-GGACTACNNGGGTATCTAAT-3' (reverse). The polymerase chain reaction (PCR) products were purified using magnetic beads and mixed at the same concentration. Finally, we detected the complementary DNA (cDNA) and recovered the target bands.

2.4 Data statistics and fecal microbiota sequencing analysis

Descriptive statistics were used to summarize the general demographic characteristics of all participants. Continuous variables were reported as medians and interquartile ranges, and the Mann-Whitney *U* test was used to compare the two groups. Categorical variables were analyzed in terms of number and percentage (*n*, %), and the Chi-square test was used to compare the two groups. We conducted binary logistic regression analyses to identify risk factors associated with PIBD. Each variable underwent univariate analysis first, and the candidate variables with $P<0.05$ in univariate analyses were chosen for inclusion in the multivariate model. The results were expressed by odds ratios (ORs) and 95% confidence intervals (95% CIs). All statistical analyses were performed using SPSS software version 26.0 (SPSS Inc., IL, USA). Statistical significance was set at $P<0.05$.

After library construction and qualification, we performed sequencing using the NovaSeq 6000 platform (Illumina, CA, USA). After trimming barcodes and primer sequences, we assembled the data using Flash (V1.2.11) (Magoč and Salzberg, 2011), filtered it using fastp (V0.23.1) (Bokulich et al., 2013), and removed chimeras after comparison with the SILVA database (Edgar et al., 2011). Next, denoising was performed using the DADA2 module of QIIME2 (V202202) software to generate amplicon sequence variants (ASVs). Phylogenetic analysis of species was conducted using the QIIME2 software with the SILVA 138.1 database (https://www.arb-silva.de). Normalization was performed on the sample with the lowest data volume, and α-diversity and β-diversity were calculated. We used the Wilcoxon test to examine α-diversity and intragroup β-diversity, and used permutational multivariate analysis of variance (PERMANOVA) to test intergroup β-diversity. We then created a Venn diagram with a threshold of occurrence frequency >10% in each group. Linear discriminant analysis (LDA) effect size (LEfSe) analysis was used to identify statistically different bacteria between the two groups, with a threshold of lg(LDA score)>3 (Segata et al., 2011). Phylogenetic investigation of communities by reconstruction of unobserved states 2 (PICRUSt2) was used to predict metabolic pathways of the gut microbiota (Douglas et al., 2020), which were then statistically analyzed using a non-paired *t*-test. Fast expectation-maximization for microbial source tracking (FEAST) was employed to trace the sources of the gut microbiota (Shenhav et al., 2019). Abundance matrices were plotted at the ASV level. We used the Spearman correlation test to calculate the correlation between different ASVs and clinical variables and conducted random forest analysis using the random forest (V4.7-1.1) R package. Receiver operating characteristic (ROC) curves were plotted using the pROC (V1.16.2) R package, and cluster analysis was performed at the genus level to determine the gut type of each sample (Arumugam et al., 2011).

3 Results

3.1 General demographic characteristics of the study population

A total of 176 mother–child pairs were recruited for the study, including 54 cases and 122 controls. The demographic characteristics of the patients with PIBD and the controls are shown in Table 1. In the case group, there were 18 UC (33.3%), 28 CD (51.9%), and 8 unclassified IBD cases (14.8%). There were no significant differences in age, gender, place of birth, or living area between the two groups. Table S1 presents the disease classification, severity, and laboratory test results for the PIBD group.

3.2 Clinical risk factors for children with IBD

The variables associated with PIBD are shown in Table 2. Our univariate analyses revealed that a family history of autoimmune disease (unadjusted OR, 6.90; 95% CI, 1.75–27.14), antibiotic use during pregnancy (unadjusted OR, 10.44; 95% CI, 2.14–50.98), and

Table 1 Demographic characteristics of the study population

Characteristics	PIBD (*n*=54)	Controls (*n*=122)	*P* value
PIBD subtype			
CD	28 (51.9%)		
UC	18 (33.3%)		
Unclassified IBD	8 (14.8%)		
Age (years)	12.00 (10.75–14.00)	11.00 (10.00–13.00)	0.060
Gender			0.941
Male	26 (48.1%)	58 (47.5%)	
Female	28 (51.9%)	64 (52.5%)	
Place of birth			0.308
Beijing	32 (59.3%)	82 (67.2%)	
Other	22 (40.7%)	40 (32.8%)	
Living area			0.964
Urban area	45 (83.3%)	102 (83.6%)	
Rural area	9 (16.7%)	20 (16.4%)	

The values are expressed as number (percentage), except ages which are expressed as mean (range). PIBD: pediatric inflammatory bowel disease (IBD); CD: Crohn's disease; UC: ulcerative colitis.

antibiotic use during lactation (unadjusted OR, 6.12; 95% CI, 1.15–32.63) were associated with an increased risk of PIBD. Conversely, a higher education level for either the mother (unadjusted OR, 0.45; 95% CI, 0.23–0.87) or the father (unadjusted OR, 0.31; 95% CI, 0.15–0.61) was correlated with a reduced PIBD risk. Upon incorporating these factors into our multivariate model, we determined that a family history of autoimmune disease (adjusted OR, 5.62; 95% CI, 1.21–26.10), antibiotic use during pregnancy (adjusted OR, 5.54; 95% CI, 1.01–30.41), and a higher education level of the father (adjusted OR, 0.34; 95% CI, 0.14–0.84) remained statistically significant factors.

3.3 Differences in the gut microbiota between children with IBD and healthy children

We randomly chose 18 mother–child pairs from both the case and control groups, and their fecal samples underwent 16S rRNA amplicon sequencing. In the subsequent results, we defined the groups as IBD-C (children with IBD), IBD-M (mothers of children with IBD), H-C (healthy children), and H-M (mothers of healthy children).

First, we compared the α-diversity of the gut microbiota between the IBD-C and H-C groups and found a significantly lower level of α-diversity in the IBD-C group, as shown by the Shannon index, Chao1 index, observed ASVs, and Simpson index (Figs. 1a, 1b, and S1a). Principal coordinates analysis (PCoA) based on Bray-Curtis distance revealed that the gut microbiota of the IBD-C and H-C groups could be clearly distinguished (Fig. 1c), and the IBD-C group exhibited higher β-diversity within the group (Fig. S1b), indicating lower similarity between samples. Furthermore, we conducted LEfSe analysis at the phylum, genus, and ASV levels to explore differences between the two groups. Among eight shared phyla, Proteobacteria and Fusobacteriota were significantly enriched in the IBD-C group (Figs. S1c–S1e). Among 102 shared genera, the IBD-C group showed the highest LDA effect sizes for *Escherichia-Shigella* and *Enterococcus*, while the H-C group exhibited the highest LDA effect sizes for *Faecalibacterium* and *Subdoligranulum* (Figs. 1d–1g). Observations at the ASV level indicated that, besides some differential genera, potential species with alleviating effects on IBD, such as *Bacteroides* (species unknown 1), *Bifidobacterium adolescentis*, and *Blautia obeum*, showed significantly lower abundance in the IBD-C group (Figs. S1f and S1g). Further prediction of functional differences in the gut microbiota between the two groups using PICRUSt2 revealed a series of different metabolic pathways. The Entner-Doudoroff pathway and certain amino acid synthesis pathways were enriched in the IBD-C group, while pathways such as NAD salvage and N10-formyl-tetrahydrofolate synthesis were depleted. Additionally, pathways involved in the synthesis of potentially pro-inflammatory compounds, such as menaquinol and taxadiene (a precursor of paclitaxel), were enriched in the gut microbiota of the IBD-C group (Fig. 1h).

We also conducted a comparison of the gut microbiota between children with CD (CD-C) and UC (UC-C) subtypes, which revealed no significant differences in α-diversity, community composition, or β-diversity between these two groups (Figs. 2a–2c and S2a–S2f). Both CD-C and UC-C were notably distinct from the healthy controls (H-C) (Fig. 2c). Nonetheless, the LEfSe analysis of the IBD subtypes showed that the *Sutterella* and *Ruminococcus torques* group exhibited the greatest LDA effect size in the CD-C group, whereas the *Ruminococcus gnavus* group and *Veillonella* had the greatest LDA effect size in the UC-C group (Figs. 2d and S2g). Moreover, to account for potential differences between pediatric patients with active and remitting phases of IBD, we compared the gut microbiota of children with active IBD (IBD-C-A), children with

Table 2 Clinical risk factors for pediatric inflammatory bowel disease

Variables	PIBD* (*n*=54)	Controls* (*n*=122)	Unadjusted		Adjusted[a]	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Personal history for children						
Antibiotic use	45 (83.3%)	112 (91.8%)	0.45 (0.17–1.17)	0.101		
Appendectomy or tonsillectomy	1 (1.9%)	3 (2.5%)	0.75 (0.08–7.36)	0.804		
Family-related factors						
Having siblings	26 (48.1%)	50 (41.0%)	1.34 (0.70–2.55)	0.377		
Passive smoke inhalation	22 (40.7%)	55 (45.1%)	0.84 (0.44–1.60)	0.593		
Family history of IBD	2 (3.7%)	0				
Family history of autoimmune diseases	8 (14.8%)	3 (2.5%)	**6.90 (1.75–27.14)**	**0.006**	**5.62 (1.21–26.10)**	**0.028**
Education level of mother						
No degree	26 (48.1%)	36 (29.5%)	1			
Bachelor's degree or above	28 (51.9%)	86 (70.5%)	**0.45 (0.23–0.87)**	**0.018**	0.79 (0.32–1.94)	0.602
Education level of father						
No degree	26 (48.1%)	27 (22.1%)	1			
Bachelor's degree or above	28 (51.9%)	95 (77.9%)	**0.31 (0.15–0.61)**	**0.001**	**0.34 (0.14–0.84)**	**0.020**
Prenatal, perinatal, and postnatal factors						
Preconception antibiotic use	2 (3.7%)	8 (6.6%)	0.55 (0.11–2.67)	0.457		
Preconception body mass index						
<18.5	5 (9.3%)	18 (14.8%)	1			
18.5–23.9	40 (74.1%)	89 (73.0%)	1.62 (0.56–4.66)	0.373		
≥24.0	9 (16.7%)	15 (12.3%)	2.17 (0.59–7.85)	0.242		
Antibiotic use during pregnancy	8 (14.8%)	2 (1.6%)	**10.44 (2.14–50.98)**	**0.004**	**5.54 (1.01–30.41)**	**0.049**
Age ≥35 years at delivery	7 (13.0%)	15 (12.3%)	1.06 (0.41–2.78)	0.902		
Premature delivery or birth asphyxia	5 (9.3%)	3 (2.5%)	4.05 (0.93–17.60)	0.062		
Cesarean section	27 (50.0%)	59 (48.4%)	1.07 (0.56–2.03)	0.841		
Breastfeeding	48 (88.9%)	118 (96.7%)	0.27 (0.07–1.00)	0.051		
Refrigerated breast milk feeding	13 (24.1%)	44 (36.1%)	0.56 (0.27–1.16)	0.119		
Lactating antibiotic use	5 (9.3%)	2 (1.6%)	**6.12 (1.15–32.63)**	**0.034**	4.10 (0.66–25.24)	0.132
Postnatal depression or anxiety	3 (5.6%)	17 (13.9%)	0.36 (0.10–1.30)	0.119		

* The values are expressed as number (percentage). PIBD: pediatric inflammatory bowel disease (IBD); OR: odds ratio; CI: confidence interval. Statistically significant results are shown in bold (P<0.05). [a] Variables with P<0.05 in univariate analyses were included in the multivariate model.

remissive IBD (IBD-C-R), and H-C. The results indicated that the α-diversity in IBD-C-A was significantly lower than that in H-C, while no significant differences were observed between IBD-C-R and H-C (Figs. 2e and S2h). The stacked bar plot results demonstrated that the gut microbiota composition of IBD-C-R patients was more similar to that of H-C than to that of IBD-C-A patients (Figs. 2f and 2g). PCoA revealed a significant difference between IBD-C-A and H-C, with a higher explained variance than that of IBD-C-R (Fig. 2h). The β-diversity of the IBD-C-A group was significantly higher than those of the other two groups using Bray-Curtis distance (Fig. S2i). At the genus level, the LEfSe analysis results indicated enrichment of *Faecalitalea*, *Flavonifractor*, and *Colidextribacter* in the IBD-C-R group, while *Streptococcus* and *Clostridium sensu stricto 1* were enriched in the IBD-C-A group (Figs. 2i and 2j).

3.4 Differences in the gut microbiota between mothers of children with IBD and mothers of healthy children

We further examined the gut microbiota composition in mothers of children with IBD and healthy controls. The α-diversity of the gut microbiota showed no significant differences between the IBD-M and H-M groups in the Shannon index, Chao1 index, observed ASVs, or Simpson index, although there was a decreasing trend in the IBD-M group (Figs. 3a, 3b, and S3a). PCoA based on the Bray-Curtis distance revealed

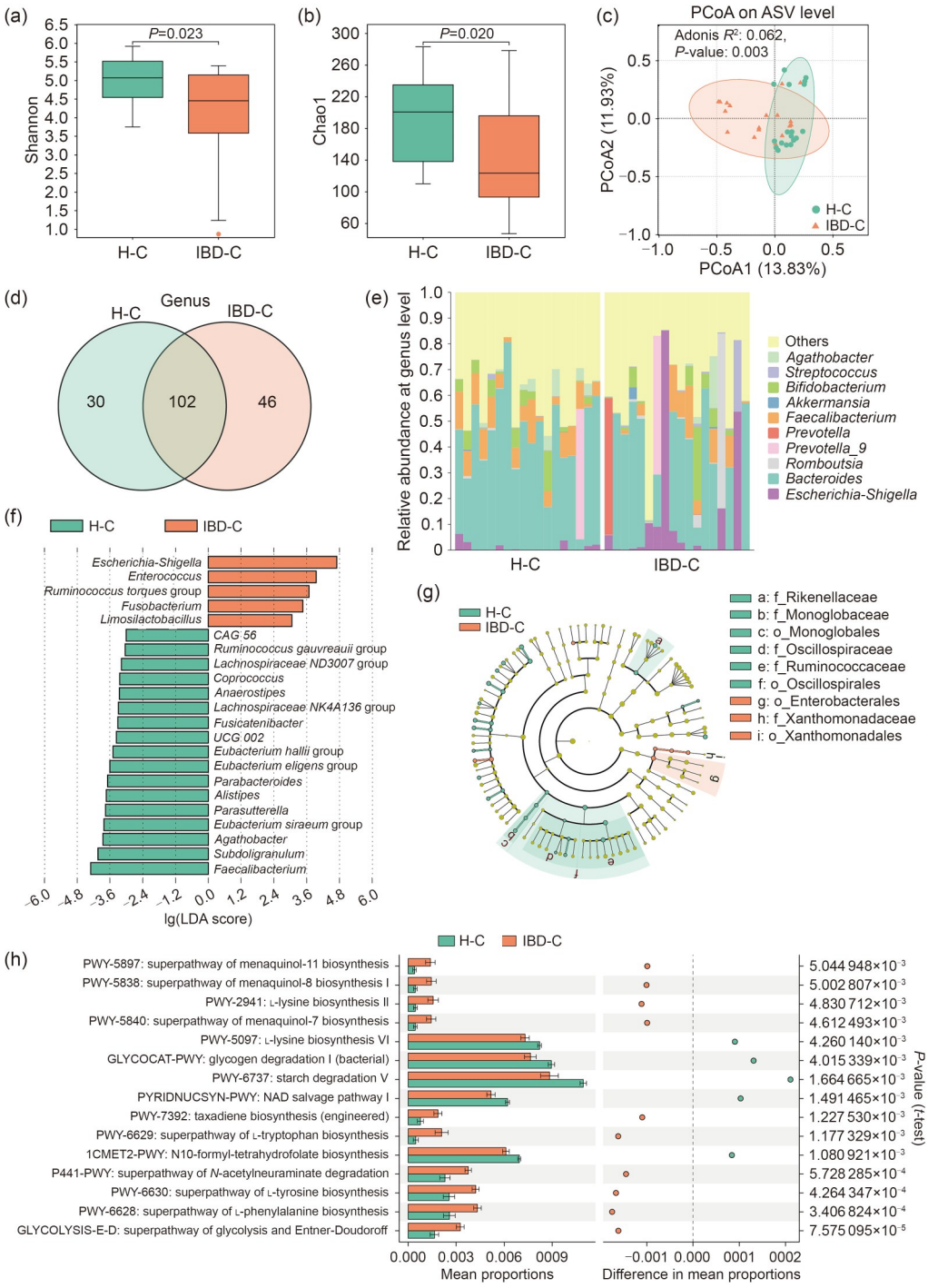

Fig. 1 Characteristics and functions of the gut microbiota in children. (a) Shannon index of the gut microbiota in healthy children (H-C) and children with inflammatory bowel disease (IBD-C). (b) Chao1 index of the gut microbiota in the two groups. (c) Principal coordinates analysis (PCoA) of the gut microbiota in the two groups based on Bray-Curtis distance, with ellipses representing 95% confidence intervals (CIs). (d) Venn diagram at the genus level showing overlapping and unique components in the two groups. (e) Stacked bar chart of the top 10 abundant genera. (f) Different genera with lg(LDA score)>3 and P<0.05 in the two groups. (g) Cladogram of different genera in the two groups, with each ring representing a taxonomic level (from phylum to genus) and the diameter of each circle representing its relative abundance. (h) Relative abundance (with 95% CIs) of the top 15 different functional pathways in the gut microbiota of the two groups. The error bar indicates the standard deviation (n=18). ASV: amplicon sequence variant; LDA: linear discriminant analysis.

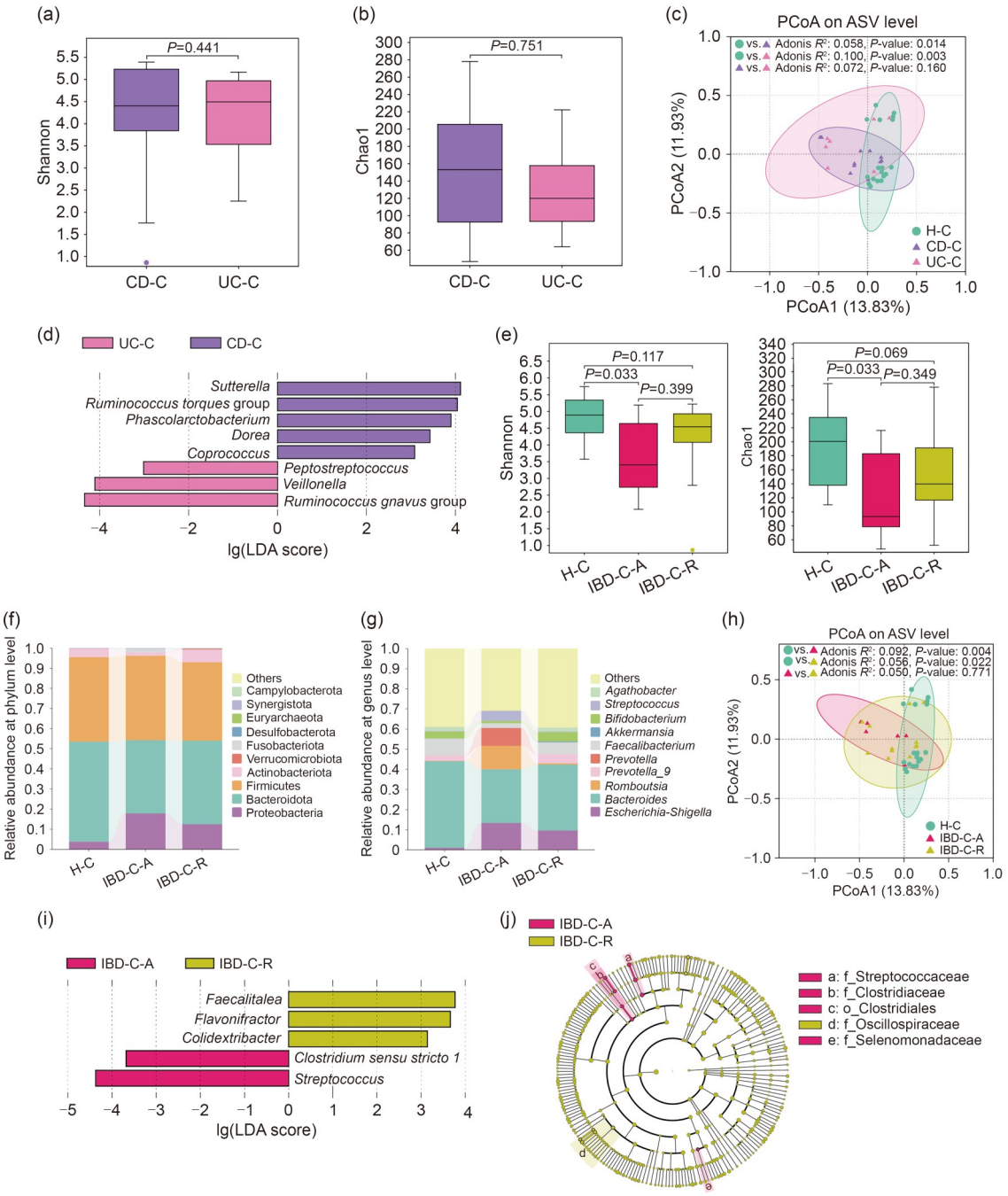

Fig. 2 Gut microbiota characteristics of children with IBD (for different subtypes or disease stages). (a) Shannon index of the gut microbiota in children with CD (CD-C) and children with UC (UC-C). (b) Chao1 index of the gut microbiota in both groups. (c) Principal coordinates analysis (PCoA) of the gut microbiota in CD-C, UC-C, and healthy children (H-C) based on Bray-Curtis distance, with ellipses representing 95% confidence intervals (CIs). (d) Different genera with lg(LDA score)>3 and P<0.05 in CD-C and UC-C patients. (e) The Shannon and Chao1 indexes of the gut microbiota in H-C and children with active IBD (IBD-C-A) or remissive IBD (IBD-C-R). (f) Stacked bar chart of the top 10 abundant phyla. (g) Stacked bar chart of the top 10 abundant genera. (h) PCoA of the gut microbiota in IBD-C-A, IBD-C-R, and H-C based on Bray-Curtis distance, with ellipses representing 95% CIs. (i) Different genera with lg(LDA score)>3 and P<0.05 in the IBD-C-A and IBD-C-R groups. (j) Cladogram of different genera in the IBD-C-A and IBD-C-R groups, with each ring representing a taxonomic level (from phylum to genus) and the diameter of each circle representing its relative abundance. ASV: amplicon sequence variant; CD: Crohn's disease; IBD: inflammatory bowel disease; LDA: linear discriminant analysis; UC: ulcerative colitis.

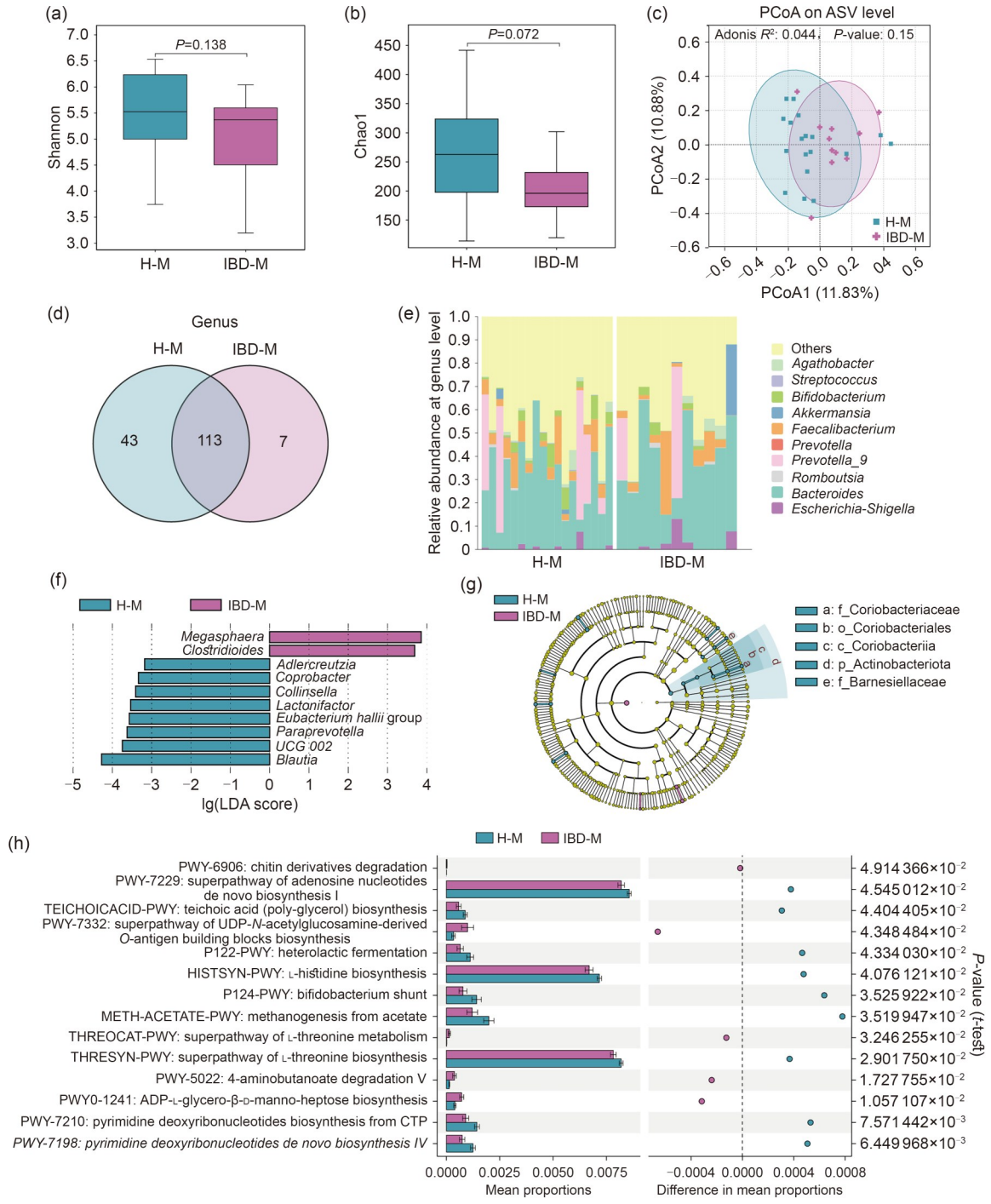

Fig. 3 Characteristics and functions of the gut microbiota in mothers. (a) Shannon index of the gut microbiota in mothers of healthy children (H-M) and mothers of children with inflammatory bowel disease (IBD-M). (b) Chao1 index of the gut microbiota in the two groups. (c) Principal coordinates analysis (PCoA) of the gut microbiota in the two groups based on Bray-Curtis distance, with ellipses representing 95% confidence intervals (CIs). (d) Venn diagram at the genus level, showing overlapping and unique components in the two groups. (e) Stacked bar chart of the top 10 abundant genera. (f) Different genera with lg(LDA score)>3 and *P*<0.05 in the two groups. (g) Cladogram of different genera in the two groups, with each ring representing a taxonomic level (from phylum to genus) and the diameter of each circle representing its relative abundance. (h) Relative abundance (with 95% CIs) of the top 14 different functional pathways in the gut microbiota of the two groups. The error bar indicates the standard deviation (*n*=18). ASV: amplicon sequence variant; LDA: linear discriminant analysis.

that the gut microbiota of the IBD-M and H-M groups was not significantly distinguishable (Fig. 3c). The IBD-M group exhibited higher β-diversity within the group, as calculated by the Bray-Curtis distance and weighted UniFrac distance (Fig. S3b). LEfSe analysis indicated some significant differences at the phylum, genus, and ASV levels. Among the ten shared phyla, the abundance of Actinobacteriota was significantly reduced in the IBD-M group (Figs. S3c–S3e). Among the 113 shared genera, *Megasphaera* and *Clostridioides* were predominant in the IBD-M group, whereas *Blautia* and *UCG 002* (belonging to Oscillospiraceae) were more prevalent in the H-M group (Figs. 3d–3g). At the ASV level, species such as *Bacteroides dorei*, *Parabacteroides merdae*, *Blautia* (species unknown), and *Bifidobacterium longum* were significantly diminished in the IBD-M group, while species such as *Bacteroides fragilis* and *Clostridiales bacterium CCNA10* were significantly enriched (Figs. S3f and S3g). Furthermore, using PICRUSt2 to predict functional differences in the gut microbiota between the two groups revealed that pathways enriched in the IBD-M group were often those involved in degradation pathways of organic compounds, such as γ-aminobutyric acid (GABA) and chitin derivatives, while the synthesis pathways of certain amino acids and nucleotides were depleted (Fig. 3h).

3.5 Clinical risk factors for the variation in children's and mothers' gut microbiota

Through PERMANOVA analysis, we found that the fathers' education level exerted the most significant influence on children's gut microbiota. Moreover, perinatal maternal antibiotic use, encompassing preconception, pregnancy, and lactation periods, potentially contributed to variations in children's gut microbiota (Fig. 4a). The results from PERMANOVA indicated that preconception body mass index (BMI) and perinatal antibiotic use significantly influenced the variations in mothers' gut microbiota (Fig. 4b).

3.6 Enterotype analysis of mother–child pairs in the case and control groups

In addition, the gut microbiota of both children and mothers was analyzed for enterotypes, resulting in classification of the four groups into two enterotypes (Fig. 5a). Enterotype 1 was distinguished by a high abundance of *Bacteroides* and *Faecalibacterium*, whereas Enterotype 2 featured a predominance of

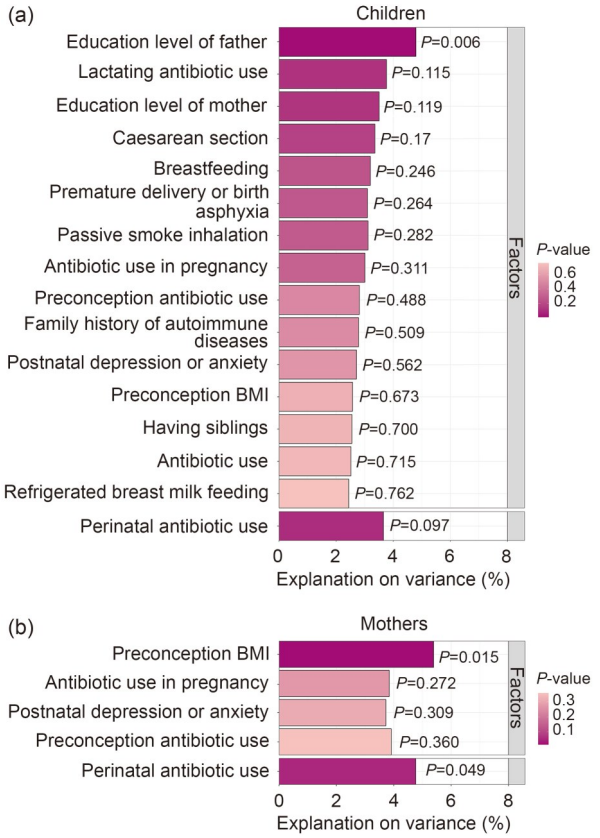

Fig. 4 Explanation of the variation in children's and mothers' gut microbiota according to clinical risk factors. (a) Permutational multivariate analysis of variance (PERMANOVA) was used to calculate the proportion of variation in children's gut microbiota explained by perinatal and family risk factors based on Bray-Curtis distance. Specifically, maternal perinatal antibiotic use was integrated as a variable in the analysis. (b) PERMANOVA was used to calculate the proportion of variation in mothers' gut microbiota explained by perinatal risk factors based on Bray-Curtis distance. Specifically, maternal perinatal antibiotic use was integrated as a variable in the analysis. BMI: body mass index.

Escherichia-Shigella and *Enterococcus* (Figs. 5b and 5c). Notably, only the IBD-C group exhibited both enterotypes. Among children with IBD presenting Enterotype 2, 40.00% of mothers had a history of perinatal antibiotic exposure, compared to just 16.13% among those with IBD presenting Enterotype 1, and among PIBD sufferers with Enterotype 1, 64.52% of the fathers had a Bachelor's degree or above, while no fathers had a Bachelor's degree or above in children with Enterotype 2. These findings further indicate that mothers' perinatal antibiotic exposure and familial factors may influence the development of PIBD by altering the gut microbiota of children.

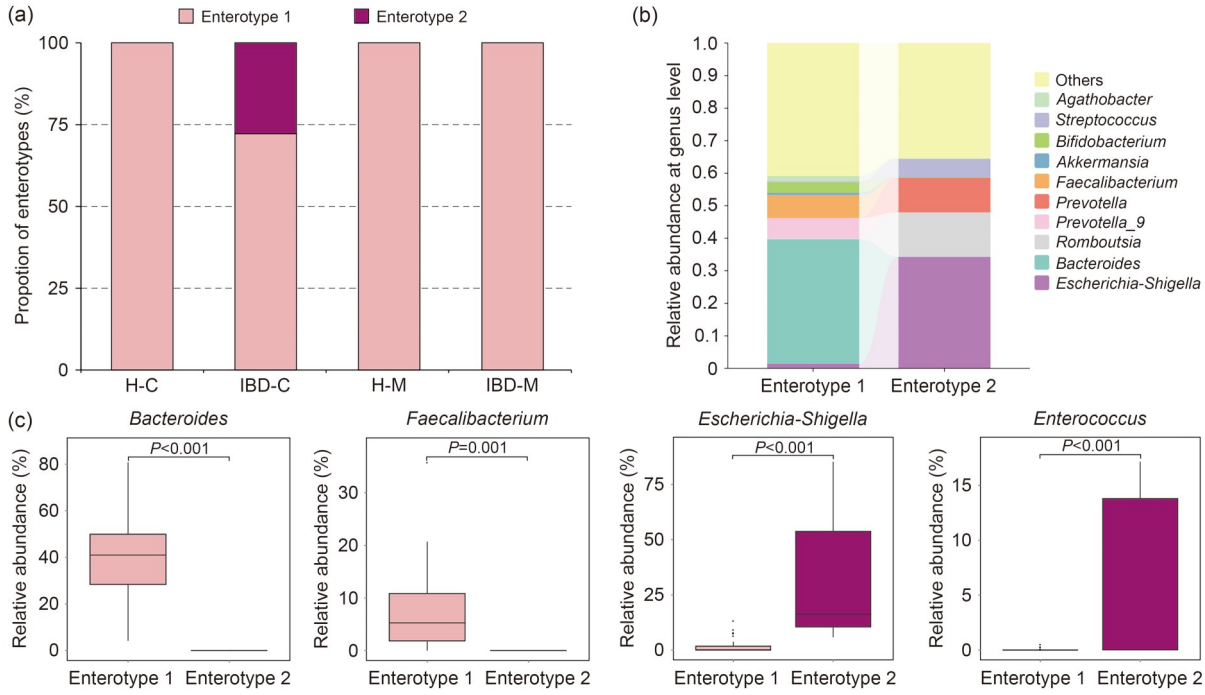

Fig. 5 Enterotype analysis of the four groups. (a) Gut microbiota of healthy children (H-C) and their mothers (H-M), as well as those of children with inflammatory bowel disease (IBD-C) and their mothers (IBD-M), can be classified into two enterotypes. (b) Stacked column plot at the genus level for Enterotype 1 and Enterotype 2. (c) Representative genera with the highest abundance for Enterotype 1 and Enterotype 2.

3.7 Similarity of gut microbiota characteristics of mother–child pairs

To investigate the similarity of the gut microbiota between mothers and their children, we first used a Venn diagram for observation and found that the number of shared ASVs among mothers and children in the same group surpassed that among mothers and children from different groups (Fig. 6a). Utilizing FEAST for microbiota tracing, we discovered that 89.11% of ASVs for children in the H-C group possibly originated from their mothers, whereas 57.80% of ASVs for children in the IBD-C group possibly originated from their mothers (Fig. 6b). Notably, despite the fact that intergenerational microbiota transmission was lower in the case group than in the control group, nearly all high-abundance strains were effectively shared between mothers and children in both groups (Fig. 6c). There were also no significant differences in gut microbiota similarity between mother–child pairs in the IBD-C and H-C groups (Fig. 6d). The overall microbial composition exhibited significantly greater similarity between mothers and their children than between mothers and unrelated children, as evidenced by metrics such as Bray-Curtis distance, Jaccard distance, and weighted UniFrac distance. Additionally, the overall microbial similarity between mothers was significantly higher than that between children (Fig. 6e).

3.8 PIBD biomarkers of gut microbiota of mothers

We performed Spearman correlation analyses between the top 10 differentially abundant ASVs of children's and mothers' gut microbiota and clinical variables. The differential ASVs in children were significantly correlated with multiple clinical indicators. Overall, the pediatric Crohn's disease activity index (PCDAI)/pediatric ulcerative colitis activity index (PUCAI) showed a positive correlation with *Escherichia-Shigella* and a negative correlation with *Faecalibacterium* (species unknown 1) (Fig. 7a). In mothers, the differential ASVs of the gut microbiota showed a negative correlation between PCDAI/PUCAI and *Parabacteroides merdae* (Fig. 7b).

Given the correlation between children's and mothers' gut microbiota and clinical indicators of children's disease, we were further able to identify potential biomarkers for distinguishing between the

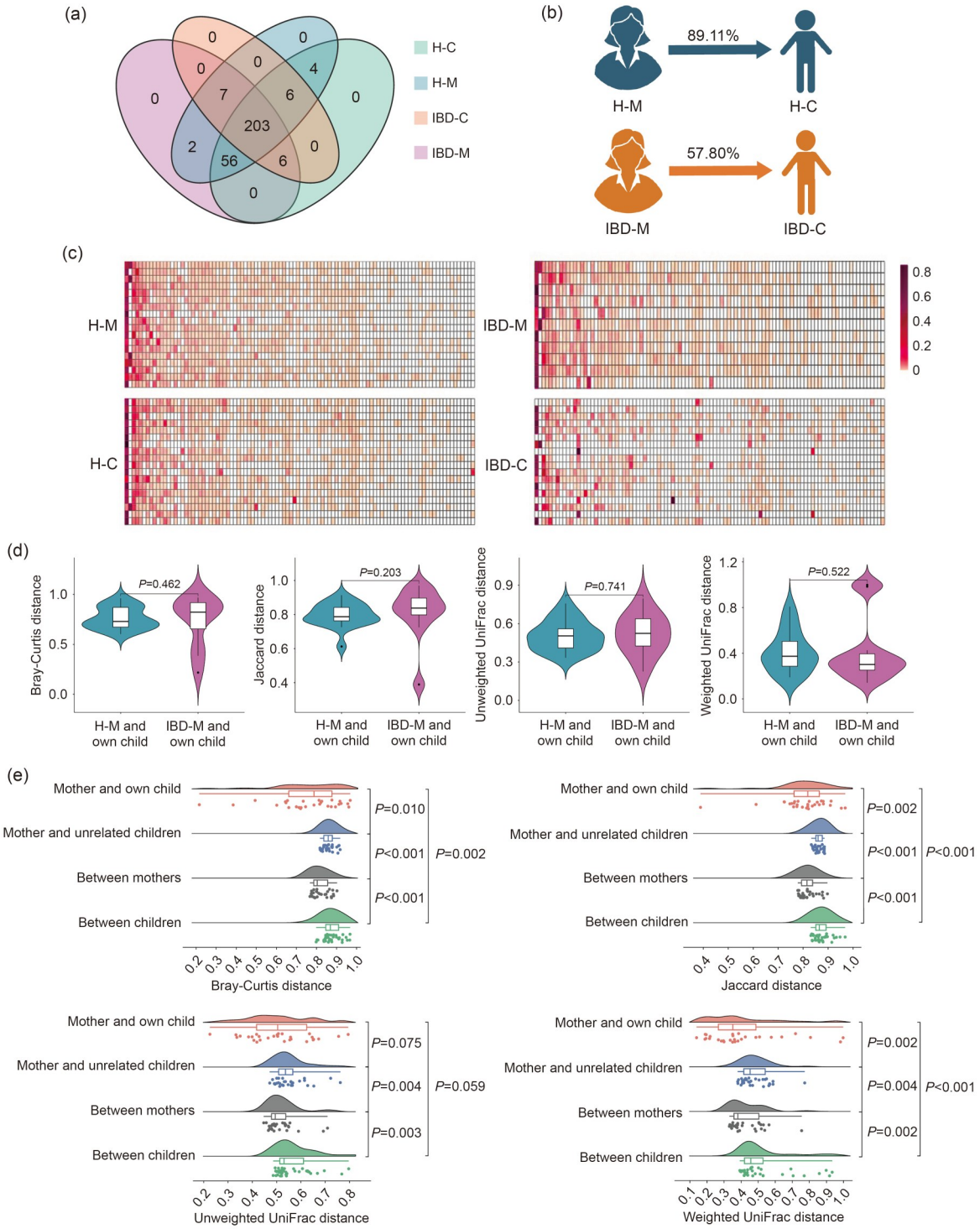

Fig. 6 Degree of similarity between mothers and children. (a) Venn diagram at the ASV level showing overlapping and unique components between healthy children (H-C) and their mothers (H-M), as well as between children with inflammatory bowel disease (IBD-C) and their mothers (IBD-M). (b) FEAST analysis indicating the transmission ratio of the gut microbiota between mothers and children within the same group. (c) Similarity of the gut microbiota between mothers and children at the ASV level. (d) Comparison of Bray-Curtis, Jaccard, unweighted UniFrac, and weighted UniFrac distances between H-M and IBD-M and their own children. (e) Comparison of Bray-Curtis, Jaccard, unweighted UniFrac, and weighted UniFrac distances between mothers and their own children, mothers and unrelated children, and all mothers and all children. ASV: amplicon sequence variant; FEAST: fast expectation-maximization for microbial source tracking.

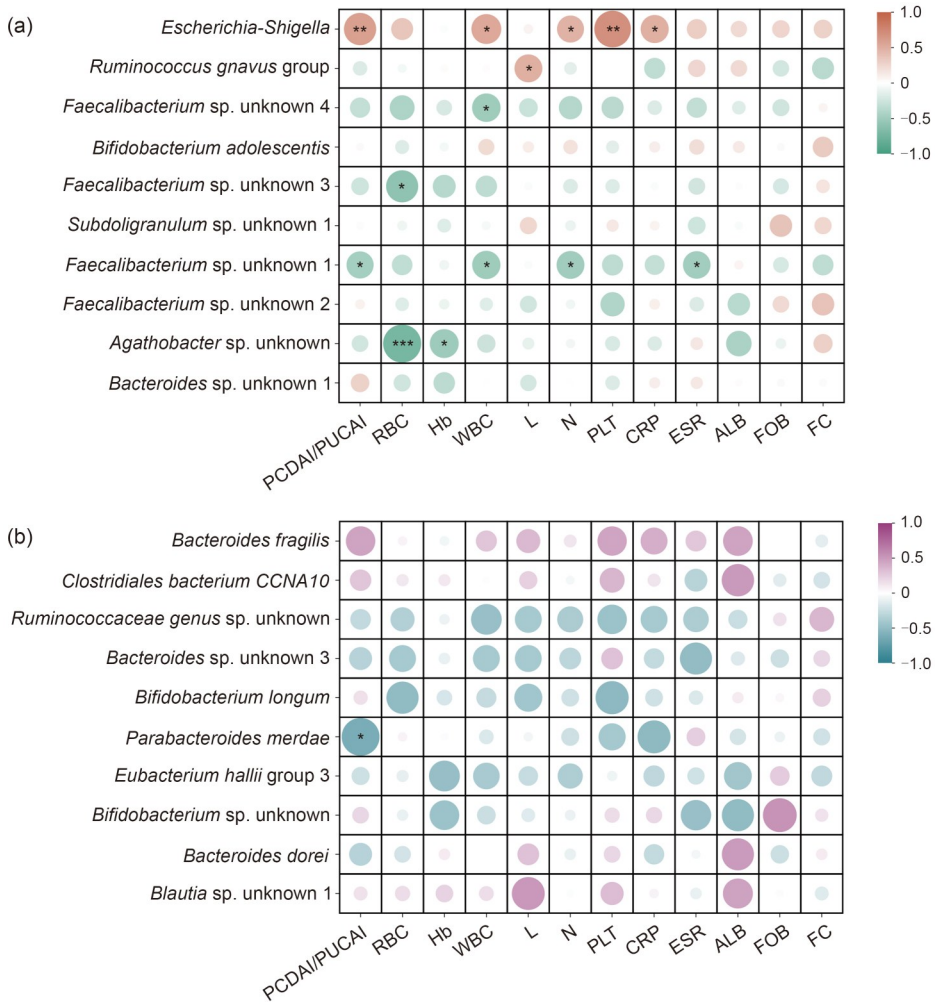

Fig. 7 Correlations between the gut microbiota of children and mothers and clinical indicators. (a) Correlations between the top 10 differentially abundant amplicon sequence variants (ASVs) in children and clinical indicators. (b) Correlations between the top 10 differentially abundant ASVs in mothers and clinical indicators. PCDAI: pediatric Crohn's disease activity index; PUCAI: pediatric ulcerative colitis activity index; RBC: red blood cell; Hb: hemoglobin; WBC: white blood cell; L: lymphocyte; N: neutrophil; PLT: platelet; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ALB: albumin; FOB: fecal occult blood; FC: fecal calprotectin. * P<0.05, ** P<0.01, *** P<0.001, ASVs vs. clinical indicators.

IBD-C and H-C groups via a random forest approach. In the gut microbiota of children, the five ASVs with the greatest decrease in the Gini index were *Lachnospiraceae bacterium GAM79*, *Blautia obeum*, *Blautia* (species unknown 3), *Escherichia-Shigella*, and *Bacteroides* (species unknown 1) (Fig. 8a). In the gut microbiota of mothers, the five ASVs with the greatest decrease in the Gini index were identified as *Blautia* (species unknown 1), Ruminococcaceae (genus species unknown), *Bacteroides fragilis*, *Eubacterium hallii* group 3, and Enterobacteriaceae (genus species unknown) (Fig. 8b).

Next, we compared the abundance of the top five potential bacterial biomarkers with the highest mean decrease in the Gini index in the gut microbiota of children and mothers. Although there was less overlap in potential biomarkers between children and mothers, eight of ten biomarkers showed a consistent fold-change of abundance (Fig. 9a), suggesting that mothers' gut microbiota may influence the development of PIBD in offspring by modulating the abundance of certain bacteria. To investigate this, we constructed ROC curves that would show the ability of these eight bacterial biomarkers in mothers' microbiota to distinguish between the IBD-C and H-C groups; the highest value for the area under the curve (AUC) was 0.8182 (Fig. 9b). After performing logistic regression on the biomarkers enriched in the H-M group, including *Blautia* (species

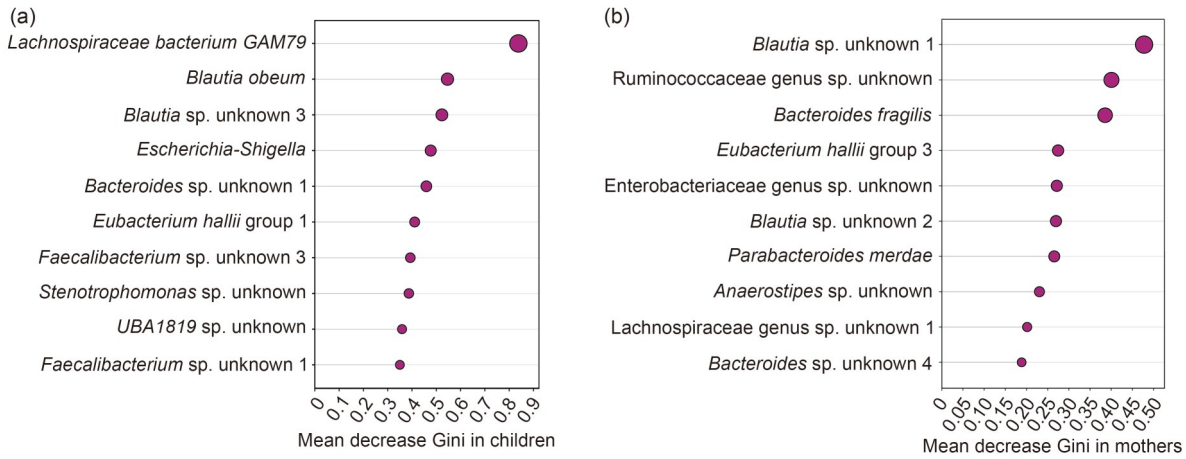

Fig. 8 Random forest analyses of the gut microbiota of children and mothers. (a) Amplicon sequence variants (ASVs) identified via the random forest method to distinguish healthy children (H-C) from children with inflammatory bowel disease (IBD-C). (b) ASVs identified via the random forest method to distinguish mothers of healthy control children (H-M) from mothers of children with inflammatory bowel disease (IBD-M).

unknown 1), *Eubacterium hallii* group 3, *Blautia obeum*, *Lachnospiraceae bacterium GAM79*, *Blautia* (species unknown 3), and *Bacteroides* (species unknown 1), as well as the biomarkers enriched in the IBD-M group (*Bacteroides fragilis* and *Escherichia-Shigella*), the ROC curve exhibited an AUC of 0.8687 for the H-M-enriched biomarkers and an AUC of 0.7828 for the IBD-M-enriched biomarkers (Fig. 9c).

4 Discussion

To the best of our knowledge, this is the first study that explores the gut microbiota composition of both children with IBD and their mothers, along with their intergenerational correlation. Our findings reveal that a family history of autoimmune disease and antibiotic use during pregnancy are positively associated with PIBD risk, while a higher education level of the father is protective. Compared with H-C, IBD-C exhibits reduced α-diversity, with enrichment of Proteobacteria, Fusobacteriota, *Escherichia-Shigella*, and *Enterococcus* and depletion of *Faecalibacterium*. IBD-M shows an increased abundance of *Clostridioides* and reduced levels of *Bacteroides dorei* and *Parabacteroides merdae*. Functional alterations in the gut microbiota were also observed in both children with IBD and their mothers. The gut microbiota in the IBD-C group exhibits two enterotypes. Intriguingly, the gut microbiota structures of mothers and children within the same group exhibit greater similarity. Some potential bacterial biomarkers of mothers discovered in this study, such as *Bacteroides fragilis* and *Eubacterium hallii*, demonstrate the ability to predict PIBD in offspring.

Exploring risk factors for PIBD is paramount not only for understanding its complex pathogenesis but also for identifying individuals at risk who may benefit from early intervention. In a large meta-analysis assessing the impact of different types of prenatal, perinatal, and postnatal exposure on IBD, researchers identified prenatal antibiotic exposure, tobacco smoke, and early-life otitis media as risk factors associated with IBD and breastfeeding as a protective factor for IBD (Agrawal et al., 2021). Our findings indicate that a family history of autoimmune disease is associated with an increased risk of PIBD, consistent with Mari et al. (2020)'s finding that first-degree relatives of patients with IBD have a higher risk of autoimmune disease, which partly reflects the role of family genetic predisposition in the development of IBD. In our study, antibiotic use during pregnancy is shown to be another risk factor for PIBD. Our previous meta-analysis demonstrated that antibiotic exposure is associated with an increased risk of PIBD and that exposure in the first year of life leads to a relatively high risk estimate (Duan et al., 2025). Furthermore, antibiotic exposure during pregnancy has been reported to affect the risk of PIBD in offspring. In a Swedish cohort study, antibiotics during pregnancy were associated with very-early-onset IBD in children (Örtqvist et al., 2019). Another nationwide study from Denmark found that exposure to ⩾3 courses of antibiotics during pregnancy increased IBD

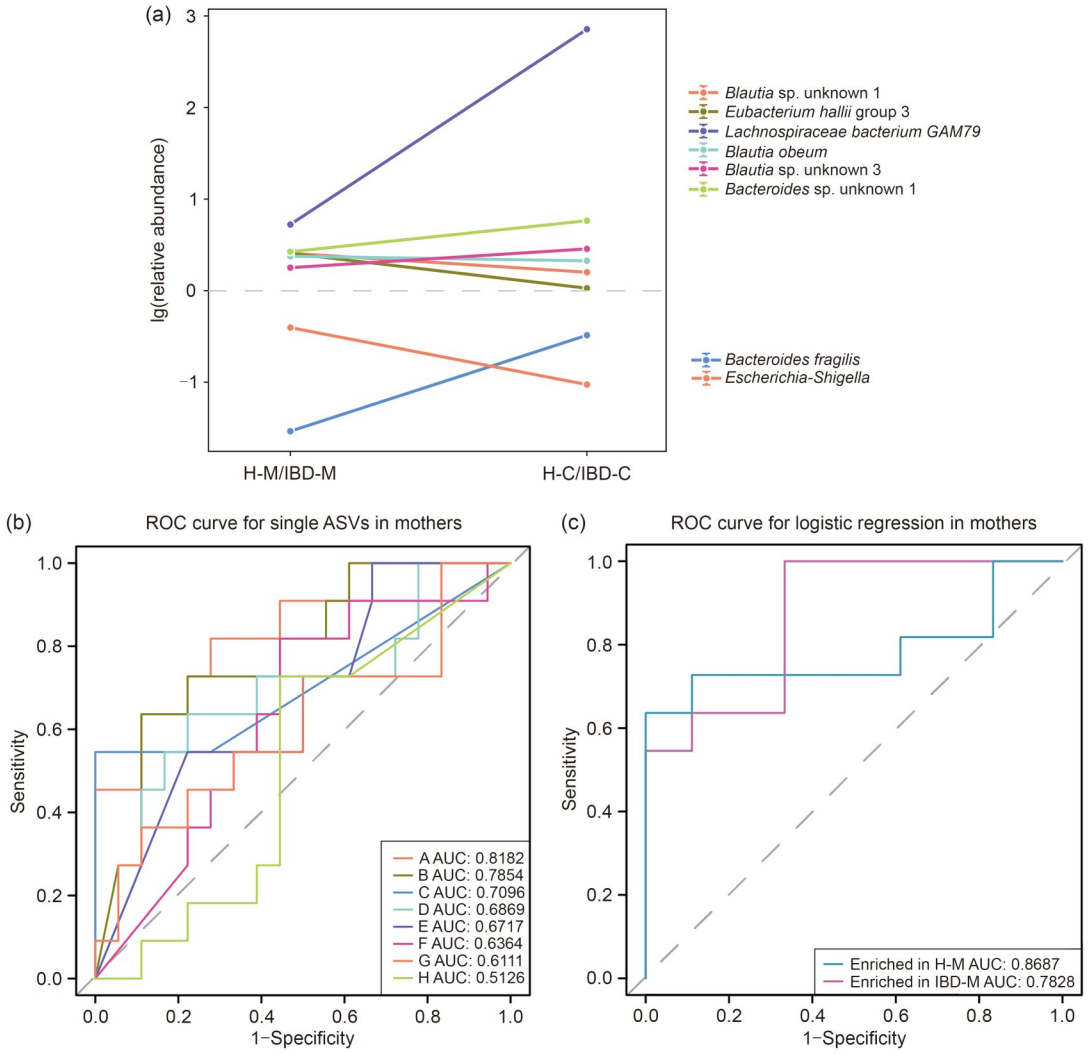

Fig. 9 Biomarkers in the gut microbiota of mothers. (a) We selected the top five biomarkers with the highest mean decrease Gini coefficient in the gut microbiota of children and mothers separately, resulting in a total of ten biomarkers. These biomarkers were further analyzed using the following approach: the average abundance of the biomarkers in mothers of healthy children (H-M) was compared with that in mothers of children with inflammatory bowel disease (IBD-M) by calculating the ratio. Subsequently, a logarithmic transformation was applied, which positioned the biomarkers enriched in the IBD-M group below the *x*-axis, while the depleted biomarkers were positioned above the *x*-axis. The same transformation was performed for healthy children (H-C) and children with inflammatory bowel disease (IBD-C). If both values of a biomarker are located on the same side of the *x*-axis, this indicates that the biomarker is simultaneously enriched/depleted in the IBD-C and IBD-M groups. Eight biomarkers with consistent change trends are presented. (b) Eight biomarkers were selected, and ROC curves were used to predict the risk of pediatric inflammatory bowel disease (PIBD) in children. A: *Blautia* sp. unknown 1; B: *Eubacterium hallii* group 3; C: *Bacteroides fragilis*; D: *Blautia obeum*; E: *Lachnospiraceae bacterium GAM79*; F: *Blautia* sp. unknown 3; G: *Escherichia-Shigella*; H: *Bacteroides* sp. unknown 1. (c) Logistic regression analysis was conducted for biomarkers enriched in the H-M and IBD-M groups separately to evaluate their ability to predict the risk of PIBD in children. ASV: amplicon sequence variant; AUC: area under the curve; ROC: receiver operating characteristic.

risk in offspring (Agrawal et al., 2023). It is biologically plausible that antibiotics can change the mother's gut microbiota, which in turn affects the offspring's gut microbiota and immune-system development, increasing their susceptibility to IBD. A higher education level of the father appears to be a protective factor for PIBD, and education level is often related to other factors that may affect IBD, such as diet, family income, and social living environment (Krishna et al., 2020).

Previous studies have indicated that PIBD patients exhibit alterations in their gut microbiota (Wang et al., 2021; D'Adamo et al., 2023). In our study, we observed

significant changes in the gut microbiota of children with IBD, particularly in the populations of Proteobacteria and Fusobacteriota, which were prominently enriched in the IBD-C group. Proteobacteria comprises various pathogenic microbiota, such as *Escherichia coli*, *Escherichia-Shigella*, *Vibrio cholerae*, and *Pseudomonas aeruginosa*, which are often enriched in individuals with IBD (Mukhopadhya et al., 2012). Notably, enrichment of Fusobacteriota, primarily attributed to *Fusobacterium*, is strongly associated with colitis and colorectal cancer pathogenesis (Liu et al., 2020; Chen et al., 2023). Moreover, we discovered that the IBD-C group displayed enriched synthesis pathways for menaquinol and taxadiene, which may contribute to the onset of inflammation (Khorsand et al., 2022; Iwamuro et al., 2023). Conversely, the IBD-C group demonstrated depleted N10-formyl-tetrahydrofolate biosynthesis, which has been shown to have anti-inflammatory effects (Pathikkal et al., 2022). We also discovered that the community compositions of IBD-C-R and H-C are more similar than those of IBD-C-A and H-C, and the composition of IBD-C-R is enriched with *Clostridium sensu stricto 1*, which has been demonstrated to influence IBD activity (Leibovitzh et al., 2022), aligning with previous research findings (Chen et al., 2024).

Consistent with our hypothesis, the gut microbiota of IBD-M exhibits substantial differences compared with H-M, despite both groups being composed of healthy individuals. IBD-M is characterized by an increased abundance of opportunistic pathogens such as *Clostridioides* (Dong et al., 2023), while beneficial bacteria such as *Bacteroides dorei* (Sun et al., 2023) and *Parabacteroides merdae* (Qiao et al., 2022) are significantly diminished. The functional pathways enriched in IBD-M are associated with inflammatory compounds, including chitin derivatives (Lee et al., 2014) and *O*-antigen (Lehri et al., 2024), which are known to be components of pathogenic bacteria. Derivatives of GABA can promote colitis through the GABA receptor A (Wang et al., 2022). The involvement of these specific bacteria in these functional pathways suggests vertical transmission that influences the development of PIBD in offspring. Additionally, we found that the factors contributing to the differences in the gut microbiota between children and mothers may stem from the perinatal period or from certain familial factors, such as the education level of the father and perinatal maternal antibiotic use. These findings align with our analyses of risk factors for PIBD, indicating that these factors likely participate in PIBD development through their impact on the gut microbiota.

We further identified two distinct enterotypes within the IBD-C group. Enterotype 1 is characterized by a dominance of *Bacteroides*, while Enterotype 2 is characterized by a dominance of *Escherichia-Shigella*. The *Bacteroides* enterotype in children with PIBD is associated with disease remission, whereas the *Escherichia-Shigella* enterotype is associated with disease progression (Chen et al., 2024). Additionally, the IBD-C group exhibited elevated levels of *Enterococcus*, which can impede intestinal stem-cell proliferation through the production of tyramine (Li et al., 2024). Interestingly, within Enterotype 2, there are higher proportions of mothers with a history of perinatal antibiotic use and fathers with no degree. These findings provide supportive evidence for the underlying factors contributing to the variation observed in this enterotype.

Furthermore, we analyzed the association between the gut microbial compositions of children and their mothers, and the results revealed high similarities in the fecal microbiota of mother–child pairs, especially in the control group. This may be the result of a combined effect of long-term maternal microbial imprinting throughout pregnancy and microbial transmission driven by a shared social environment later in life (Valles-Colomer et al., 2023). The mother-offspring vertical transmission of microbiota is the earliest and most important factor influencing microbial structure in infants (Asnicar et al., 2017). Based on metagenomic profiling of the microbiome from 25 mother–infant pairs across multiple body sites, Ferretti et al. (2018) found that the maternal gut was the largest source of colonizing microbiota in the gastrointestinal tract of healthy infants. The large number of strains shared at birth confirms maternal microbiome seeding of the infant's gut, and in addition, strain sharing remains significant in senior individuals, with one study showing that non-cohabiting mother-offspring pairs still share significantly more strains than children do with unrelated mothers (Valles-Colomer et al., 2023). This is consistent with our finding that the closest microbiome proximity is between mothers and their own children. Emerging evidence indicates that the early colonized microbiota is an essential driver of a range of processes, including development, immunity, and metabolism, ultimately affecting host health in the long

term (Tian et al., 2023). Any factors that affect the maternal microbiota can also disrupt optimal microbial acquisition for infants, leading to an increased lifetime risk for various diseases (Martino et al., 2022). Based on the above, we propose a hypothesis that perturbation of the maternal gut microbiota during pregnancy due to various factors (such as antibiotic exposure, mother-to-child vertical transmission of the microbiota, and microbial alterations during the critical developmental window) is associated with greater susceptibility to IBD later in life. Interventions that favorably modify microbial composition would provide opportunities for overcoming microbial imbalances in early life, for example, providing probiotic supplements to mothers (Korpela et al., 2018). In addition, the high microbial similarities in mother–child pairs in our findings may be because gut microbes can be co-acquired due to shared environmental factors. However, the cross-sectional nature of the study prevented us from elucidating these mechanisms and providing a longitudinal view. Additional large cohort studies are needed to determine mother–child pairs in chronological order and to evaluate alterations in the gut microbiota of mothers and children mechanistically.

We have identified eight bacterial biomarkers that exhibit shared patterns of variation between the case and control groups. The typical vertical transmission of the gut microbiota underscores the significant predictive value of maternal biomarkers for PIBD risk in offspring. The function of *Bacteroides fragilis*, which we found to be enriched in IBD-M, has been extensively studied. A subset of *Bacteroides fragilis* secretes *Bacteroides fragilis* toxin, known as enterotoxigenic *Bacteroides fragilis* (ETBF), which can disrupt the colonic epithelial barrier by cleaving E-cadherin (Sears et al., 2014), leading to chronic colitis (Rhee et al., 2009). Another subset of *Bacteroides fragilis* acts as a commensal microbe, providing metabolic benefits (Chan et al., 2019). ETBF reveals a high transmission capacity from mother to offspring (Valles-Colomer et al., 2023). It establishes colonization within the lamina propria and persists into adulthood, further antagonizing beneficial bacteria and disrupting intestinal homeostasis (Hill et al., 2024). *Blautia*, which exhibits decreased abundance in both IBD-M and IBD-C, encompasses potentially beneficial bacteria with anti-inflammatory properties that improve the host's gut homeostasis, inhibit colonization by pathogens, and influence lipid metabolism (Benítez-Páez et al., 2020; Liu et al., 2021). The vertical transmission of *Blautia* depends on breastfeeding (Qi et al., 2022). Maternal overweight and stress are associated with a decreased abundance of *Blautia*, making offspring more susceptible to conditions such as colitis and cognitive abnormalities (Sun et al., 2021; Buchenauer et al., 2023). *Eubacterium hallii* shows reduced abundance in mothers' and children's gut microbiota in the IBD group. It plays a role in producing butyrate and propionate, supporting intestinal integrity, and suppressing pro-inflammatory factors to prevent intestinal inflammation (Mukherjee et al., 2020). *Eubacterium hallii* is also recognized as an early producer of butyrate in the infant gut (Pham et al., 2016). Additionally, *Escherichia-Shigella*, which is enriched in the IBD-C group and exhibits higher abundance in the IBD-M group, is a pathogen consistently found in the gut microbiota of individuals with disease (Baltazar-Díaz et al., 2022; Zhao et al., 2022). It induces colitis by penetrating epithelial cells to induce apoptosis in infected macrophages and release interleukin-1β (IL-1β) (Mirsepasi-Lauridsen et al., 2019).

Our study has significant strengths. It serves as a pilot study to investigate the microbiota of mother–child pairs simultaneously and their relationship with the development of IBD in children, filling the gap in current research on the maternal gut microbiota and subsequent IBD. The study has also identified potential biomarkers for PIBD susceptibility, which suggests that modulating the abundance of bacterial biomarkers in the maternal gut microbiota during the perinatal period may be an effective preventive strategy against disease development in offspring.

However, there were some limitations that warrant discussion for future applications. First, due to the low incidence of PIBD and the relatively small sample size, clinically stratified analyses based on PIBD subtype and severity were not feasible. Additionally, it was challenging to collect fecal samples from mothers and children simultaneously, which resulted in insufficient data for gut microbiota analyses. Second, as with other case-control studies and questionnaire surveys, the results are inherently prone to recall bias and should be interpreted with caution. Further large-scale cohort studies will be necessary. Finally, 16S rRNA sequencing cannot provide sequences at a high resolution, such as shotgun sequencing.

5 Conclusions

Our study identified familial and perinatal risk factors for PIBD and elucidated differences in the gut microbiota structure, composition, and functionality between PIBD children and their mothers and healthy controls. These risk factors partially explain the differences observed in the gut microbiota. We observed remarkable similarities in the gut microbiota between mothers and children. The gut microbiota of children and mothers is associated with the occurrence and severity of PIBD, and mothers' bacterial biomarkers effectively predict PIBD, independently or in combination. Our findings suggest a potential intergenerational influence of the maternal microbiota on IBD development in children. Further large cohort studies are warranted to determine mother–child pairs in chronological order and evaluate gut microbiota alterations in mothers and children mechanistically.

Data availability statement

The 16S rRNA sequencing data of the gut microbiota have been deposited into the Sequence Read Archive (SRA) database and can be accessed at https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1125871. Other research data can be obtained from the authors upon reasonable request.

Acknowledgments

This work was supported by the National Key R&D Program of China (Nos. 2021YFA1301300, 2019YFA0905600, and 2023YFC2706503) and the National Natural Science Foundation of China (Nos. 82170557 and 82000510). Some of the figures were generated via https://www.chiplot.online.

Author contributions

Liping DUAN, Cunzheng ZHANG, and Ruqiao DUAN proposed the scientific question. Cunzheng ZHANG and Ruqiao DUAN designed the study, analyzed the data, and wrote the draft of the manuscript. Liping DUAN and Zailing LI obtained funding. Cunzheng ZHANG and Yuzhu CHEN conducted the bioinformatics analyses. Cunzheng ZHANG, Ruqiao DUAN, Nini DAI, Gaonan LI, Xiao'ang LI, Xiaolin JI, and Xuemei ZHONG collected clinical samples and obtained patient information through consent forms and questionnaires. Liping DUAN performed project management and conducted critical revisions of the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Cunzheng ZHANG, Ruqiao DUAN, Nini DAI, Yuzhu CHEN, Gaonan LI, Xiao'ang LI, Xiaolin JI, Xuemei ZHONG, Zailing LI, and Liping DUAN declare no conflicts of interest.

This study was approved by the Institutional Review Board of Peking University Third Hospital (No. 2022-652-02). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients for being included in the study.

References

Agrawal M, Sabino J, Frias-Gomes C, et al., 2021. Early life exposures and the risk of inflammatory bowel disease: systematic review and meta-analyses. *EClinicalMedicine*, 36:100884. https://doi.org/10.1016/j.eclinm.2021.100884

Agrawal M, Poulsen G, Colombel JF, et al., 2023. Maternal antibiotic exposure during pregnancy and risk of IBD in offspring: a population-based cohort study. *Gut*, 72(4):804-805. https://doi.org/10.1136/gutjnl-2022-327724

Arumugam M, Raes J, Pelletier E, et al., 2011. Enterotypes of the human gut microbiome. *Nature*, 473(7346):174-180. https://doi.org/10.1038/nature09944

Asnicar F, Manara S, Zolfo M, et al., 2017. Studying vertical microbiome transmission from mothers to infants by strain-level metagenomic profiling. *mSystems*, 2(1):e00164-16. https://doi.org/10.1128/mSystems.00164-16

Baltazar-Díaz TA, González-Hernández LA, Aldana-Ledesma JM, et al., 2022. *Escherichia/Shigella*, SCFAs, and metabolic pathways—the triad that orchestrates intestinal dysbiosis in patients with decompensated alcoholic cirrhosis from western Mexico. *Microorganisms*, 10(6):1231. https://doi.org/10.3390/microorganisms10061231

Benítez-Páez A, del Pugar EMG, López-Almela I, et al., 2020. Depletion of *Blautia* species in the microbiota of obese children relates to intestinal inflammation and metabolic phenotype worsening. *mSystems*, 5(2):e00857-19. https://doi.org/10.1128/mSystems.00857-19

Bokulich NA, Subramanian S, Faith JJ, et al., 2013. Quality-filtering vastly improves diversity estimates from illumina amplicon sequencing. *Nat Methods*, 10(1):57-59. https://doi.org/10.1038/nmeth.2276

Bouhuys M, Lexmond WS, van Rheenen PF, 2023. Pediatric inflammatory bowel disease. *Pediatrics*, 151(1):e2022058037. https://doi.org/10.1542/peds.2022-058037

Buchenauer L, Haange SB, Bauer M, et al., 2023. Maternal exposure of mice to glyphosate induces depression- and anxiety-like behavior in the offspring via alterations of the gut–brain axis. *Sci Total Environ*, 905:167034. https://doi.org/10.1016/j.scitotenv.2023.167034

Chan JL, Wu SG, Geis AL, et al., 2019. Non-toxigenic *Bacteroides fragilis* (NTBF) administration reduces bacteria-driven chronic colitis and tumor development independent of

polysaccharide A. *Mucosal Immunol*, 12(1):164-177. https://doi.org/10.1038/s41385-018-0085-5

Chen HY, Tong TY, Lu SY, et al., 2023. Urea cycle activation triggered by host-microbiota maladaptation driving colorectal tumorigenesis. *Cell Metab*, 35(4):651-666.E7. https://doi.org/10.1016/j.cmet.2023.03.003

Chen W, Wang DS, Deng X, et al., 2024. Bile acid profiling as an effective biomarker for staging in pediatric inflammatory bowel disease. *Gut Microbes*, 16(1):2323231. https://doi.org/10.1080/19490976.2024.2323231

D'Adamo GL, Chonwerawong M, Gearing LJ, et al., 2023. Bacterial clade-specific analysis identifies distinct epithelial responses in inflammatory bowel disease. *Cell Rep Med*, 4(7):101124. https://doi.org/10.1016/j.xcrm.2023.101124

Dolinger M, Torres J, Vermeire S, 2024. Crohn's disease. *Lancet*, 403(10432):1177-1191. https://doi.org/10.1016/s0140-6736(23)02586-2

Dong DF, Su TX, Chen W, et al., 2023. *Clostridioides difficile* aggravates dextran sulfate solution (DSS)-induced colitis by shaping the gut microbiota and promoting neutrophil recruitment. *Gut Microbes*, 15(1):2192478. https://doi.org/10.1080/19490976.2023.2192478

Douglas GM, Maffei VJ, Zaneveld JR, et al., 2020. PICRUSt2 for prediction of metagenome functions. *Nat Biotechnol*, 38(6):685-688. https://doi.org/10.1038/s41587-020-0548-6

Duan RQ, Zhang CZ, Li GN, et al., 2025. Antibiotic exposure and risk of new-onset inflammatory bowel disease: a systematic review and dose-response meta-analysis. *Clin Gastroenterol Hepatol*, 23(1):45-58.e15. https://doi.org/10.1016/j.cgh.2024.02.010

Edgar RC, Haas BJ, Clemente JC, et al., 2011. UCHIME improves sensitivity and speed of chimera detection. *Bioinformatics*, 27(16):2194-2200. https://doi.org/10.1093/bioinformatics/btr381

Ferretti P, Pasolli E, Tett A, et al., 2018. Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. *Cell Host Microbe*, 24(1):133-145.e5. https://doi.org/10.1016/j.chom.2018.06.005

Hill CA, Casterline BW, Valguarnera E, et al., 2024. *Bacteroides fragilis* toxin expression enables lamina propria niche acquisition in the developing mouse gut. *Nat Microbiol*, 9(1):85-94. https://doi.org/10.1038/s41564-023-01559-9

Iwamuro M, Tanaka T, Kagawa S, et al., 2023. Collagenous colitis in a patient with gastric cancer who underwent chemotherapy. *Cureus*, 15(5):e39466. https://doi.org/10.7759/cureus.39466

Jezernik G, Mičetić-Turk D, Potočnik U, 2020. Molecular genetic architecture of monogenic pediatric IBD differs from complex pediatric and adult IBD. *J Pers Med*, 10(4):243. https://doi.org/10.3390/jpm10040243

Khorsand B, Asadzadeh Aghdaei H, Nazemalhosseini-Mojarad E, et al., 2022. Overrepresentation of Enterobacteriaceae and *Escherichia coli* is the major gut microbiome signature in Crohn's disease and ulcerative colitis; a comprehensive metagenomic analysis of IBDMDB datasets. *Front Cell Infect Microbiol*, 12:1015890. https://doi.org/10.3389/fcimb.2022.1015890

Koren O, Konnikova L, Brodin P, et al., 2024. The maternal gut microbiome in pregnancy: implications for the developing immune system. *Nat Rev Gastroenterol Hepatol*, 21(1):35-45. https://doi.org/10.1038/s41575-023-00864-2

Korpela K, Salonen A, Vepsäläinen O, et al., 2018. Probiotic supplementation restores normal microbiota composition and function in antibiotic-treated and in caesarean-born infants. *Microbiome*, 6:182. https://doi.org/10.1186/s40168-018-0567-4

Krishna M, Salako A, Fofanova T, et al., 2020. Parental education may differentially impact pediatric inflammatory bowel disease phenotype risk. *Inflamm Bowel Dis*, 26(7):1068-1076. https://doi.org/10.1093/ibd/izz225

Kuenzig ME, Fung SG, Marderfeld L, et al., 2022. Twenty-first century trends in the global epidemiology of pediatric-onset inflammatory bowel disease: systematic review. *Gastroenterology*, 162(4):1147-1159.E4. https://doi.org/10.1053/j.gastro.2021.12.282

le Berre C, Honap S, Peyrin-Biroulet L, 2023. Ulcerative colitis. *Lancet*, 402(10401):571-584. https://doi.org/10.1016/s0140-6736(23)00966-2

Lee IA, Kamba A, Low D, et al., 2014. Novel methylxanthine derivative-mediated anti-inflammatory effects in inflammatory bowel disease. *World J Gastroenterol*, 20(5):1127-1138. https://doi.org/10.3748/wjg.v20.i5.1127

Lehri B, Atkins E, Scott TA, et al., 2024. Investigation into the efficiency of diverse *N*-linking oligosaccharyltransferases for glycoengineering using a standardised cell-free assay. *Microb Biotechnol*, 17(6):e14480. https://doi.org/10.1111/1751-7915.14480

Leibovitzh H, Lee SH, Xue MY, et al., 2022. Altered gut microbiome composition and function are associated with gut barrier dysfunction in healthy relatives of patients with Crohn's disease. *Gastroenterology*, 163(5):1364-1376.E10. https://doi.org/10.1053/j.gastro.2022.07.004

Li CL, Zhang PR, Xie YD, et al., 2024. *Enterococcus*-derived tyramine hijacks α_{2A}-adrenergic receptor in intestinal stem cells to exacerbate colitis. *Cell Host Microbe*, 32(6):950-963.E8. https://doi.org/10.1016/j.chom.2024.04.020

Liu H, Hong XL, Sun TT, et al., 2020. *Fusobacterium nucleatum* exacerbates colitis by damaging epithelial barriers and inducing aberrant inflammation. *J Dig Dis*, 21(7):385-398. https://doi.org/10.1111/1751-2980.12909

Liu XM, Mao BY, Gu JY, et al., 2021. *Blautia*—a new functional genus with potential probiotic properties? *Gut Microbes*, 13(1):1875796. https://doi.org/10.1080/19490976.2021.1875796

Magoč T, Salzberg SL, 2011. FLASH: fast length adjustment of short reads to improve genome assemblies. *Bioinformatics*, 27(21):2957-2963.

https://doi.org/10.1093/bioinformatics/btr507

Mari A, Khoury T, Ahamad HS, et al., 2020. Autoimmune diseases in first- and second-degree relatives of patients with inflammatory bowel diseases: a case-control survey in Israel. *Minerva Med*, 111(2):107-14. https://doi.org/10.23736/s0026-4806.19.06389-4

Martino C, Dilmore AH, Burcham ZM, et al., 2022. Microbiota succession throughout life from the cradle to the grave. *Nat Rev Microbiol*, 20(12):707-720. https://doi.org/10.1038/s41579-022-00768-z

Mirsepasi-Lauridsen HC, Vallance BA, Krogfelt KA, et al., 2019. *Escherichia coli* pathobionts associated with inflammatory bowel disease. *Clin Microbiol Rev*, 32(2):e00060-18. https://doi.org/10.1128/cmr.00060-18

Mukherjee A, Lordan C, Ross RP, et al., 2020. Gut microbes from the phylogenetically diverse genus *Eubacterium* and their various contributions to gut health. *Gut Microbes*, 12(1):1802866. https://doi.org/10.1080/19490976.2020.1802866

Mukhopadhya I, Hansen R, El-Omar EM, et al., 2012. IBD—what role do proteobacteria play? *Nat Rev Gastroenterol Hepatol*, 9(4):219-230. https://doi.org/10.1038/nrgastro.2012.14

Nameirakpam J, Rikhi R, Rawat SS, et al., 2020. Genetics on early onset inflammatory bowel disease: an update. *Genes Dis*, 7(1):93-106. https://doi.org/10.1016/j.gendis.2019.10.003

Örtqvist AK, Lundholm C, Halfvarson J, et al., 2019. Fetal and early life antibiotics exposure and very early onset inflammatory bowel disease: a population-based study. *Gut*, 68(2):218-225. https://doi.org/10.1136/gutjnl-2017-314352

Pathikkal A, Puthusseri B, Divya P, et al., 2022. Folate derivatives, 5-methyltetrahydrofolate and 10-formyltetrahydrofolate, protect BEAS-2B cells from high glucose–induced oxidative stress and inflammation. *In Vitro Cell Dev Biol-Anim*, 58(5):419-428. https://doi.org/10.1007/s11626-022-00691-w

Pham VT, Lacroix C, Braegger CP, et al., 2016. Early colonization of functional groups of microbes in the infant gut. *Environ Microbiol*, 18(7):2246-2258. https://doi.org/10.1111/1462-2920.13316

Piovani D, Danese S, Peyrin-Biroulet L, et al., 2019. Environmental risk factors for inflammatory bowel diseases: an umbrella review of meta-analyses. *Gastroenterology*, 157(3):647-659.E4. https://doi.org/10.1053/j.gastro.2019.04.016

Pittayanon R, Lau JT, Leontiadis GI, et al., 2020. Differences in gut microbiota in patients with vs without inflammatory bowel diseases: a systematic review. *Gastroenterology*, 158(4):930-946.E1. https://doi.org/10.1053/j.gastro.2019.11.294

Qi C, Zhou JB, Tu HY, et al., 2022. Lactation-dependent vertical transmission of natural probiotics from the mother to the infant gut through breast milk. *Food Funct*, 13(1):304-315. https://doi.org/10.1039/D1FO03131G

Qiao SS, Liu C, Sun L, et al., 2022. Gut *Parabacteroides merdae* protects against cardiovascular damage by enhancing branched-chain amino acid catabolism. *Nat Metab*, 4(10):1271-1286. https://doi.org/10.1038/s42255-022-00649-y

Rhee KJ, Wu SG, Wu XQ, et al., 2009. Induction of persistent colitis by a human commensal, enterotoxigenic *Bacteroides fragilis*, in wild-type C57BL/6 mice. *Infect Immun*, 77(4):1708-1718. https://doi.org/10.1128/iai.00814-08

Sears CL, Geis AL, Housseau F, 2014. *Bacteroides fragilis* subverts mucosal biology: from symbiont to colon carcinogenesis. *J Clin Invest*, 124(10):4166-4172. https://doi.org/10.1172/jci72334

Segata N, Izard J, Waldron L, et al., 2011. Metagenomic biomarker discovery and explanation. *Genome Biol*, 12(6):R60. https://doi.org/10.1186/gb-2011-12-6-r60

Shenhav L, Thompson M, Joseph TA, et al., 2019. FEAST: fast expectation-maximization for microbial source tracking. *Nat Methods*, 16(7):627-632. https://doi.org/10.1038/s41592-019-0431-x

Sun XW, Chen ZH, Yu L, et al., 2023. *Bacteroides dorei* BDX-01 alleviates DSS-induced experimental colitis in mice by regulating intestinal bile salt hydrolase activity and the FXR-NLRP3 signaling pathway. *Front Pharmacol*, 14:1205323. https://doi.org/10.3389/fphar.2023.1205323

Sun Y, Xie RX, Li L, et al., 2021. Prenatal maternal stress exacerbates experimental colitis of offspring in adulthood. *Front Immunol*, 12:700995. https://doi.org/10.3389/fimmu.2021.700995

Tian M, Li QH, Zheng TH, et al., 2023. Maternal microbe-specific modulation of the offspring microbiome and development during pregnancy and lactation. *Gut Microbes*, 15(1):2206505. https://doi.org/10.1080/19490976.2023.2206505

Valles-Colomer M, Blanco-Míguez A, Manghi P, et al., 2023. The person-to-person transmission landscape of the gut and oral microbiomes. *Nature*, 614(7946):125-135. https://doi.org/10.1038/s41586-022-05620-1

Velosa M, Hochner H, Yerushalmi B, et al., 2022. Pre- and perinatal factors predicting inflammatory bowel disease: a population-based study with fifty years of follow-up. *J Crohns Colitis*, 16(9):1397-1404. https://doi.org/10.1093/ecco-jcc/jjac043

Wang SP, Ryan CA, Boyaval P, et al., 2020. Maternal vertical transmission affecting early-life microbiota development. *Trends Microbiol*, 28(1):28-45. https://doi.org/10.1016/j.tim.2019.07.010

Wang QZ, Deng ZT, Lan J, et al., 2022. Inhibition of $GABA_AR$ or application of *Lactobacillus casei* Zhang alleviates ulcerative colitis in mice: $GABA_AR$ as a potential target for intestinal epithelial renewal and repair. *Int J Mol Sci*, 23(19):11210. https://doi.org/10.3390/ijms231911210

Wang XQ, Xiao Y, Xu X, et al., 2021. Characteristics of fecal microbiota and machine learning strategy for fecal invasive biomarkers in pediatric inflammatory bowel disease. *Front Cell Infect Microbiol*, 11:711884. https://doi.org/10.3389/fcimb.2021.711884

Xiao LW, Zhao FQ, 2023. Microbial transmission, colonisation and succession: from pregnancy to infancy. *Gut*, 72(4): 772-786. https://doi.org/10.1136/gutjnl-2022-328970

Zhao J, Bai M, Ning XX, et al., 2022. Expansion of *Escherichia-Shigella* in gut is associated with the onset and response to immunosuppressive therapy of IgA nephropathy. *J Am Soc Nephrol*, 33(12):2276-2292. https://doi.org/10.1681/asn.2022020189

Supplementary information

Figs. S1–S3; Table S1