

Multi-omics reveals gastrointestinal metabolic disorder-induced diarrhea in postpartum dairy cows

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Background

Diet changes after calving challenge digestion

A shift from high-forage to high-concentrate diets may disturb nutrient breakdown and fermentation, increasing the risk of noninfectious diarrhea.

The link between the rumen and hindgut remains unclear

Feed is first processed by rumen microbes. Remaining nutrients then enter the hindgut.

Most earlier studies focused on the hindgut without examining both sites together.

Scientific question

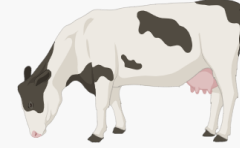
Do microbial functions change in both the rumen and hindgut, and are these changes linked to diarrhea and host metabolism?

Study design

On day 9 after calving, 24 cows were selected from the herd after pathogen screening and assessment of diarrhea.

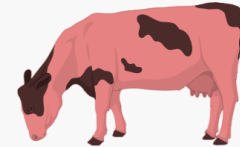
Day 9

No diarrhea



×12

Diarrhea



×12

Multiparous Holstein cows (body weight 637 ± 28 kg; parity 2.65 ± 0.27 ; body condition score 2.78 ± 0.19)

Sampling

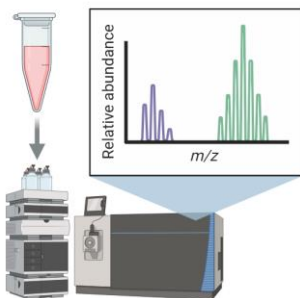
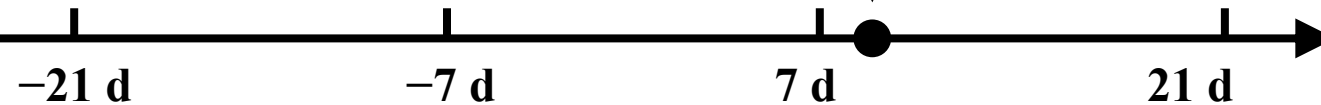
Serum



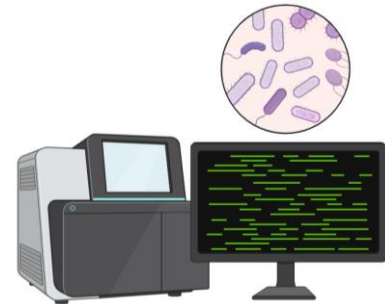
Rumen fluid



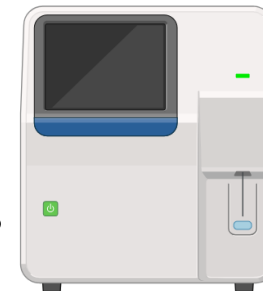
Feces



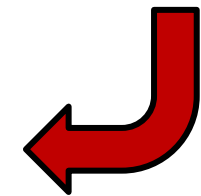
Untargeted metabolomics of rumen fluid, feces, and serum



Rumen and fecal metagenomics

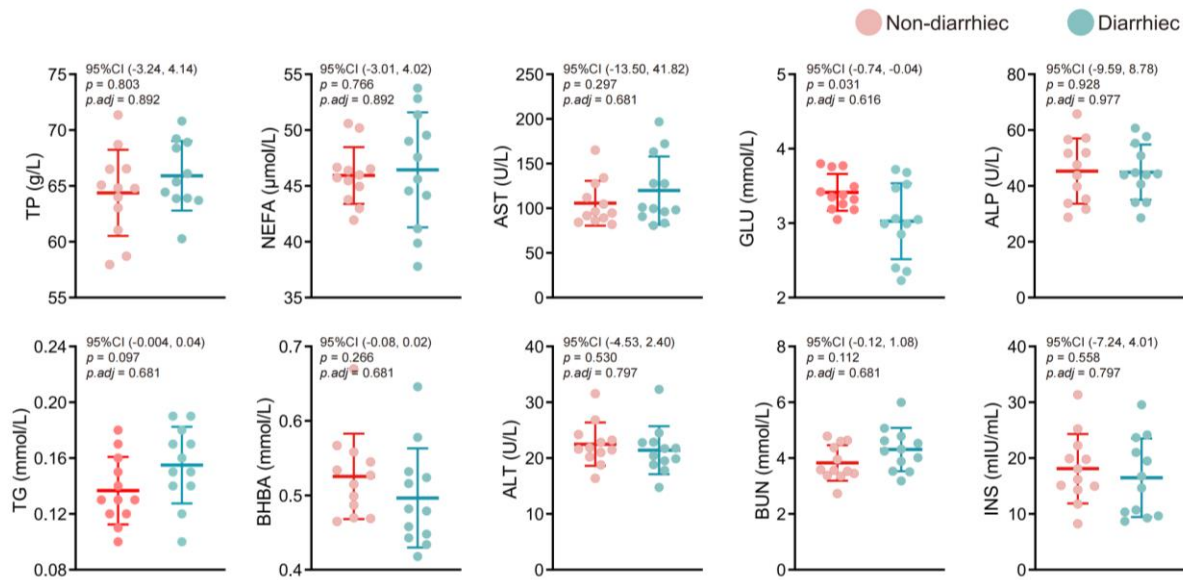


Blood counts, immune and antioxidant markers

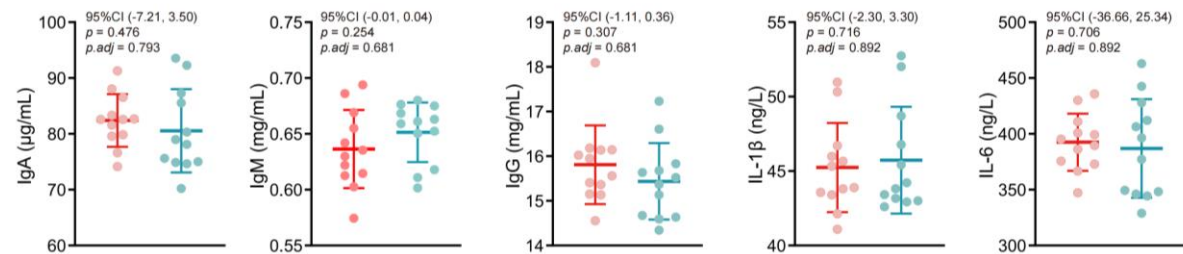


Diarrhea phenotype and routine measures

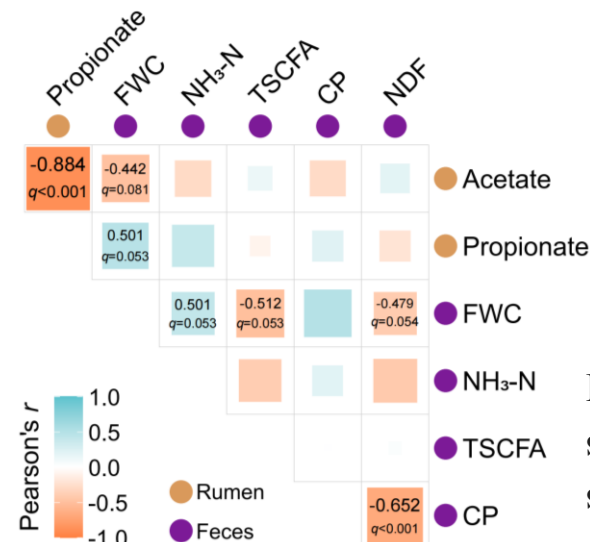
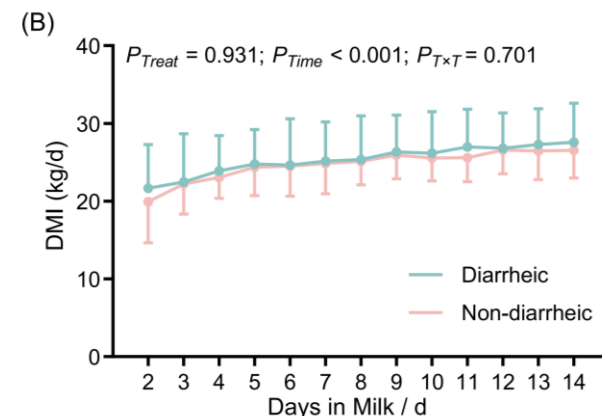
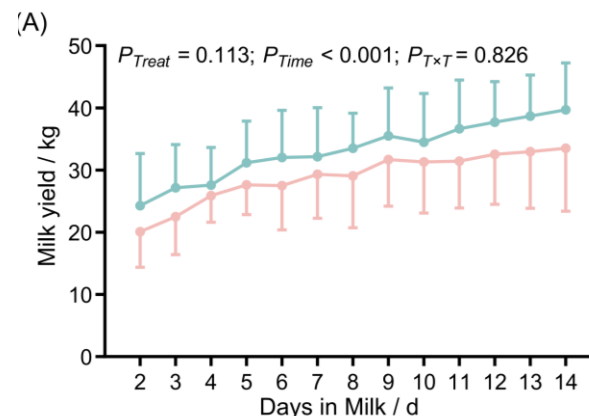
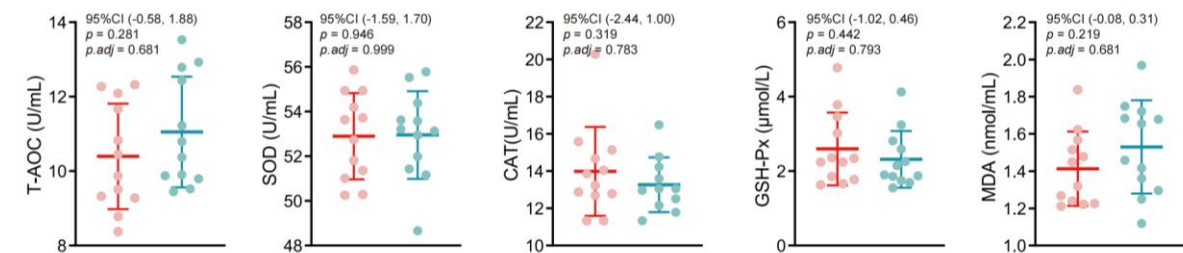
Biochemical



Immune



Antioxidant



Fecal water content (FWC)

90.83%

Case

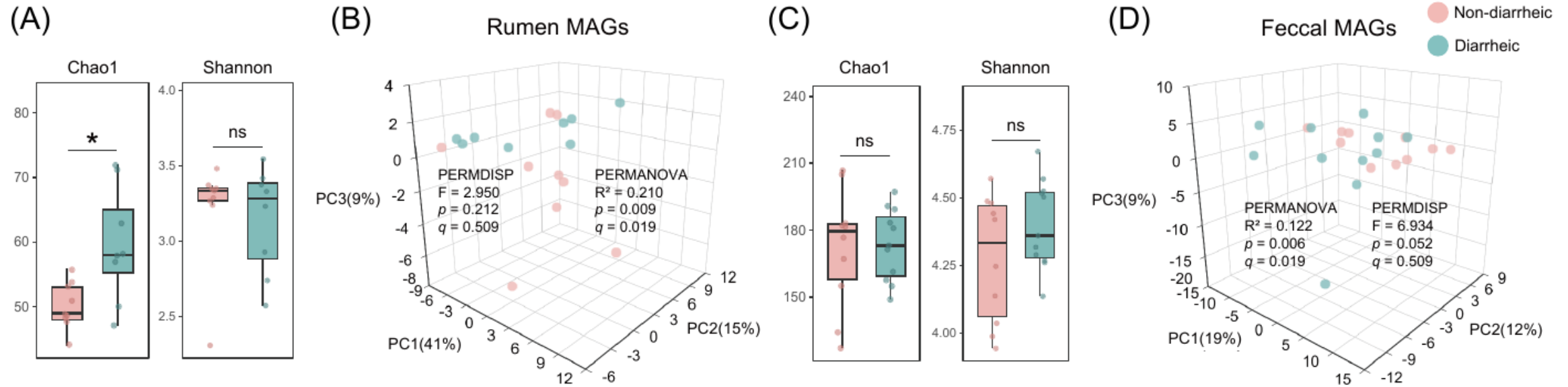
86.47%

Control

Milk yield, feed intake, and 20 serum markers showed no FDR-significant group differences.

FWC correlated with rumen acetate/propionate, fecal NH₃-N, total VFAs, and NDF.

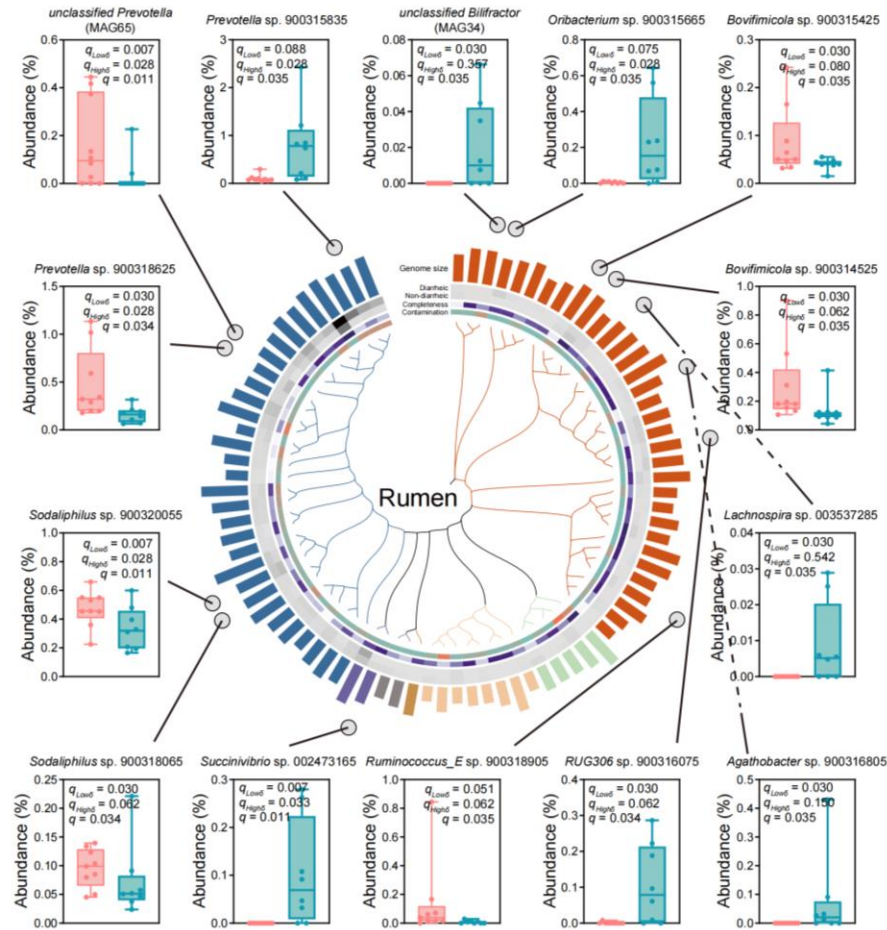
Microbial composition differs in the rumen and hindgut



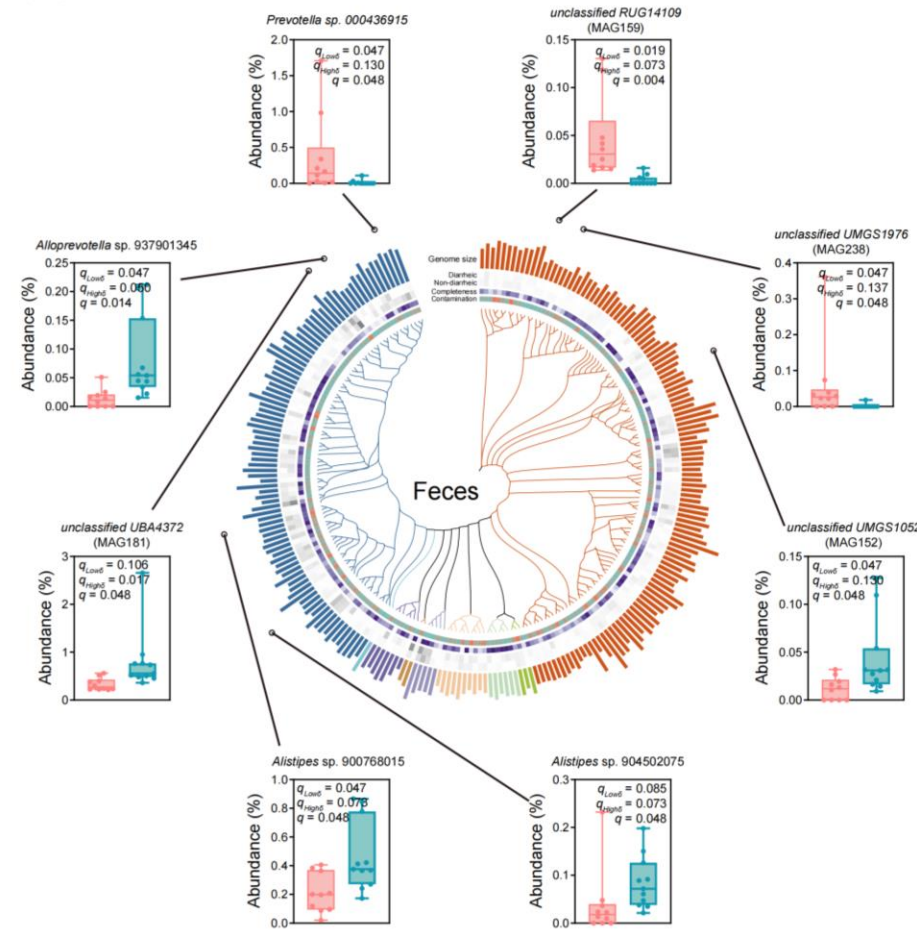
MAG-level composition differed between groups at both sites. Rumen Chao1 diversity was higher in cows with diarrhea, and beta diversity differed in both the rumen and hindgut.

Phylogenetic analysis based on high-quality MAGs of the rumen and hindgut

(E)

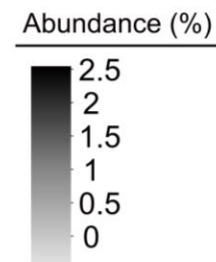
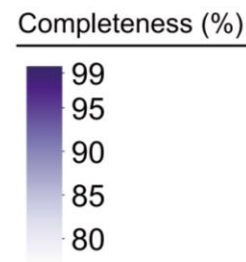
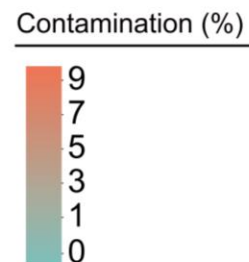
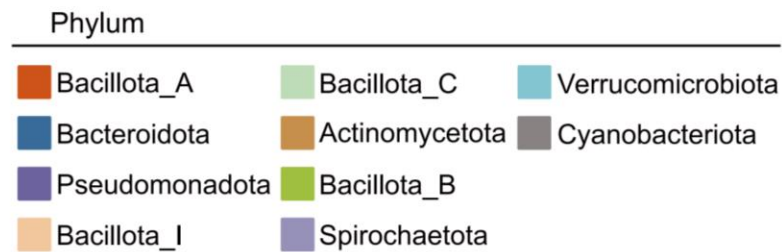


(F)

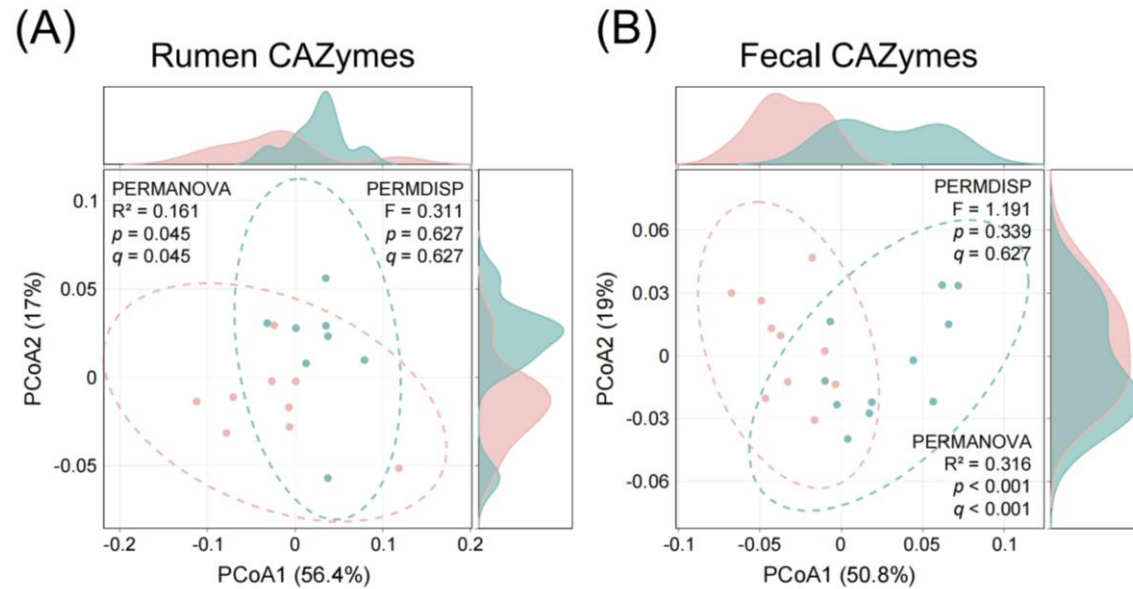


Rumen: 14 differential MAGs, including *Prevotella* sp. 900315835, *Prevotella* sp. 900318625, *Succinivibrio* sp. 002473165, *Ruminococcus_E* sp. 900318905, etc.

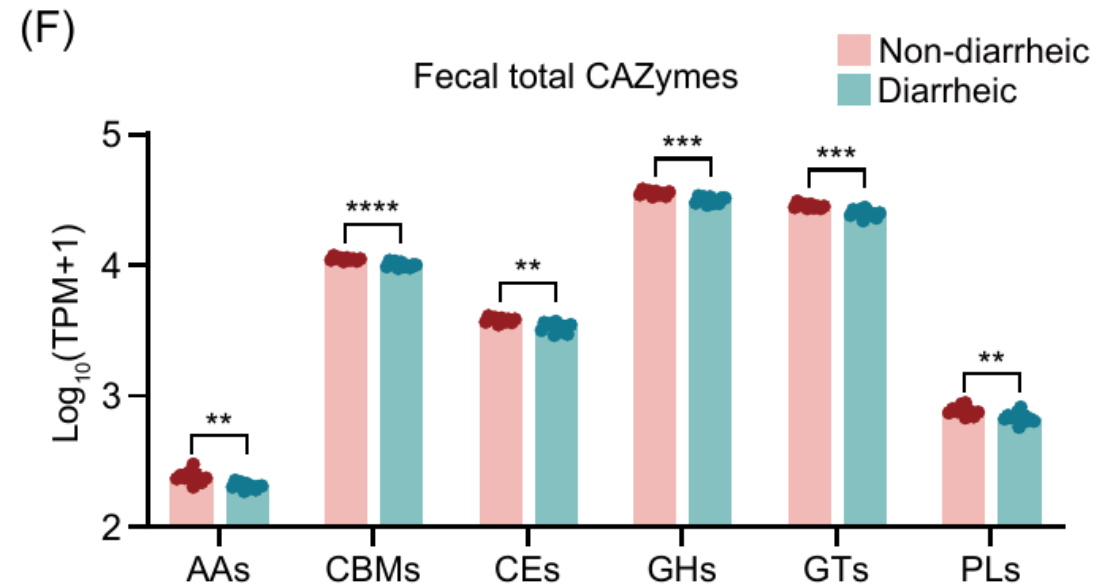
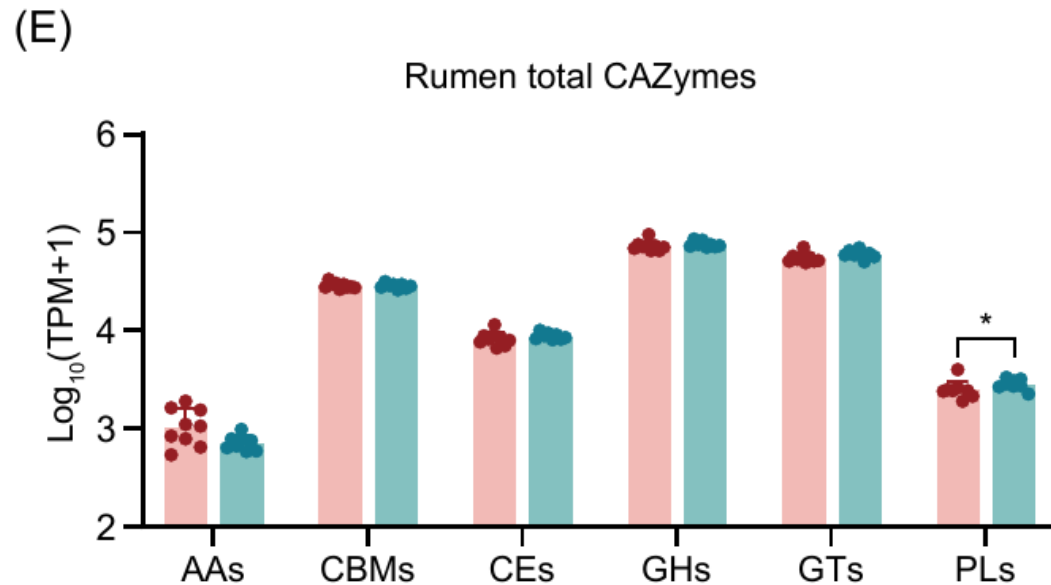
Hindgut: 8 candidate MAGs, including *Prevotella* sp. 000436915, *Alistipes* sp. 900768015, and *Alistipes* sp. 904502075, etc.



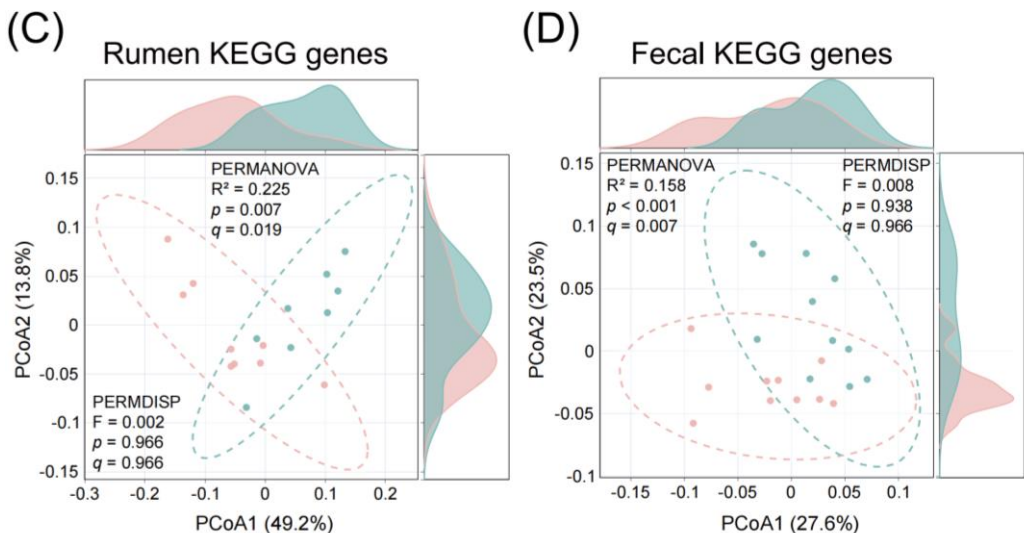
Hindgut carbohydrate-use potential declines



CAZyme profiles differed at both sites.
Rumen: polysaccharide lyases (PL) were more abundant in cows with diarrhea.
Hindgut: all six CAZyme classes were less abundant in cows with diarrhea.



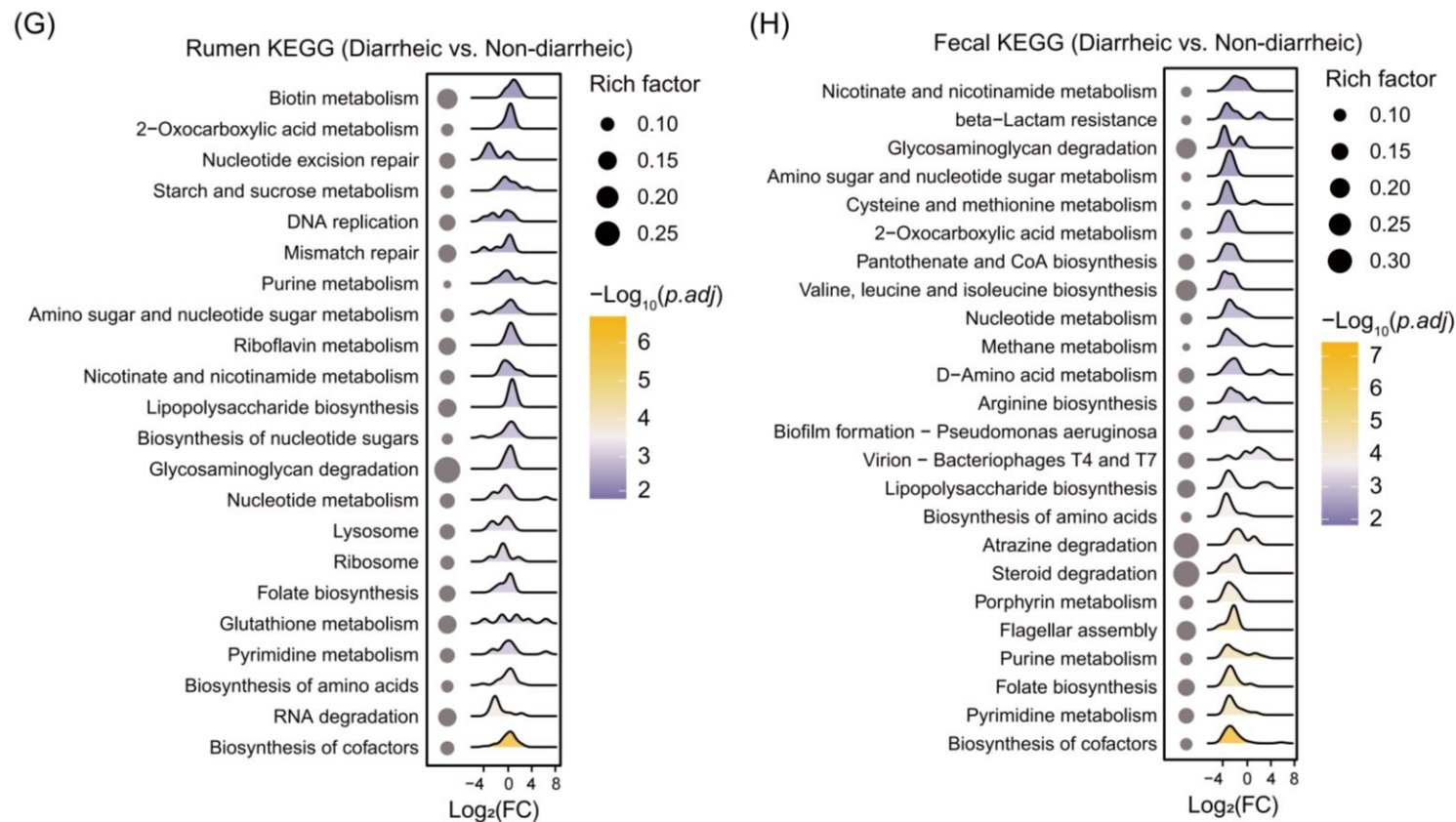
Rumen and fecal microbial pathways differ



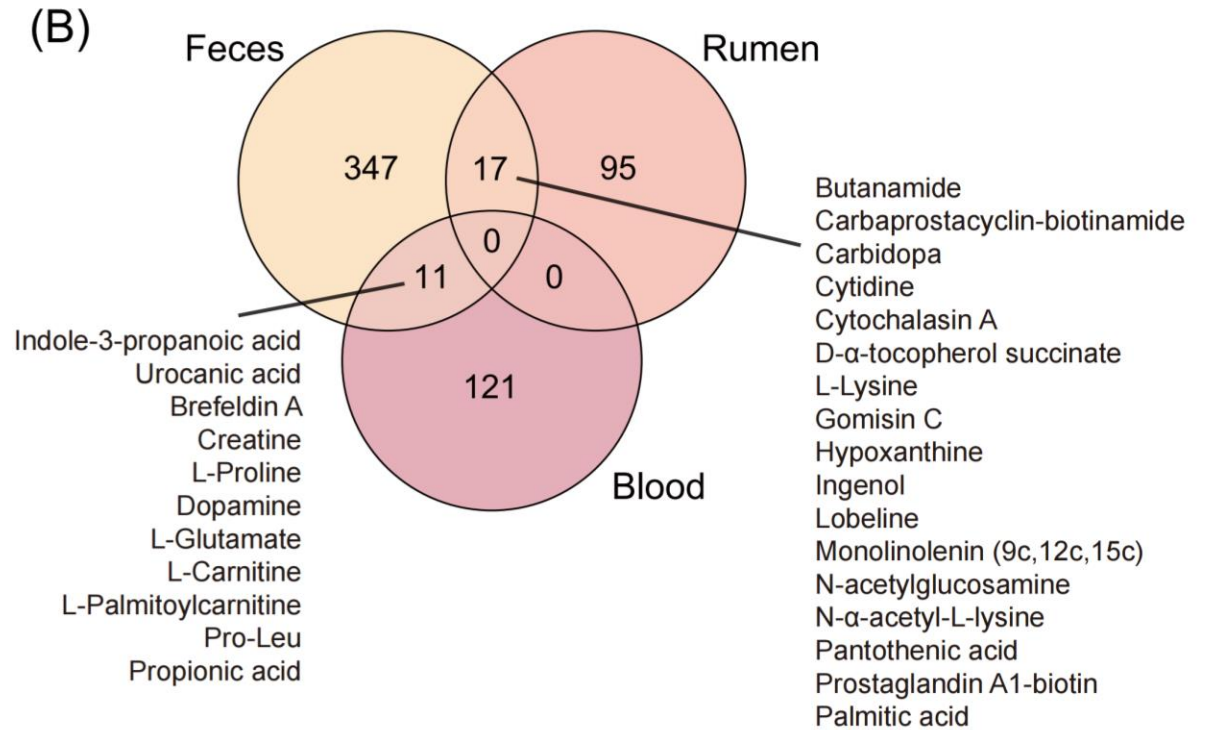
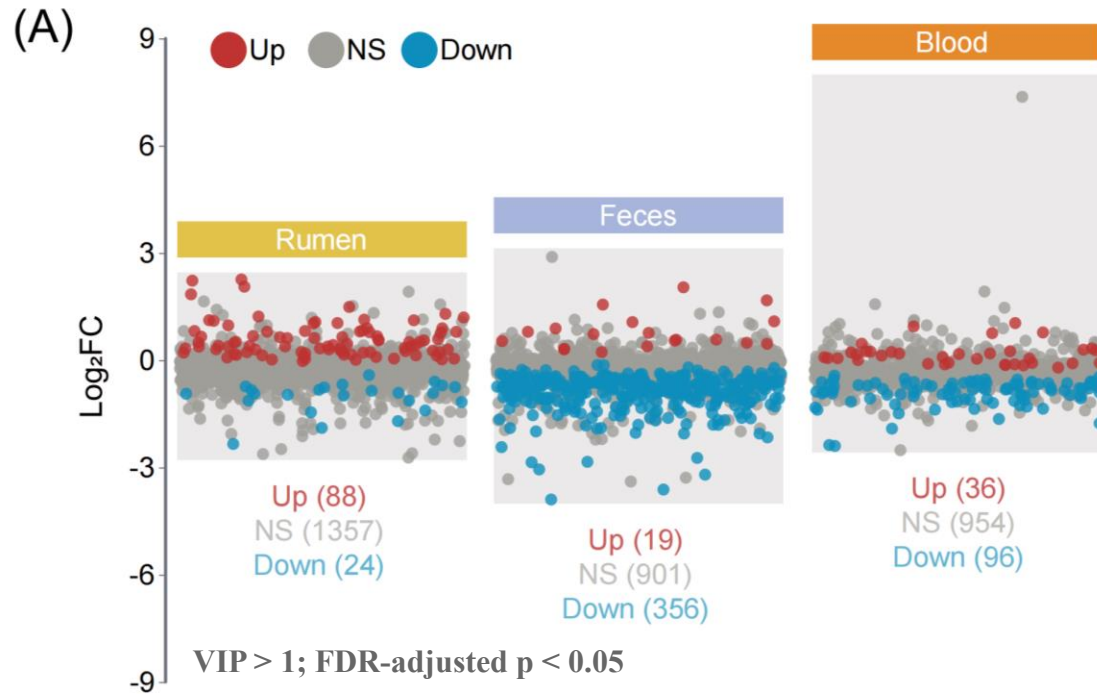
PCoA analyses with PERMANOVA and PERMDISP showed that KEGG functional profiles differed between groups in both the rumen and hindgut.

Rumen (G): Changes involved nucleotide and amino acid metabolism, including purine, pyrimidine, folate, glutathione, and sugar pathways. Cofactor biosynthesis was enriched in the positive direction.

Feces (H): Altered pathways involved amino acid and nucleotide metabolism, pantothenate/CoA, and nicotinate. Both sites showed metabolic remodeling.



Multi-site metabolomics points to hindgut disruption



Up / down

Rumen

88 / 24

Feces

19 / 356

Serum

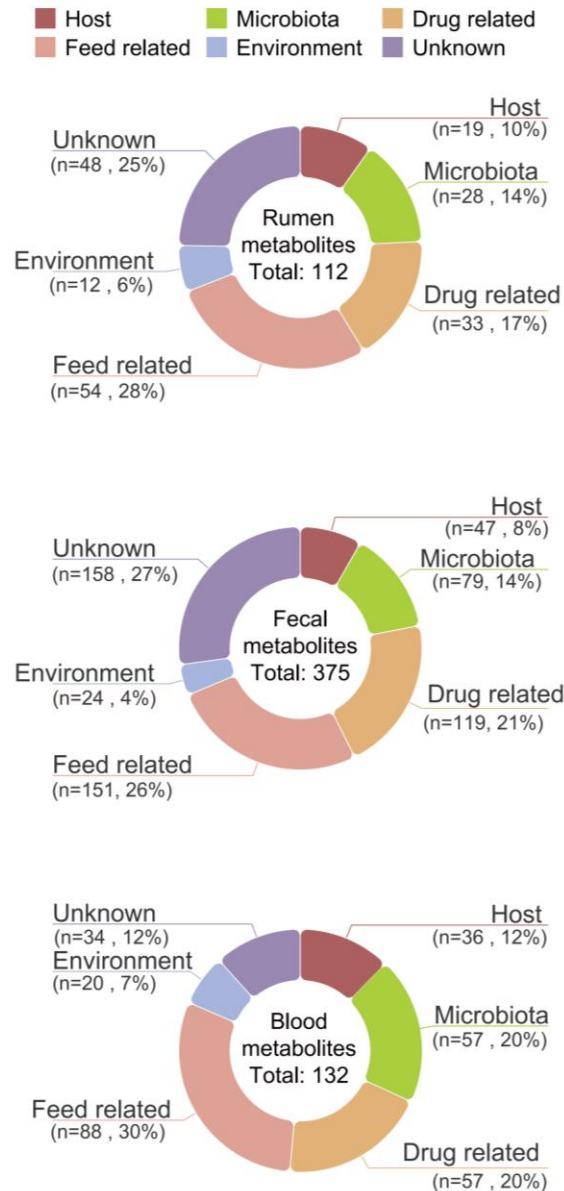
36 / 96

Feces showed the largest metabolite decline, consistent with weaker hindgut function. Serum changes show that disruption extended into circulation.

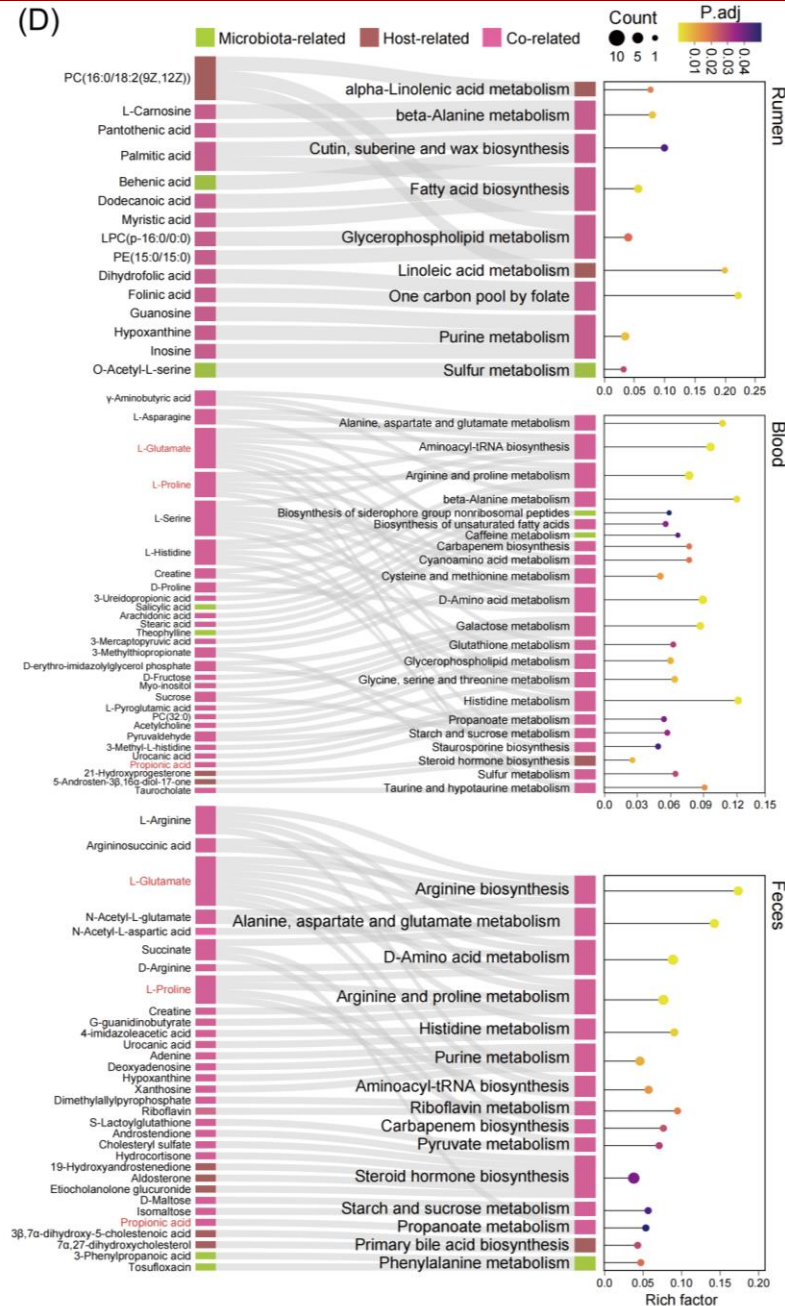
Overlap analysis identified metabolites shared by the rumen and feces, including butyramide, biotin derivatives, L-lysine derivatives, pantothenate, palmitate, and hypoxanthine. Feces and serum shared indole-3-propionic acid, uric acid, creatine, L-proline, L-glutamate, Pro-Leu, and propionate.

Cross-compartment metabolic traceability and pathway enrichment

(C)



(D)

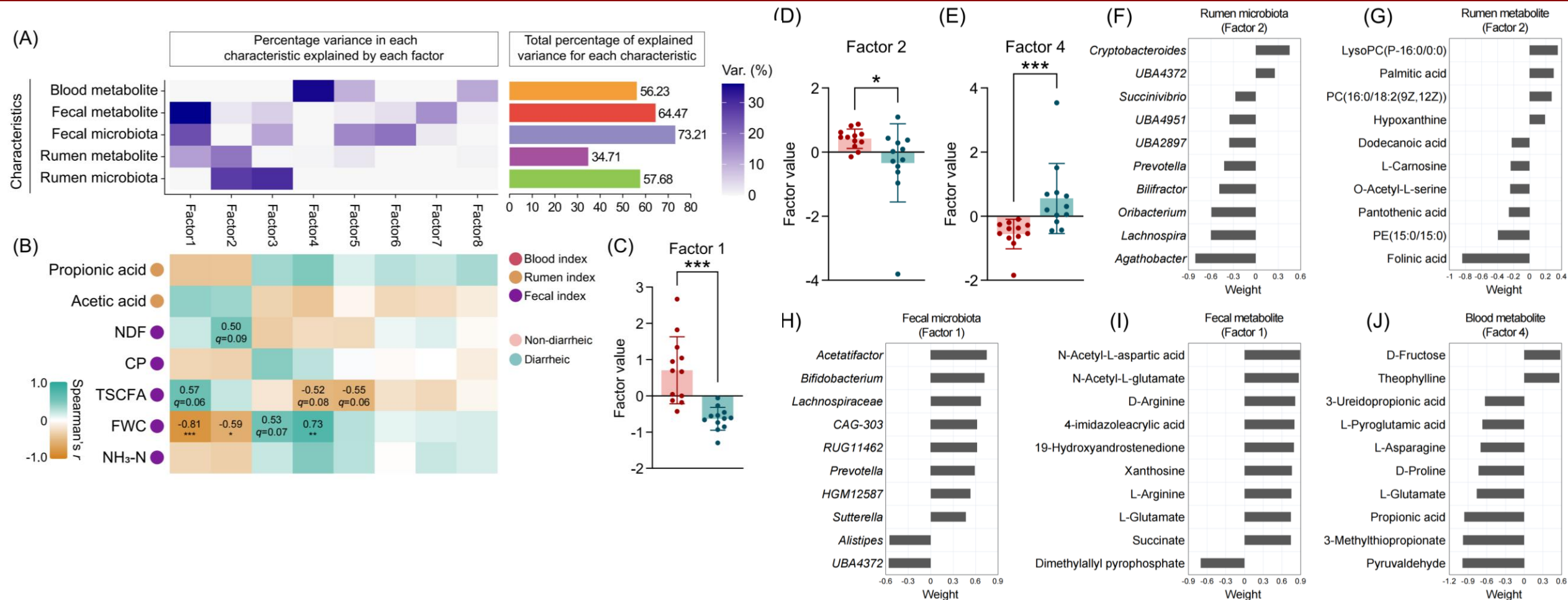


Metabolite sources and shared pathways

Source attribution (C): Feed-related metabolites accounted for 26–30% across sites. Unknown sources were common in rumen and feces. Microbiota-related sources contributed about 14% in rumen and feces and 20% in blood.

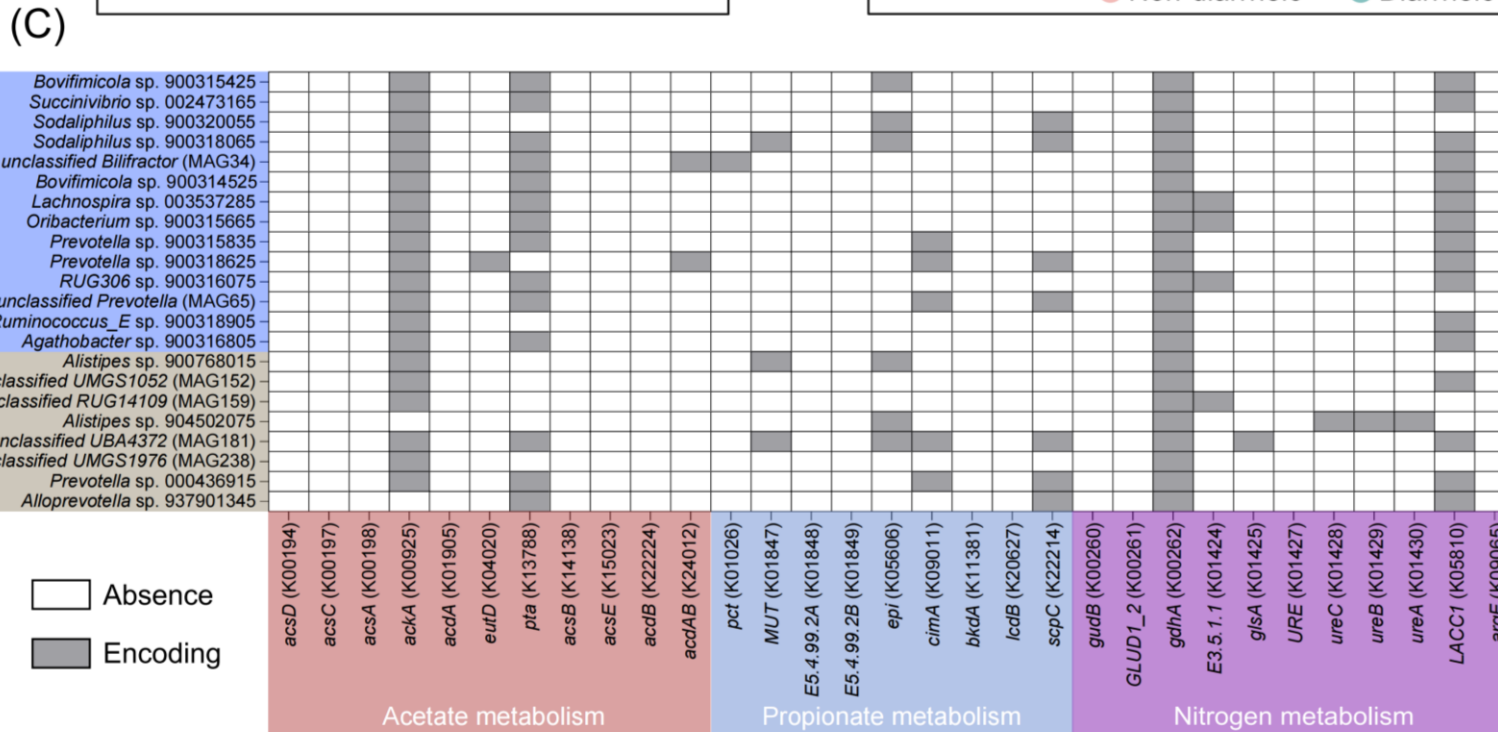
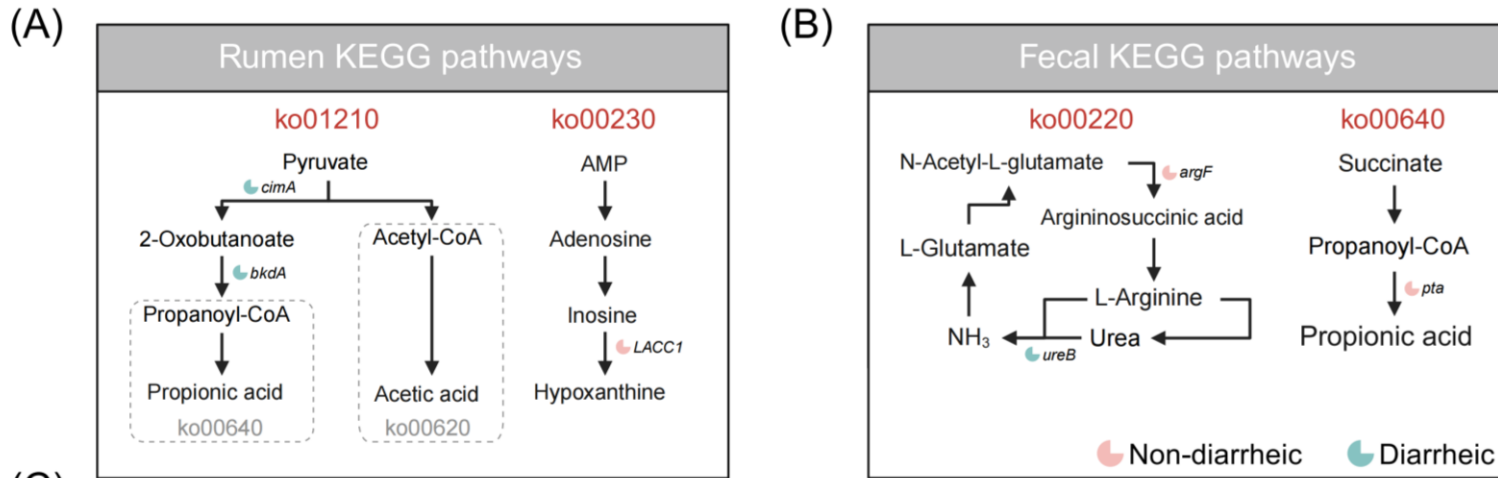
Enrichment (D): Shared pathways involved fatty acids/glycerophospholipids, arginine/proline and glutathione, purines, folate/one-carbon, and sulfur metabolism. Dot size shows the number of genes or metabolites.

MOFA links distinct omics layers to diarrhea



Latent factors captured variation in the fecal microbiome (73.21%), fecal metabolome (64.47%), rumen microbiome (57.68%), serum metabolome (56.23%), and rumen metabolome (34.71%). Factors 1, 2, and 4 separated the groups and were associated with FWC. Factor 1 was driven mainly by fecal microbial and metabolic features; Factor 2 by rumen metabolites; and Factor 4 by rumen microbes and serum metabolites. Factor 1 also related to dietary and rumen fermentation measures.

Microbial genes link VFA and nitrogen metabolism



Functional potential: rumen and fecal microbes showed diarrhea-associated differences in volatile fatty acid (VFA) and nitrogen pathways.

KEGG pathways: rumen changes involved pyruvate-to-acetate/propionate and AMP-to-hypoxanthine reactions; fecal changes involved arginine/urea cycling and succinate-to-propionate pathways.

Gene profiles: microbial genes linked to acetate, propionate, and nitrogen metabolism differed between groups. Prevotella, Lachnospira, Bifactor, Ruminococcus, and Alloprevotella contributed to these functions.

Summary and outlook

Main findings

Postpartum diarrhea was linked to microbial and metabolic changes across the rumen, hindgut, and blood. Rumen features included altered carbohydrate use, acetate/propionate fermentation, and purine metabolism. The hindgut showed lower carbohydrate-fermentation potential and fecal SCFAs, altered nitrogen metabolism, and shifts in *Prevotella*- and *Alistipes*-affiliated MAGs.

Potential application

The linked microbial, functional, and metabolic features provide candidate markers for nutritional diarrhea. They may support future monitoring and nutrition-intervention studies.

Future expectations

Future studies should test whether combined measures of rumen fermentation, fecal short-chain fatty acids and ammonia nitrogen, selected microbial functional genes, and circulating metabolites improve early risk assessment and guide targeted nutrition or microbiome interventions.

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