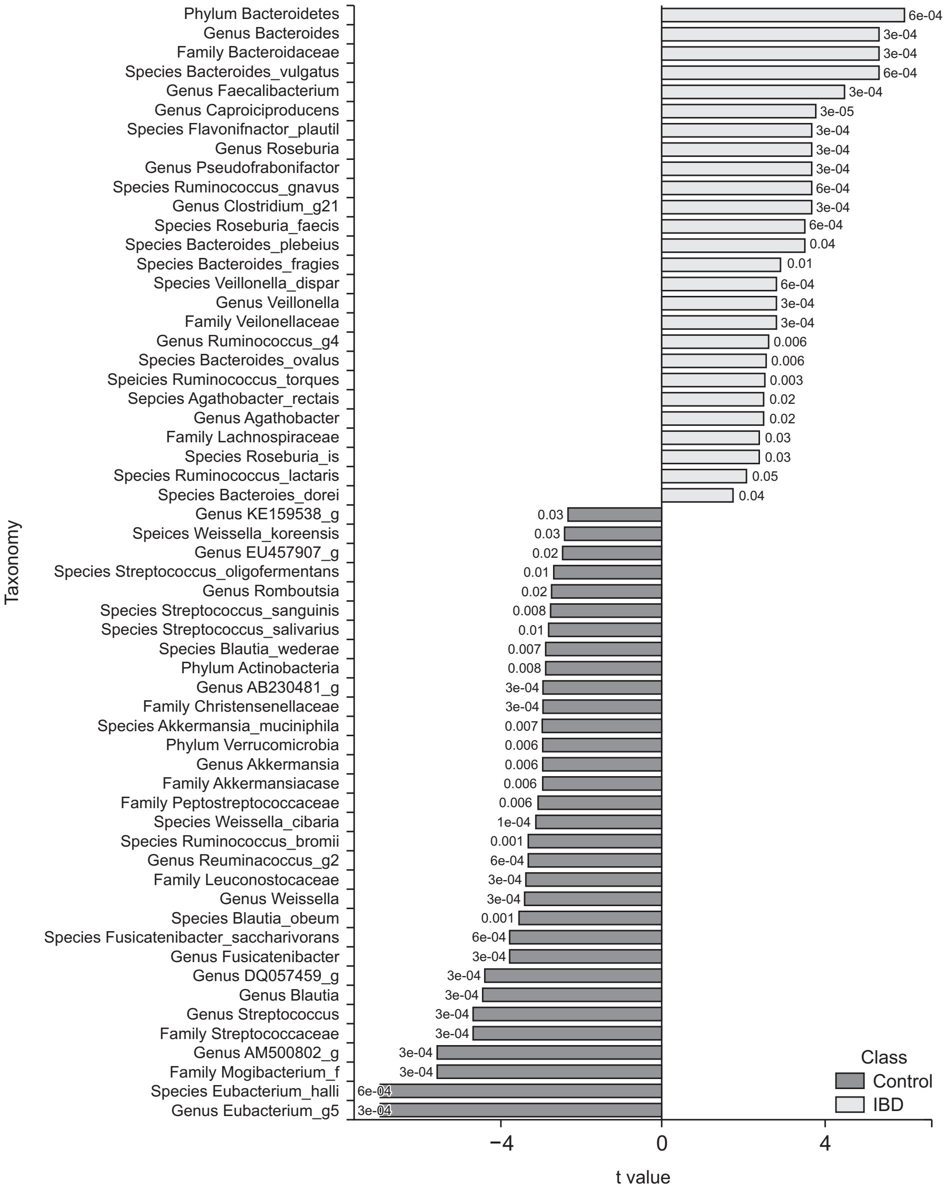
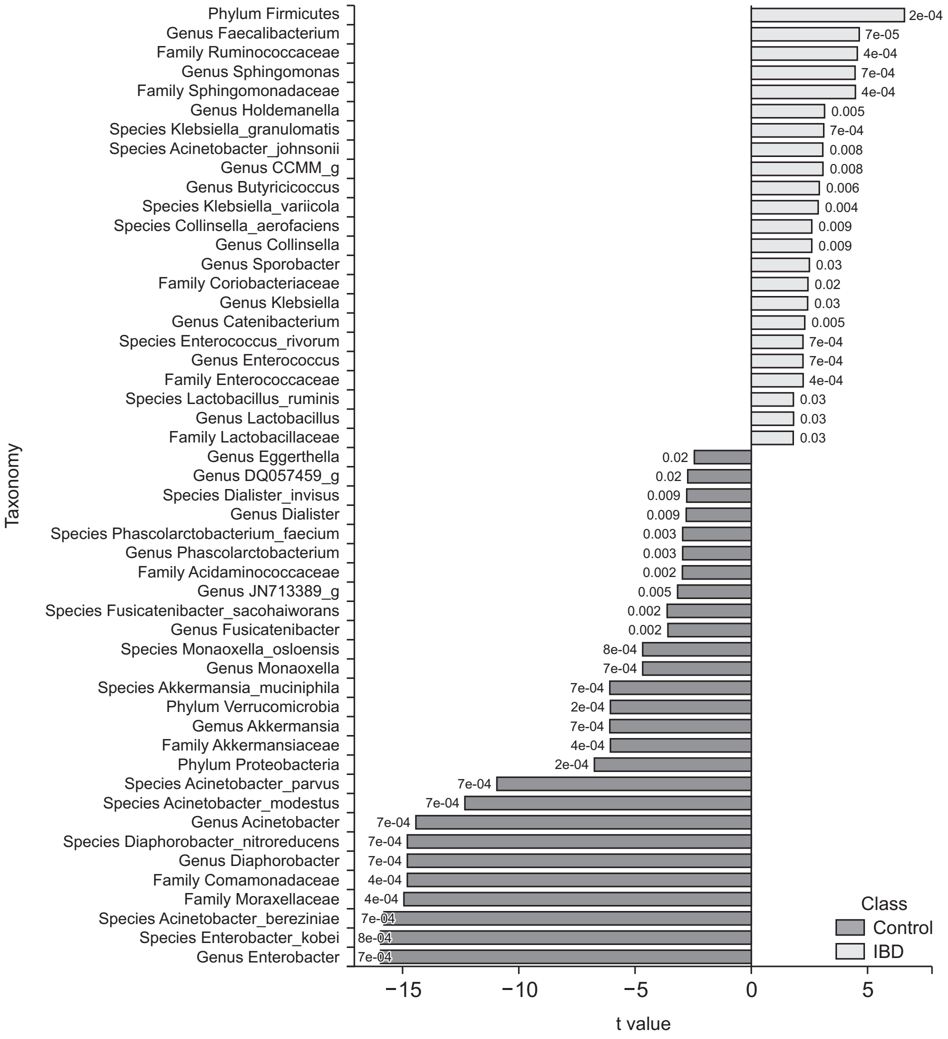
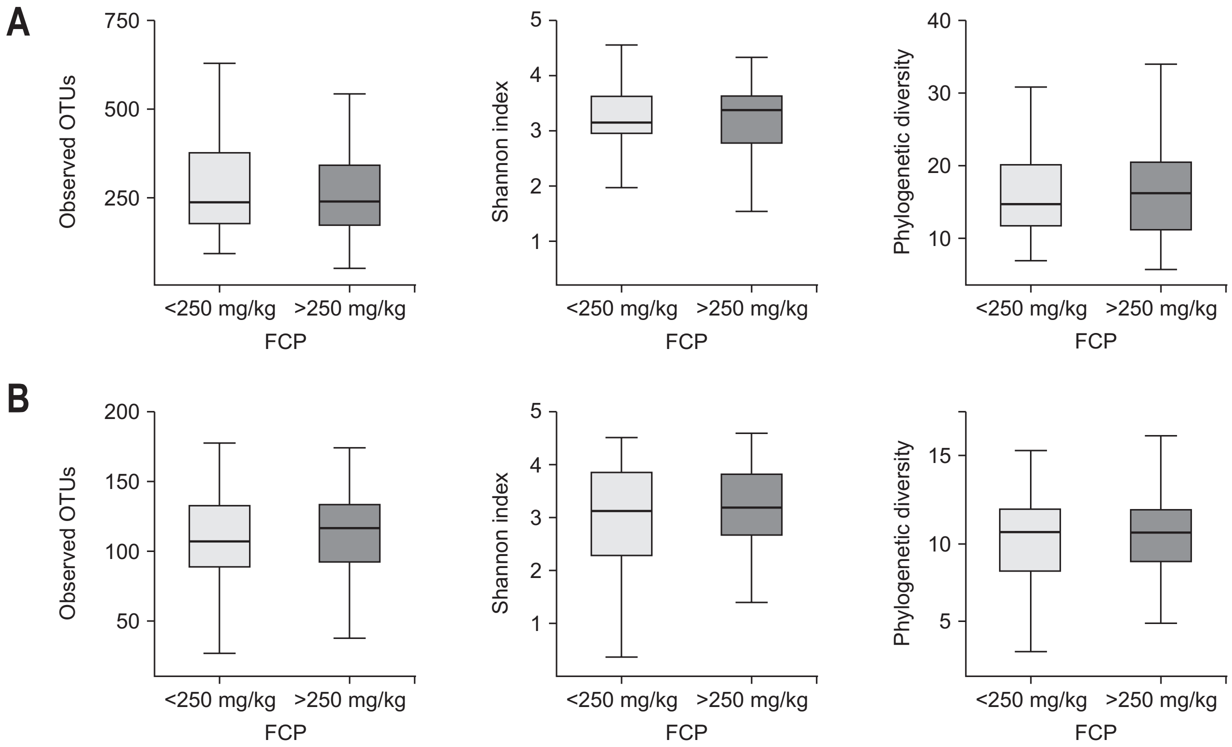


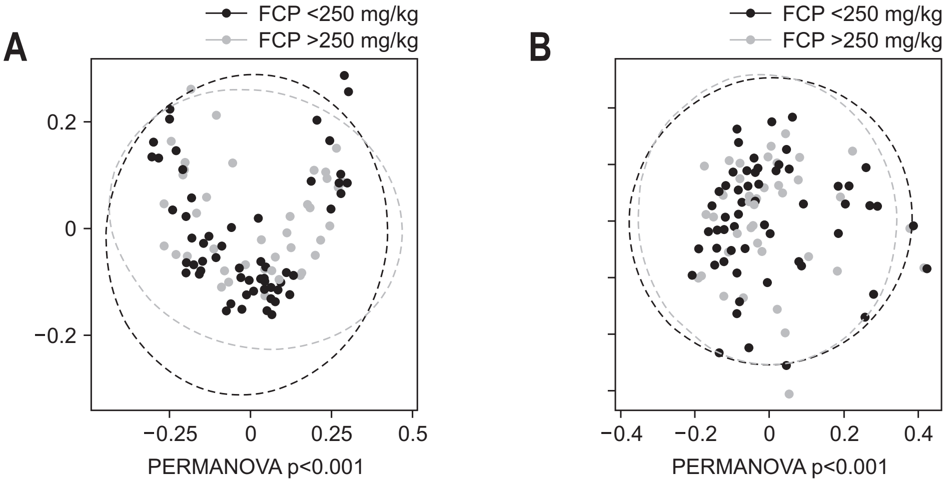
Supplementary Fig. 1. T-values of taxa that showed a significant difference in the abundance between healthy controls and patients with inflammatory bowel disease (IBD) in the stool microbiome. Each color indicates which group has more taxa abundance. Each label shows the false discovery rate-adjusted p-value.



Supplementary Fig. 2. T-values of taxa that show a significant difference in the abundance between healthy controls and patients with inflammatory bowel disease (IBD) in gut microbe-derived extracellular vesicles. Each color indicates which group has more taxa abundance. Each label shows the false discovery rate-adjusted p-value.



Supplementary Fig. 3 Alpha diversity of the stool microbiome (A), and gut microbe-derived extracellular vesicles (B), according to disease activity in patients with inflammatory bowel disease.
FCP, fecal calprotectin; OTUs, operational taxonomic units.



Supplementary Fig. 4 Principal coordinate analysis of the stool microbiome (A) and gut microbe-derived extracellular vesicles (B) according to disease activity in patients with inflammatory bowel disease.
FCP, fecal calprotectin; PERMANOVA, permutational analysis of variance.

Supplementary Table 1. Baseline Characteristics of the Study Participants

Variables	IBD (n=110)	Control (n=110)	p-value
Age, median (range), yr	39 (17–72)	38 (20–80)	0.859
Male sex	75 (68.2)	28 (25.5)	<0.001
Current smoking	19 (17.3)	0	<0.001
Body mass index, mean±SD, kg/m^2	23.2±3.2	27.6±4.3	<0.001
Bristol Stool Form Scale			<0.001
1–2	8 (7.3)	25 (22.7)	
3–5	73 (66.4)	59 (53.6)	
6–7	21 (19.1)	26 (23.6)	
Disease duration, median (IQR), yr	2.4 (0–17)		
UC	71 (64.6)		
UC, extent (n=71)			
UC proctitis	19 (26.8)		
Left-sided colitis	20 (28.2)		
Pancolitis	32 (45.1)		
CD, age (n=39)			
A1 (<17 yr)	3 (7.7)		
A2 (17–40 yr)	32 (82.1)		
A3 (>40 yr)	4 (10.3)		
CD, location (n=39)			
L1 (ileum)	13 (33.3)		
L2 (colon)	0		
L3 (ileocolonic)	26 (66.7)		
CD, behavior (n=39)			
B1 (inflammatory)	20 (51.3)		
B2 (stricturing)	8 (20.5)		
B3 (penetrating)	11 (28.2)		
History of abdominal surgery	8 (7.3)		
CRP (>0.5 mg/dL)	22 (20.0)		
FCP (>250 mg/kg)	46 (43.8)		
Medication use			
Steroids	62 (56.4)		
Immune modulators	50 (45.5)		
TNF-α inhibitors	15 (13.6)		

Data are presented as number (%) unless otherwise indicated.
IBD, inflammatory bowel disease; IQR, interquartile range; UC, ulcerative colitis; CD, Crohn's disease; CRP, C-reactive protein; FCP, fecal calprotectin; TNF, tumor necrosis factor.

Supplementary Table 2. Taxa Showing a Significant Difference in the Abundance in the Stool Microbiome between Healthy Controls and Patients with Inflammatory Bowel Disease Using Microbiome-Based Methods

Taxon	FDR-edgeR	FDR-OMiAT	Beta-TMAT	FDR-TMAT
Family				
Christensenellaceae	1.26E-05	0.01008	−0.26	2.41E-06
Leuconostocaceae	1.28E-06	1.00E-04	−0.26	5.47E-06
Mogibacterium_f	2.03E-09	0	−0.33	1.71E-09
Peptostreptococcaceae	0.001637759	1.00E-04	−0.19	0.001470189
Streptococcaceae	0.000155964	1.00E-04	−0.23	0.000639829
Genus				
AB239481_g	5.23E-05	0.02145	−0.26	3.95E-06
AM500802_g	3.70E-08	0	−0.33	9.82E-10
Blautia	9.16E-10	0.000212	−0.39	3.27E-10
Caproiciproducens	4.18E-05	0.000367	0.17	0.004403
DQ057459_g	0.000108	0.002406	−0.20	0.00063
Eubacterium_g5	2.28E-07	0	−0.35	9.82E-10
Fusicatenibacter	8.48E-09	0.0055	−0.36	9.82E-10
Pseudoflavonifractor	0.002805	0.04884	0.22	7.99E-05
Streptococcus	9.39E-06	0.000212	−0.23	0.000932
Weissella	9.16E-10	0.000212	−0.26	9.75E-06
Species				
Blautia obeum	0.000222	0.005658	−0.28	6.41E-06
Blautia wexlerae	1.18E-09	0.005889	−0.31	1.03E-06
Eubacterium hallii	4.38E-07	0	−0.36	3.36E-09
Flavonifractor plautii	0.014653	0.013227	0.26	1.68E-05
Fusicatenibacter saccharivorans	4.43E-07	0.013496	−0.38	1.64E-09
Ruminococcus bromii	0.000131	0.001078	−0.34	2.72E-08
Ruminococcus gnavus	0.047261	0.013227	0.19	0.001886
Streptococcus salivarius	1.42E-07	0.018681	−0.22	0.000719
Weissella cibaria	4.61E-12	0.013227	−0.33	9.37E-09

FDR, false discovery rate; edgeR, R Bioconductor package for the differential analysis of sequence read count data; OMiAT, optimal microbiome-based association test; TMAT, phylogenetic-tree-based microbiome association test. In the beta-TMAT column, negative numbers represent decreased abundance in patients with inflammatory bowel disease compared with healthy controls.

Supplementary Table 3. Taxa Showing a Significant Difference in the Abundance in Gut Microbe-Derived Extracellular Vesicles between Patients with Inflammatory Bowel Disease and Healthy Controls Using Microbiome-Based Methods

Taxon	FDR-edgeR	FDR-OMiAT	Beta-TMAT	FDR-TMAT
Family				
Acidaminococcaceae	0.000127199	0.034928	−0.23	2.49E-05
Akkermansiaceae	0.000880305	0	−0.27	1.24E-06
Comamonadaceae	2.22E-48	0	−0.42	0
Sphingomonadaceae	7.48E-11	0.005	0.20	0.000267379
Genus				
Akkermansia	6.68E-06	0	−0.27	2.47E-06
Diaphorobacter	5.50E-48	0	−0.42	0
Enterobacter	4.50E-76	0	−0.40	0
Klebsiella	0.008275	0.001667	0.23	0.000312
Moraxella	0.003594	0	−0.22	0.000191
Sphingomonas	1.46E-09	0.012	0.20	0.000486
Species				
Acinetobacter bereziniae	2.55E-70	0	−0.40	0
Acinetobacter modestus	1.24E-49	0	−0.40	2.66E-14
Acinetobacter parvus	5.12E-14	0	−0.36	1.17E-11
Akkermansia muciniphila	1.36E-06	0	−0.27	1.87E-06
Diaphorobacter nitroreducens	7.74E-48	0	−0.42	0
Enterobacter kobei	5.94E-85	0	−0.41	0
Moraxella osloensis	0.00343	0.001111	−0.22	0.000329

FDR, false discovery rate; edgeR, R Bioconductor package for the differential analysis of sequence read count data; OMiAT, optimal microbiome-based association test; TMAT, phylogenetic-tree-based microbiome association test. In the beta-TMAT column, negative numbers represent decreased abundance in patients with inflammatory bowel disease compared with healthy controls.

Supplementary Table 4. Taxa Showing a Significant Different in the Abundance between Enterotype 1 and Enterotype 2 in Gut Microbe-Derived Extracellular Vesicles of Patients with Inflammatory Bowel Disease Using Microbiome-Based Methods

Taxon	FDR-edgeR	FDR-OMiAT	Beta-TMAT	FDR-TMAT
Family				
Prevotellaceae	5.91E-16	0.0012	0.92	7.43E-08
Genus				
Prevotella	1.90E-15	0.0024	0.92	1.49E-07

FDR, false discovery rate; edgeR, R Bioconductor package for the differential analysis of sequence read count data; OMiAT, optimal microbiome-based association test; TMAT, phylogenetic-tree-based microbiome association test. In the beta-TMAT column, negative numbers represent decreased abundance in enterotype 2 compared with enterotype 1.