Key taxa of the gut microbiome associated with the relationship between environmental sensitivity and inflammation-related biomarkers

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Abstract: Background: Individual differences in environmental sensitivity are linked to stress-related psychiatric symptoms. In previous research, we found that high environmental sensitivity can be a risk factor for increased inflammation and gut permeability, particularly when gut microbiome diversity is low. However, the specific gut bacterial taxa involved in this interaction remain unclear. This study aimed to identify the key gut microbiome taxa associated with this relationship. **Methods**: Environmental sensitivity, gut microbiome composition, gut permeability (lipopolysaccharide-binding protein, LBP) and inflammation (C-reactive protein, CRP) biomarkers were evaluated in 88 participants. **Results**: The interaction between environmental sensitivity and the relative abundance of the family *Marinifilaceae* (genus *Butyricimonas*) was a predictor of CRP levels. Similarly, the interaction between environmental sensitivity and relative abundance of the family *Barnesiellaceae* (genus *Coprobacter*), the family *Akkermansiace* (genus *Akkermansia*), the genus *Family XIII AD3011 group*, the genus *GCA-900066225*, or the genus *Ruminiclostridium 1* predicted LBP levels. Individuals with high environmental sensitivity exhibited elevated CRP or LBP levels when the relative abundance of these taxa was low. Conversely, highly sensitive individuals had lower CRP or LBP levels when the relative abundance of these taxa was high. **Conclusion**: This study suggests that specific taxa serve as one of the protective factors against inflammation and gut permeability in individuals with high environmental sensitivity.

Keywords: Environmental sensitivity; Sensory processing sensitivity; Gut microbiome; Inflammation; Gut barrier; Gut-brain axis; *Butyricimonas*; *Coprobacter*; *Akkermansia*

Introduction

Environmental sensitivity, also known as sensory processing sensitivity (SPS), is a genetic, biological, and psychological trait that accounts for individual differences in how people perceive and process both negative and positive environments [1]. Some individuals are more sensitive to environmental influences due to their genetic or temperamental predispositions. As a result, they are more negatively affected by stressful environments and more positively impacted by supportive ones. This suggests that individuals with high environmental sensitivity are more likely to be influenced "for better and for worse" by both positive and negative environments [2-4].

Examining the darker aspects of this concept, it has been reported that high environmental sensitivity is linked to both physical and psychiatric symptoms. In a previous study involving a large sample size, we demonstrated that individuals with higher environmental sensitivity were more likely to self-report gastrointestinal symptoms, even after adjusting for sociodemographic characteristics [5]. Additionally, several studies have found positive associations between environmental sensitivity and physical symptoms [6,7] such as back pain, diarrhea, heartburn, sore throat [8], as well as cardiovascular,

respiratory, and gastrointestinal issues [9]. Conversely, one study indicated that there was no clear correlation between SPS and somatic symptoms [10]. Consequently, it remains a topic of debate whether environmental sensitivity is associated with physical health.

Accumulating evidence indicates that individuals with high environmental sensitivity are not only more vulnerable to worsening psychopathology in stressful environments than those with low sensitivity, but they are also less likely to experience worsening psychopathology if they can enhance protective factors (i.e., vantage sensitivity) [11-13]. Thus, the relationship between environmental sensitivity and physical/mental health is influenced by the quality of internal or external environmental factors.

In a previous study, we explored the correlations among individual differences in environmental sensitivity, inflammation-related biomarkers (C-reactive protein: CRP and lipopolysaccharide-binding protein: LBP), and gut microbiome diversity as one of the internal environmental factors. CRP is recognized as a risk factor associated with various psychological and physical symptoms, including cognitive function [14,15], depression [16], cardiovascular disease [17-22], and irritable bowel syndrome (IBS) [23]. Our study revealed that the relationship between environmental sensitivity and these inflammation-related biomarkers (CRP and LBP) was not merely a simple cause-and-effect relationship; rather, the levels of both biomarkers can vary depending on the interaction between environmental sensitivity and gut microbiome diversity [24]. Specifically, individuals with higher environmental sensitivity and lower gut microbiome diversity exhibited elevated levels of both biomarkers. In contrast, higher gut microbiome diversity did not elevate the levels of either biomarker, even among highly susceptible individuals. These findings suggest that individual differences in environmental sensitivity may play a role in the brain-gut-microbiome interaction, with gut microbiome diversity serving a protective function against inflammatory responses in individuals with high environmental sensitivity.

However, the role of specific gut bacterial taxa in moderating the link between environmental sensitivity and inflammatory reactions is not yet fully understood. Addressing this gap will enhance our understanding of why individuals with high environmental sensitivity and low gut microbiota diversity exhibit heightened inflammatory responses. Therefore, this study aims to identify for the first time key taxa in the gut microbiome that are associated with the relationship between environmental sensitivity and inflammation biomarkers.

Materials and Methods

Study procedure.

This study was a follow-up analysis of a previous report [24]. Initially, we recruited 110 adults who had previously participated in another study measuring fecal and/or blood biomarkers. Informed consent to participate in this study and complete additional questionnaire was obtained from 90 of these individuals. The participants underwent a physical examination, blood tests, and fecal microbiome analysis. Two years later, they completed a web-based questionnaire. Fecal samples were unavailable from two participants, so data from 88 participants were included in the analysis. The study was preregistered with the University Hospital Medical Information Network (https://www.umin.ac.jp/english/) (Identifier: UMIN000047571) and was approved by the Ethics Committee of Meiji Co., Ltd. (Tokyo, Japan) Institutional Review Board (No. 2021-012) on February 24, 2022, in accordance with the guidelines of the Declaration of Helsinki. All participants signed the informed consent form digitally.

Environmental sensitivity

To measure the personality traits associated with environmental sensitivity, we utilized the 10-item Japanese version of the Highly Sensitive Person Scale (HSP-J10) [25]. This scale evaluates susceptibility to both negative and positive environmental influences and includes the following items: “Do changes in your life shake you up?”, “Are you easily overwhelmed by strong sensory input?”, “Do other people’s moods affect you?”, “Do you get rattled when you have a lot to do in a short amount of time?”, “When you must

compete or be observed while performing a task, do you become so nervous or shaky that you do much worse than you would otherwise?", "Are you bothered by intense stimuli, like loud noises or chaotic scenes?", "Are you made uncomfortable by loud noises?", "Are you easily overwhelmed by things like bright lights, strong smells, coarse fabrics, or sirens close by?", "Do you notice and enjoy delicate or fine scents, tastes, sounds, works of art?" and "Are you deeply moved by the arts or music?". Each item was rated on a 7-point Likert-type scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Cronbach's alpha, a measure of the scale's internal consistency, was adequate at 0.85 (McDonald's omega total = 0.86). The mean scores of the 10 items were used for the analyses. Personality traits, including environmental sensitivity [26], are psychological factors that tend to remain stable within individuals over time [27].

Blood biomarkers

Fasting venous blood was collected, and serum was obtained through centrifugation and stored at -80°C until analysis. Serum high-sensitivity CRP, an inflammation biomarker, was measured using the V-PLEX Vascular Injury Panel 2 Human Kit (Meso Scale Diagnostics, MD, US). Serum LBP, a gut permeability biomarker [28,29], was measured using an LBP Human ELISA Kit (Hycult Biotech, Uden, The Netherlands). Both biomarker data were log-transformed prior to analysis, as previously reported [30,31] due to the data not being normally distributed.

Gut microbiome

Fecal samples were collected and prepared as previously described [24]. Briefly, participants collected feces on any day during the study. The fecal samples were homogenized using a FastPrep-24 5G (MP Biomedicals, Irvine, CA, US) with 0.1 mm zirconia beads (EZ-Extract for DNA/RNA, AMR, Tokyo, Japan). DNA was then extracted from the fecal samples using the QIAamp DNA Stool Mini Kit (QIAGEN, Hilden, Germany) following "Protocol Q" [32], with minor modifications. The V3-V4 region of the 16S ribosomal RNA gene was amplified by PCR using universal bacterial primer sets (5′-TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCCTACGGGNGGCWGCAG-3′ and 5′-GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC-3′) and sequenced using the MiSeq Reagent kit v3 (600 cycle) (Illumina Inc., California, US). The sequence data were processed using QIIME2 (version 2020.2, https://qiime2.org/), including quality filtering and the identification of amplicon sequence variants (ASVs) using the DADA2 algorism. For downstream analysis, 32,000 reads were randomly selected from each sample. Taxonomic classification was performed by conducting BLAST searches of representative ASV sequences against the SILVA 132 database (https://www.arb-silva.de/documentation/release-132/). The ratio of each family and genus, as well as the alpha diversity indices, was calculated using QIIME2. Alpha diversity was evaluated for richness using observed operational taxonomic units (OTUs; observed species) and for biodiversity using Faith's phylogenetic diversity (PD) [33]. The relative abundance of the gut microbiome at the family and genus levels was calculated. Taxa with very low prevalence at the family or genus level (<5%) were excluded from further analyses.

Data Analyses

The statistical significance level for the series of analyses was set at $\alpha = 0.05$. All statistical analyses were conducted using R version 4.4.1 [34] and its interface, RStudio version 2024.04.2 [35]. Prior to the main analysis, Gender differences in the taxa of gut microbiome were also tested.

In the previous study, we found that the interactions between environmental sensitivity and alpha diversity indices (OTUs and PD) of the gut microbiome accounted for the levels of CRP and LBP. Therefore, we initially conducted a Pearson correlation analysis to examine the relationship between alpha diversity indices and gut microbiome taxa at the

family and genus levels to investigate the key taxa of the gut microbiome associated with the interaction between environmental sensitivity and these biomarkers.

Second, a series of hierarchical multiple regression analyses were conducted to identify the interaction effect between environmental sensitivity and specific gut microbiome taxa. Interaction effect analysis was conducted solely for the gut microbiome taxa at the family level, where significant moderate ($|r| > 0.30$) or high ($|r|>0.50$) correlations were observed. Following this, interaction effect analysis was performed at the genus level for both those bacterial taxa that exhibited significant interactions at the family level or significant moderate ($|r| > 0.30$) or high ($|r|>0.50$) correlations at the genus level. The interaction effects of environmental sensitivity and gut microbiome taxa, at both the family and genus levels, on CRP and LBP were examined using hierarchical multiple regression analysis [36]. As previously reported [24], in Step 1, sex, age, BMI, environmental sensitivity, and the relative abundance of gut microbiome taxa at the family or genus level were entered as independent variables, while the two biomarkers (CRP and LBP) were entered as dependent variables. In Step 2, an interaction term representing the relationship between environmental sensitivity and the relative abundance of gut microbiome taxa was added to the independent variables entered in Step 1.

Finally, if the interaction term was significant in Step 2, a simple slope test was conducted to assess the moderating effect of the relative abundance of the gut microbiome on the relationship between environmental sensitivity and the biomarkers. Regression coefficients were estimated by substituting *M*-1*SD*, *Mean*, and *M*+1*SD* for the gut microbiome taxa at either the family or genus level in the model, respectively [36].

Results

Clinical and biochemical characteristics of the subjects

The clinical and biochemical characteristics of the 88 subjects from whom fecal samples were collected are presented in Table 1.

Table 1. Clinical and biochemical characteristics of the subjects.

	Mean*±*SD	**95% CI**
Age (years)	42±10	40-44
Sex (Female/Male)	44/44 (50%/50%)	
Body weight (kg)	62.6±12.7	60.0-65.3
Height (m)	1.65±0.08	1.63-1.67
BMI (kg/m^2)	22.8±3.4	22.1-23.5
Environmental sensitivity	4.4±1.0	4.2-4.6
CRP (ng/ml)	7994±31040	1509-14480
LBP (μg/mL)	13.6±4.0	12.8-14.5
Log-normalized CRP	7.33±1.45	7.03-7.64
Log-normalized LBP	2.58±0.26	2.52-2.63

Note. SD: standard deviation; CI: confidence interval; BMI: body mass index; CRP: C-reactive protein, LBP: lipopolysaccharide-binding protein.

Relative abundance and prevalence of gut microbiome taxa, along with the correlations between alpha diversity indices and bacterial taxa

The relative abundance and prevalence of gut microbiome taxa at the family and genus levels are presented in Table 2 and 3, respectively, both of which exclude taxa with a prevalence of less than 5%.

Females showed significantly higher means of relative abundance in *Eggerthellaceae*, *Coriobacteriales unclassified family*, *Marinifilaceae*, *Porphyromonadaceae*, *Rikenellaceae*, *Christensenellaceae*, *Clostridiales vadinBB60 group*, *Defluviitaleaceae*, *Eubacteriaceae*, *Clostridiales Family XIII*, *Ruminococcaceae* and *Akkermansiaceae* at the family level, and *Varibaculum*, *Gordonibacter*, *Coriobacteriales unclassified family unclassified genus*, *Butyricimonas*, *Porphyromonas*, *Alistipes*, *Christensenellaceae R-7 group*, *Christensenellaceae uncultured bacterium*, *Christensenellaceae unclassified genus*, *Clostridiales vadinBB60 group uncultured bacterium*, *Defluviitaleaceae UCG-011*, *Anaerofustis*, *Eubacterium*, *Anaerococcus*, *Family XIII AD3011 group*,

[Eubacterium] brachy group, Eisenbergiella, GCA900066575, Lachnospiraceae NK4A136 group, Shuttleworthia, Peptococcaceae uncultured bacterium, Anaerofilum, Anaerotruncus, DTU089, Oscillibacter, Ruminiclostridium, Ruminococcaceae UCG-005, Subdoligranulum, UBA1819, Ruminococcaceae uncultured bacterium, and *Akkermansia* at the genus level than males (Data not shown). Males showed significantly higher means of relative abundance in *Veillonellaceae* at the family level, and *Actinomyces, Dorea, Lachnoclostridium, Lachnospiraceae UCG-004, Lachnospiraceae UCG-010, Butyricicoccus*, and *Megasphaera* at the genus level than females (Data not shown).

We identified significant moderate to high correlations between alpha diversity indices (OTUs and/or PD) and gut microbiome taxa at the family level in the following 17 taxa: *Methanobacteriaceae*, *Coriobacteriales Incertae Sedis*, *Coriobacteriales unclassified family*, *Barnesiellaceae*, *Marinifilaceae*, *Rikenellaceae*, *Christensenellaceae*, *Clostridiales vadinBB60 group*, *Defluviitaleaceae*, *Family XIII (Clostridiales)*, *Lachnospiraceae*, *Ruminococcaceae*, *Clostridiales unclassified family*, *DTU014 uncultured bacterium*, *Synergistaceae*, *Mollicutes RF39 uncultured bacterium* and *Akkermansiaceae*. Furthermore, we identified significant moderate to high correlations between alpha diversity indices (OTUs and/or PD) and gut microbiome taxa at the genus level in the following 63 taxa: *Methanobrevibacter, Varibaculum, Enterorhabdus, Senegalimassilia, Coriobacteriales unclassified family unclassified genus, Barnesiella, Butyricimonas, Odoribacter, Alistipes, Christensenellaceae R-7 group, Christensenellaceae uncultured bacterium, Christensenellaceae unclassified genus, Clostridiales vadinBB60 group uncultured bacterium, Defluviitaleaceae UCG-011, Family XIII AD3011 group, Family XIII UCG-001, Coprococcus 1, Coprococcus 2, Eisenbergiella, GCA900066575, Lachnoclostridium, Lachnospiraceae FCS020 group, Lachnospiraceae NK4A136 group, Marvinbryantia, Sellimonas, Shuttleworthia, [Ruminococcus] gnavus group, Peptococcaceae uncultured bacterium, Romboutsia, Anaerofilum, Anaerotruncus, Butyricicoccus, DTU089, GCA-900066225, Hydrogenoanaerobacterium, Negativibacillus, Papillibacter, Ruminiclostridium, Ruminiclostridium 1, Ruminococcaceae NK4A214 group, Ruminococcaceae UCG-002, Ruminococcaceae UCG-005, Ruminococcaceae UCG-007, Ruminococcaceae UCG-009, Ruminococcaceae UCG-010, Ruminococcaceae UCG-014, Ruminococcus 1, Ruminococcus 2, UBA1819, [Eubacterium] coprostanoligenes group, Ruminococcaceae unclassified genus, Clostridiales unclassified family unclassified genus, DTU014 uncultured bacterium uncultured bacterium, Holdemania, Erysipelotrichaceae unclassified genus, Veillonella, Coriobacteriales Incertae Sedis uncultured bacterium, Desulfovibrio, Desulfovibrionaceae uncultured bacterium, Burkholderiaceae unclassified genus, Cloacibacillus, Mollicutes RF39 uncultured bacterium uncultured bacterium,* and *Akkermansia.*

Table 2. Relative abundance of the gut microbiome at the family level and Pearson correlation coefficients between alpha diversity indices and gut microbiome taxa.

	Prevalence (%)	Relative abundance (%)			Correlation coefficients			
					OTUs		PD	
		Mean		*SD*	*r*		*r*	
Family								
Methanobacteriaceae	8.0	0.035	±	0.182	0.380	**	0.399	**
Actinomycetaceae	93.2	0.050	±	0.037	-0.193	†	-0.138	
Bifidobacteriaceae	98.9	15.542	±	10.569	-0.197	†	-0.199	†
Corynebacteriaceae	15.9	0.003	±	0.015	-0.020		-0.039	
Micrococcaceae	28.4	0.005	±	0.014	-0.164		-0.159	
Atopobiaceae	39.8	0.086	±	0.220	0.105		0.081	
Coriobacteriaceae	89.8	6.444	±	4.769	0.004		-0.047	
Coriobacteriales Incertae Sedis	38.6	0.052	±	0.115	0.405	**	0.341	**
Eggerthellaceae	98.9	0.728	±	0.570	0.271	*	0.203	†
Coriobacteriales unclassified family	20.5	0.036	±	0.121	0.320	**	0.265	*
Bacteroidaceae	100.0	11.113	±	6.507	-0.217	*	-0.115	
Barnesiellaceae	64.8	0.420	±	0.603	0.323	**	0.361	**
Marinifilaceae	81.8	0.161	±	0.218	0.510	**	0.485	**
Muribaculaceae	18.2	0.085	±	0.297	0.120		0.075	

Porphyromonadaceae	8.0	0.002	±	0.009	0.134		0.136	
Prevotellaceae	60.2	1.561	±	3.280	-0.059		-0.143	
Rikenellaceae	87.5	0.923	±	0.890	0.613	**	0.586	**
Tannerellaceae	90.9	1.444	±	2.328	-0.122		-0.164	
Bacteroidia unclassified order unclassified family	6.8	0.004	±	0.020	0.277	**	0.288	**
Campylobacteraceae	5.7	0.004	±	0.025	0.000		0.083	
Bacillaceae	47.7	0.278	±	0.838	0.058		0.055	
Bacillales Family XI	53.4	0.011	±	0.019	-0.199	†	-0.160	
Aerococcaceae	5.7	0.001	±	0.002	-0.097		-0.127	
Carnobacteriaceae	48.9	0.010	±	0.013	-0.280	**	-0.256	*
Enterococcaceae	27.3	0.021	±	0.059	-0.261	*	-0.274	**
Lactobacillaceae	50.0	0.100	±	0.298	-0.148		-0.156	
Leuconostocaceae	9.1	0.009	±	0.048	0.281	**	0.210	*
Streptococcaceae	98.9	1.837	±	2.553	-0.248	*	-0.229	*
Christensenellaceae	65.9	0.532	±	1.069	0.669	**	0.609	**
Clostridiaceae 1	61.4	0.259	±	0.848	0.298	**	0.221	*
Clostridiales vadinBB60 group	26.1	0.013	±	0.038	0.519	**	0.509	**
Defluviitaleaceae	37.5	0.011	±	0.019	0.710	**	0.653	**
Eubacteriaceae	61.4	0.053	±	0.129	0.044		0.096	
Clostridiales Family XI	33.0	0.011	±	0.038	0.162		0.224	*
Clostridiales Family XIII	90.9	0.246	±	0.269	0.603	**	0.570	**
Lachnospiraceae	100.0	26.567	±	9.196	-0.359	**	-0.369	**
Peptococcaceae	36.4	0.029	±	0.120	0.276	**	0.258	*
Peptostreptococcaceae	97.7	1.497	±	1.864	0.283	**	0.225	*
Ruminococcaceae	100.0	18.208	±	8.074	0.691	**	0.639	**
Clostridiales unclassified family	13.6	0.003	±	0.012	0.434	**	0.405	**
DTU014 uncultured bacterium	11.4	0.002	±	0.007	0.477	**	0.491	**
Erysipelotrichaceae	100.0	2.792	±	2.801	0.185	†	0.200	†
Acidaminococcaceae	80.7	1.184	±	1.222	-0.196	†	-0.103	
Veillonellaceae	90.9	4.426	±	6.978	-0.286	**	-0.255	*
Fusobacteriaceae	43.2	0.168	±	0.479	-0.170		-0.117	
Saccharimonadaceae	22.7	0.003	±	0.007	-0.097		-0.106	
Saccharimonadales uncultured bacterium	5.7	0.001	±	0.003	0.151		0.158	
Rhodospirillales uncultured bacterium	14.8	0.028	±	0.151	0.182	†	0.178	†
Desulfovibrionaceae	81.8	0.129	±	0.168	0.236	*	0.274	**
Succinivibrionaceae	5.7	0.002	±	0.011	-0.101		-0.090	
Burkholderiaceae	86.4	0.232	±	0.362	-0.215	*	-0.077	
Enterobacteriaceae	81.8	0.349	±	0.691	-0.118		-0.017	
Pasteurellaceae	33.0	0.035	±	0.163	-0.092		-0.123	
Synergistaceae	18.2	0.020	±	0.119	0.370	**	0.351	**
Izimaplasmatales unclassified family	6.8	0.003	±	0.017	0.151		0.266	*
Mollicutes RF39 uncultured bcterium	9.1	0.006	±	0.028	0.425	**	0.400	**
Akkermansiaceae	56.8	2.211	±	4.247	0.279	**	0.333	**

Note. SD: standard deviation; OTUs: observed operational taxonomic units; PD: Faith's phylogenetic diversity, ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$.

Table 3. Relative abundance of the gut microbiome at the genus level and Pearson correlation coefficients between alpha diversity indices and gut microbiome taxa.

	Prevalence (%)	Relative abundance (%)			Correlation coefficients			
					OTUs		PD	
		Mean		*SD*	*r*		*r*	
Genus								
Methanobrevibacter	8.0	0.035	±	0.182	0.380	**	0.399	**
Actinomyces	93.2	0.048	±	0.036	-0.270	*	-0.201	†
F0332	5.7	0.001	±	0.002	0.018		0.009	

Varibaculum	6.8	0.002	±	0.007	0.302	**	0.235	*
Bifidobacterium	98.9	15.539	±	10.570	-0.197	†	-0.199	†
Corynebacterium	11.4	0.003	±	0.015	-0.047		-0.062	
Rothia	28.4	0.005	±	0.014	-0.164		-0.159	
Atopobium	11.4	0.001	±	0.004	-0.164		-0.154	
Olsenella	27.3	0.075	±	0.210	0.091		0.066	
Collinsella	89.8	6.410	±	4.777	-0.005		-0.054	
Coriobacteriaceae unclassified genus	8.0	0.033	±	0.206	0.204	†	0.152	
Raoultibacter	22.7	0.005	±	0.011	0.262	*	0.238	*
Coriobacteriales Incertae Sedis uncultured bacterium	28.4	0.047	±	0.112	0.386	**	0.324	**
Adlercreutzia	51.1	0.077	±	0.157	0.291	**	0.195	†
Eggerthella	88.6	0.337	±	0.375	-0.140		-0.099	
Enterorhabdus	23.9	0.036	±	0.090	0.312	**	0.291	**
Gordonibacter	56.8	0.034	±	0.058	0.271	*	0.288	**
Senegalimassilia	15.9	0.073	±	0.194	0.351	**	0.307	**
Slackia	28.4	0.108	±	0.337	0.020		-0.031	
Eggerthellaceae uncultured bacterium	12.5	0.049	±	0.158	0.234	*	0.162	
Eggerthellaceae unclassified genus	39.8	0.015	±	0.034	0.168		0.133	
Coriobacteriales unclassified family unclassified genus	20.5	0.036	±	0.121	0.320	**	0.265	*
Bacteroides	100.0	11.113	±	6.507	-0.217	*	-0.115	
Barnesiella	51.1	0.355	±	0.561	0.302	**	0.344	**
Coprobacter	43.2	0.058	±	0.141	0.138		0.142	
Barnesiellaceae uncultured bacterium	18.2	0.006	±	0.020	0.271	*	0.224	*
Butyricimonas	55.7	0.056	±	0.089	0.355	**	0.402	**
Odoribacter	78.4	0.106	±	0.168	0.473	**	0.417	**
Muribaculaceae uncultured bacterium	18.2	0.085	±	0.297	0.120		0.073	
Porphyromonas	8.0	0.002	±	0.009	0.134		0.136	
Alloprevotella	9.1	0.193	±	1.244	-0.160		-0.158	
Paraprevotella	20.5	0.203	±	0.566	-0.060		-0.078	
Prevotella	15.9	0.006	±	0.028	0.175		0.180	†
Prevotella 2	18.2	0.245	±	1.096	-0.114		-0.146	
Prevotella 9	23.9	0.808	±	2.228	0.054		-0.047	
Alistipes	86.4	0.914	±	0.895	0.613	**	0.586	**
Parabacteroides	90.9	1.444	±	2.328	-0.122		-0.164	
Bacteroidia unclassified order unclassified family unclassified genus	6.8	0.004	±	0.020	0.277	**	0.288	**
Campylobacter	5.7	0.004	±	0.025	0.000		0.083	
Bacillus	47.7	0.278	±	0.838	0.058		0.055	
Gemella	53.4	0.011	±	0.019	-0.199	†	-0.160	
Abiotrophia	5.7	0.001	±	0.002	-0.097		-0.127	
Granulicatella	48.9	0.010	±	0.013	-0.280	**	-0.256	*
Enterococcus	27.3	0.021	±	0.059	-0.261	*	-0.274	**
Lactobacillus	50.0	0.091	±	0.235	-0.134		-0.150	
Leuconostoc	8.0	0.006	±	0.038	0.274	**	0.212	*
Lactococcus	25.0	0.036	±	0.260	0.236	*	0.188	†
Streptococcus	98.9	1.801	±	2.555	-0.272	*	-0.247	*
Christensenellaceae R-7 group	59.1	0.492	±	1.026	0.657	**	0.597	**
Christensenellaceae uncultured bacterium	50.0	0.030	±	0.065	0.558	**	0.512	**
Christensenellaceae unclassified genus	44.3	0.010	±	0.016	0.394	**	0.376	**
Clostridium sensu stricto1	61.4	0.259	±	0.848	0.298	**	0.221	*
Clostridiales vadinBB60 group uncultured bacterium	26.1	0.013	±	0.034	0.521	**	0.511	**

Defluviitaleaceae UCG-011	37.5	0.011	±	0.019	0.710	**	0.653	**
Anaerofustis	30.7	0.005	±	0.009	0.266	*	0.295	**
Eubacterium	37.5	0.048	±	0.127	0.027		0.079	
Anaerococcus	8.0	0.001	±	0.003	0.257	*	0.251	*
Ezakiella	10.2	0.002	±	0.009	0.132		0.145	
Finegoldia	5.7	0.001	±	0.002	-0.021		-0.038	
Parvimonas	15.9	0.005	±	0.025	0.113		0.184	†
Peptoniphilus	11.4	0.002	±	0.009	0.172		0.230	*
Family XIII AD3011 group	75.0	0.156	±	0.207	0.606	**	0.549	**
Family XIII UCG-001	56.8	0.029	±	0.039	0.464	**	0.459	**
[Eubacterium] brachy group	70.5	0.042	±	0.061	0.244	*	0.246	*
[Eubacterium] nodatum group	40.9	0.017	±	0.057	0.086		0.127	
Anaerostipes	100.0	1.914	±	1.880	-0.181	†	-0.198	†
Blautia	100.0	6.486	±	4.263	-0.253	*	-0.158	
CAG-56	21.6	0.047	±	0.133	0.196	†	0.157	
Coprococcus 1	35.2	0.104	±	0.185	0.327	**	0.242	*
Coprococcus 2	10.2	0.115	±	0.500	0.313	**	0.218	*
Coprococcus 3	42.0	0.346	±	0.600	0.086		0.012	
Dorea	79.5	1.331	±	1.363	-0.137		-0.163	
Eisenbergiella	50.0	0.052	±	0.119	0.212	*	0.323	**
Fusicatenibacter	85.2	2.052	±	2.045	-0.195	†	-0.290	**
GCA900066575	46.6	0.016	±	0.022	0.479	**	0.410	**
Howardella	5.7	0.006	±	0.031	0.147		0.159	
Hungatella	39.8	0.019	±	0.034	-0.165		-0.043	
Lachnoclostridium	100.0	1.356	±	1.096	-0.406	**	-0.286	**
Lachnospira	69.3	0.458	±	0.761	-0.230	*	-0.295	**
Lachnospiraceae FCS020 group	64.8	0.094	±	0.132	0.316	**	0.278	**
Lachnospiraceae ND3007 group	73.9	0.283	±	0.336	0.064		-0.036	
Lachnospiraceae NK4A136 group	77.3	0.391	±	0.737	0.302	**	0.271	*
Lachnospiraceae UCG-001	19.3	0.050	±	0.166	0.129		0.073	
Lachnospiraceae UCG-004	53.4	0.078	±	0.168	-0.179	†	-0.192	†
Lachnospiraceae UCG-008	14.8	0.004	±	0.012	0.148		0.077	
Lachnospiraceae UCG-010	36.4	0.008	±	0.016	-0.110		-0.143	
Lactonifactor	44.3	0.009	±	0.014	0.100		0.065	
Marvinbryantia	43.2	0.072	±	0.150	0.429	**	0.389	**
Roseburia	89.8	0.790	±	1.062	-0.106		-0.198	†
Sellimonas	65.9	0.266	±	0.432	-0.332	**	-0.267	*
Shuttleworthia	44.3	0.030	±	0.055	0.313	**	0.330	**
Tyzzerella	40.9	0.058	±	0.122	0.122		0.176	
Tyzzerella 3	27.3	0.107	±	0.274	-0.030		-0.073	
Tyzzerella 4	29.5	0.205	±	0.527	-0.262	*	-0.124	
[Eubacterium] eligens group	33.0	0.114	±	0.303	0.077		0.032	
[Eubacterium] fissicatena group	50.0	0.012	±	0.017	0.066		0.203	†
[Eubacterium] hallii group	88.6	1.587	±	1.355	0.020		-0.042	
[Eubacterium] ruminantium group	12.5	0.163	±	0.563	0.240	*	0.159	
[Eubacterium] ventriosum group	78.4	0.333	±	0.389	0.222	*	0.093	
[Eubacterium] xylanophilum group	14.8	0.014	±	0.056	0.162		0.218	*
[Ruminococcus] gauvreauii group	60.2	0.413	±	0.789	0.065		-0.002	
[Ruminococcus] gnavus group	86.4	1.248	±	2.124	-0.537	**	-0.387	**
[Ruminococcus] torques group	96.6	1.620	±	1.664	0.086		0.076	
Lachnospiraceae uncultured bacterium	96.6	0.622	±	0.592	-0.076		-0.100	
Lachnospiraceae unclassified genus	100.0	3.695	±	2.897	-0.094		-0.155	
Peptococcus	11.4	0.019	±	0.116	0.162		0.146	
Peptococcaceae uncultured bacterium	31.8	0.011	±	0.025	0.566	**	0.559	**

Intestinibacter	75.0	0.347	±	0.593	-0.026		-0.019	
Peptostreptococcus	9.1	0.001	±	0.004	-0.145		0.008	
Romboutsia	92.0	1.062	±	1.540	0.369	**	0.301	**
Terrisporobacter	18.2	0.036	±	0.149	0.097		0.055	
Anaerofilum	17.0	0.002	±	0.005	0.378	**	0.300	**
Anaerotruncus	51.1	0.015	±	0.021	0.413	**	0.461	**
Butyricicoccus	98.9	0.624	±	0.575	-0.346	**	-0.347	**
Candidatus Soleaferrea	12.5	0.003	±	0.010	-0.029		0.123	
DTU089	75.0	0.034	±	0.036	0.352	**	0.333	**
Faecalibacterium	96.6	4.966	±	3.755	-0.127		-0.148	
Flavonifractor	92.0	0.224	±	0.268	-0.247	*	-0.094	
Fournierella	20.5	0.011	±	0.044	-0.001		0.090	
GCA-900066225	53.4	0.017	±	0.031	0.426	**	0.422	**
Hydrogenoanaerobacterium	6.8	0.002	±	0.011	0.337	**	0.325	**
Negativibacillus	68.2	0.093	±	0.154	0.415	**	0.491	**
Oscillibacter	92.0	0.279	±	0.332	0.233	*	0.290	**
Oscillospira	10.2	0.011	±	0.061	0.093		0.061	
Papillibacter	8.0	0.001	±	0.004	0.314	**	0.290	**
Ruminiclostridium	47.7	0.011	±	0.021	0.452	**	0.379	**
Ruminiclostridium 1	9.1	0.001	±	0.005	0.368	**	0.299	**
Ruminiclostridium 5	98.9	0.852	±	1.256	0.284	**	0.217	*
Ruminiclostridium 6	13.6	0.173	±	1.006	0.127		0.180	†
Ruminiclostridium 9	83.0	0.213	±	0.215	0.156		0.251	*
Ruminococcaceae NK4A214 group	53.4	0.292	±	0.692	0.462	**	0.414	**
Ruminococcaceae UCG-002	59.1	0.704	±	1.170	0.550	**	0.544	**
Ruminococcaceae UCG-003	31.8	0.034	±	0.091	0.216	*	0.245	*
Ruminococcaceae UCG-004	25.0	0.130	±	0.239	0.124		0.207	†
Ruminococcaceae UCG-005	63.6	0.323	±	0.531	0.647	**	0.587	**
Ruminococcaceae UCG-007	8.0	0.001	±	0.004	0.426	**	0.416	**
Ruminococcaceae UCG-009	43.2	0.017	±	0.029	0.388	**	0.329	**
Ruminococcaceae UCG-010	31.8	0.040	±	0.109	0.606	**	0.533	**
Ruminococcaceae UCG-013	88.6	0.479	±	0.508	0.059		0.023	
Ruminococcaceae UCG-014	28.4	0.590	±	1.781	0.433	**	0.404	**
Ruminococcus 1	48.9	0.719	±	1.113	0.390	**	0.318	**
Ruminococcus 2	54.5	1.820	±	2.636	0.335	**	0.349	**
Subdoligranulum	95.5	3.194	±	2.771	0.150		0.084	
UBA1819	83.0	0.116	±	0.191	0.352	**	0.356	**
[Eubacterium] coprostanoligenes group	76.1	1.308	±	1.701	0.623	**	0.558	**
Ruminococcaceae uncultured bacterium	95.5	0.795	±	1.991	0.214	*	0.251	*
Ruminococcaceae unclassified genus	81.8	0.098	±	0.176	0.400	**	0.344	**
Clostridiales unclassified family unclassified genus	13.6	0.003	±	0.012	0.434	**	0.405	**
DTU014 uncultured bacterium uncultured bacterium	11.4	0.002	±	0.007	0.477	**	0.491	**
Catenibacterium	11.4	0.515	±	1.706	0.173		0.140	
Catenisphaera	12.5	0.059	±	0.315	0.193	†	0.144	
Dielma	13.6	0.002	±	0.007	0.106		0.107	
Erysipelatoclostridium	88.6	0.398	±	0.606	-0.127		-0.024	
Erysipelotrichaceae UCG-003	36.4	0.511	±	1.020	0.047		0.024	
Faecalitalea	35.2	0.109	±	0.297	-0.127		-0.070	
Holdemanella	21.6	0.820	±	2.032	0.054		0.079	
Holdemania	63.6	0.023	±	0.028	0.345	**	0.349	**
Solobacterium	23.9	0.014	±	0.105	-0.054		0.031	
Turicibacter	70.5	0.163	±	0.309	0.260	*	0.189	†
[Clostridium] innocuum group	81.8	0.055	±	0.072	-0.281	**	-0.139	
Erysipelotrichaceae unclassified genus	77.3	0.100	±	0.158	0.345	**	0.414	**
Acidaminococcus	35.2	0.309	±	0.820	-0.207	†	-0.221	*

Phascolarctobacterium	72.7	0.872	±	1.024	-0.068		0.054	
Allisonella	26.1	0.029	±	0.077	-0.152		-0.173	
Dialister	44.3	0.899	±	1.870	0.047		0.014	
Megamonas	26.1	1.667	±	6.081	-0.130		-0.093	
Megasphaera	35.2	0.946	±	2.058	-0.213	*	-0.199	†
Mitsuokella	12.5	0.321	±	1.466	-0.098		-0.104	
Veillonella	46.6	0.533	±	1.594	-0.413	**	-0.394	**
Fusobacterium	43.2	0.168	±	0.479	-0.170		-0.117	
Saccharimonadaceae uncultured bacterium	22.7	0.003	±	0.006	-0.185	†	-0.180	†
Saccharimonadales uncultured bacterium uncultured bacterium	5.7	0.001	±	0.003	0.151		0.158	
Rhodospirillales uncultured bacterium uncultured bacterium	14.8	0.028	±	0.151	0.182	†	0.178	†
Bilophila	78.4	0.083	±	0.117	0.024		0.074	
Desulfovibrio	26.1	0.040	±	0.105	0.302	**	0.295	**
Desulfovibrionaceae uncultured bacterium	13.6	0.005	±	0.019	0.261	*	0.307	**
Parasutterella	48.9	0.124	±	0.347	-0.171		-0.002	
Sutterella	67.0	0.104	±	0.178	-0.135		-0.181	†
Burkholderiaceae unclassified genus	5.7	0.003	±	0.015	0.313	**	0.282	**
Citrobacter	9.1	0.009	±	0.059	0.269	*	0.242	*
Enterobacter	10.2	0.031	±	0.163	-0.021		-0.078	
Escherichia-Shigella	71.6	0.267	±	0.584	-0.143		0.021	
Raoultella	5.7	0.006	±	0.048	-0.069		-0.094	
Haemophilus	33.0	0.035	±	0.163	-0.092		-0.123	
Cloacibacillus	17.0	0.019	±	0.119	0.369	**	0.350	**
Izimaplasmatales unclassified family unclassified genus	6.8	0.003	±	0.017	0.151		0.266	*
Mollicutes RF39 uncultured bacterium uncultured bacterium	9.1	0.006	±	0.028	0.425	**	0.400	**
Akkermansia	56.8	2.211	±	4.247	0.279	**	0.333	**

Note. SD: standard deviation; OTUs: observed operational taxonomic units; PD: Faith's phylogenetic diversity, ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$.

Interaction between environmental sensitivity and gut microbiome taxa at the family level

- Effect on CRP

We examined the interaction effects using hierarchical multiple regression analysis exclusively for the gut microbiome taxa that exhibited significant moderate ($|r| > 0.30$) or high ($|r| > 0.50$) correlations. Among the 17 taxa, the interaction term between environmental sensitivity and the family *Marinifilaceae* was identified as a significant predictor for CRP ($\beta = -0.183$, $p < 0.05$) (Table 4). The coefficient of determination, R^2, increased from that observed in Step 1 when the interaction term between environmental sensitivity and the family *Marinifilaceae* was incorporated in Step 2 ($\Delta R^2 = 0.033$, $p < 0.05$). The coefficient of determination for the final regression model in Step 2, was $R^2 = 0.375$ ($p < 0.01$). The interaction between environmental sensitivity and the other bacterial taxa did not show a significant association with CRP.

Table 4. Interaction effects between environmental sensitivity and family *Marinifilaceae* predicting CRP ($n = 88$).

	Log-normalized CRP			
	Step1		Step2	
Predictors	β	p	β	p
Age	-0.151		-0.162	†
Sex	-0.090		-0.109	
BMI	0.542	**	0.537	**
HSP-J10	0.166	†	0.162	†
Family *Marinifilaceae*	0.015		0.032	

HSP-J10 × Family *Marinifilaceae*			-0.183	*
R^2	0.342	**	0.375	**
ΔR^2			0.033	*

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. CRP: C-reactive protein; BMI: body mass index; HSP-J10: environmental sensitivity.

- Effect on LBP

Among the 17 taxa, the interaction term between environmental sensitivity and the family *Barnesiellaceae* emerged as a significant predictor of LBP ($\beta = -0.200$, $p < 0.05$) (Table 5). The coefficient of determination, R^2, increased from that observed in Step 1 when the interaction term between environmental sensitivity and family *Barnesiellaceae* was included in Step 2 ($\Delta R^2 = 0.036$, $p < 0.05$). The final regression model in Step 2 yielded a coefficient of determination of $R^2 = 0.340$ ($p < 0.01$). Similar results were observed for the family *Akkermansiace* ($\Delta R^2 = 0.035$, $p < 0.05$) (Table 6), family *Marinifilaceae* ($\Delta R^2 = 0.030$, $p = 0.062$) (Table 7), family *Defluviitaleaceae* ($\Delta R^2 = 0.027$, $p < 0.05$) (Table 8), and family *XIII* ($\Delta R^2 = 0.023$, $p = 0.099$) (Table 9). The p-values for the interaction between environmental sensitivity and the other bacterial taxa were > 0.1 in relation to LBP.

Table 5. Interaction effects between environmental sensitivity and family *Barnesiellaceae* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.041		0.059	
Sex	-0.035		-0.041	
BMI	0.507	**	0.443	**
HSP-J10	0.140		0.122	
Family *Barnesiellaceae*	0.126		0.136	
HSP-J10 × Family *Barnesiellaceae*			-0.200	*
R^2	0.304	**	0.340	**
ΔR^2			0.036	*

Note. ** $p < 0.01$; * $p < 0.05$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Table 6. Interaction effects between environmental sensitivity and family *Akkermansiace* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.042		0.033	
Sex	-0.021		-0.031	
BMI	0.506	**	0.526	**
HSP-J10	0.134		0.109	
Family *Akkermansiace*	0.028		0.058	
HSP-J10 × Family *Akkermansiace*			-0.192	*
R^2	0.290	**	0.325	**
ΔR^2			0.035	*

Note. ** $p < 0.01$; * $p < 0.05$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Table 7. Interaction effects between environmental sensitivity and family *Marinifilaceae* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.034		0.023	
Sex	-0.001		-0.019	
BMI	0.504	**	0.499	**

HSP-J10	0.129		0.126	
Family *Marinifilaceae*	-0.050		-0.034	
HSP-J10 × Family *Marinifilaceae*			-0.175	†
R^2	0.291	**	0.321	**
ΔR^2			0.030	†

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Table 8. Interaction effects between environmental sensitivity and family *Defluviitaleaceae* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.041		0.038	
Sex	-0.035		-0.046	
BMI	0.533	**	0.538	**
HSP-J10	0.143		0.119	
Family *Defluviitaleaceae*	0.101		0.095	
HSP-J10 × Family *Defluviitaleaceae*			-0.166	†
R^2	0.298	**	0.324	**
ΔR^2			0.027	†

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Table 9. Interaction effects between environmental sensitivity and family *Family XIII* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.043		0.015	
Sex	0.027		0.022	
BMI	0.501	**	0.516	**
HSP-J10	0.142		0.127	
Family *Family XIII*	-0.114		-0.043	
HSP-J10 × Family *Family XIII*			-0.169	†
R^2	0.300	**	0.323	**
ΔR^2			0.023	†

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP10: environmental sensitivity.

Interaction between environmental sensitivity and gut microbiome taxa at the genus level

- Effect on CRP

We examined the interaction effects using hierarchical multiple regression analysis for the gut microbiome taxa (genus) within the family where a significant interaction effect was observed (family *Marinifilaceae*) or for the taxa that exhibited significant moderate ($|r| > 0.30$) or high ($|r|>0.50$) correlations at the genus level. The interaction term between environmental sensitivity and genus *Butyricimonas* emerged as a significant predictor for CRP ($\beta = -0.218$, $p < 0.05$) (Table 10). The coefficient of determination, R^2, increased from that in Step 1 when the interaction term between environmental sensitivity and genus *Butyricimonas* was added in Step 2 ($\Delta R^2 = 0.044$, $p < 0.05$). The final regression model in Step 2 yielded a coefficient of determination of $R^2 = 0.385$ ($p < 0.01$). In contrast, the interaction between environmental sensitivity and the other taxa did not show a significant association with CRP.

Table 10. Interaction effects between environmental sensitivity and genus *Butyricimonas* predicting CRP ($n = 88$).

	Log-normalized CRP			
	Step1		Step2	
Predictors	β	p	β	p
Age	-0.152		-0.141	
Sex	-0.089		-0.106	
BMI	0.541	**	0.516	**
HSP-J10	0.165	†	0.206	*
Genus *Butyricimonas*	0.005		-0.035	
HSP-J10 × Genus *Butyricimonas*			-0.218	*
R^2	0.342	**	0.385	**
ΔR^2			0.044	*

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. CRP: C-reactive protein; BMI: body mass index; HSP-J10: environmental sensitivity.

- Effect on LBP

We conducted hierarchical multiple regression analysis on the gut microbiome taxa (genus) associated with families where a significant interaction effect was observed (family *Barnesiellaceae* and family *Akkermansiace*) or for the taxa that exhibited significant moderate ($|r| > 0.30$) or high ($|r| > 0.50$) correlations at the genus level. The interaction between environmental sensitivity and genus *Coprobacter* was found to be a significant predictor for LBP ($\beta = -0.233$, $p < 0.05$) (Table 11). The coefficient of determination, R^2, increased from that in Step 1 when the interaction term between environmental sensitivity and genus *Coprobacter* was added in Step 2 ($\Delta R^2 = 0.042$, $p < 0.05$). The coefficient of determination for the final regression model, Step 2, was $R^2 = 0.331$ ($p < 0.01$). Similar findings were observed for genus *Barnesiella* ($\Delta R^2 = 0.027$, $p = 0.077$) (Table 12), genus *Akkermansia* ($\Delta R^2 = 0.035$, $p < 0.05$) (Table 13), genus *Family XIII AD3011 group* ($\Delta R^2 = 0.053$, $p < 0.05$) (Table 14), genus *GCA-900066225* ($\Delta R^2 = 0.043$, $p < 0.05$) (Table 15), and genus *Ruminiclostridium 1* ($\Delta R^2 = 0.035$, $p < 0.05$) (Table 16).

Table 11. Interaction effects between environmental sensitivity and genus *Coprobacter* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Variables	β	p	B	p
Age	0.041		-0.005	
Sex	-0.014		-0.018	
BMI	0.507	**	0.484	**
HSP-J10	0.134		0.163	†
Genus *Coprobacter*	0.019		-0.077	
HSP-J10 × Genus *Coprobacter*			-0.233	*
R^2	0.289	**	0.331	**
ΔR^2			0.042	*

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Table 12. Interaction effects between environmental sensitivity and genus *Barnesiella* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.037		0.063	
Sex	-0.030		-0.030	
BMI	0.511	**	0.456	**
HSP-J10	0.138		0.112	
Genus *Barnesiella*	0.130		0.147	
HSP-J10 × Genus *Barnesiella*			-0.175	†
R^2	0.305	**	0.332	**
ΔR^2			0.027	†

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Table 13. Interaction effects between environmental sensitivity and genus *Akkermansia* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.042		0.033	
Sex	-0.021		-0.031	
BMI	0.506	**	0.526	**
HSP-J10	0.134		0.109	
Genus *Akkermansia*	0.028		0.058	
HSP-J10 × Genus *Akkermansia*			-0.192	*
R^2	0.290	**	0.325	**
ΔR^2			0.035	*

Note. ** $p < 0.01$; * $p < 0.05$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Table 14. Interaction effects between environmental sensitivity and genus *Family XIII AD3011 group* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.045		-0.014	
Sex	0.015		0.020	
BMI	0.493	**	0.556	**
HSP-J10	0.148		0.134	
Genus *Family XIII AD3011 group*	-0.102		0.065	
HSP-J10 × Genus *Family XIII AD3011 group*			-0.284	*
R^2	0.298	**	0.351	**
ΔR^2			0.053	*

Note. ** $p < 0.01$; * $p < 0.05$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Table 15. Interaction effects between environmental sensitivity and genus *GCA-900066225* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.031		0.001	
Sex	0.004		-0.025	
BMI	0.500	**	0.521	**
HSP-J10	0.148		0.091	
Genus *GCA-900066225*	-0.121		-0.050	
HSP-J10 × Genus *GCA-900066225*			-0.228	*
R^2	0.303	**	0.346	**
ΔR^2			0.043	*

Note. ** $p < 0.01$; * $p < 0.05$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Table 16. Interaction effects between environmental sensitivity and genus *Ruminiclostridium 1* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.039		0.047	
Sex	-0.012		-0.037	
BMI	0.511	**	0.508	**

HSP-J10	0.134		0.115	
Genus *Ruminiclostridium 1*	0.016		-0.068	
HSP-J10 × Genus *Ruminiclostridium 1*			-0.208	*
R^2	0.289	**	0.324	**
ΔR^2			0.035	*

Note. ** $p < 0.01$; * $p < 0.05$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Simple slope analysis

We conducted simple slope tests on the gut microbiome taxa that showed an interaction effect with CRP (Figure 1) and LBP (Figure 2). These taxa include family *Marinifilaceae* and genus *Butyricimonas* (associated with CRP), and family *Barnesiellaceae*, family *Akkermansiace*, genus *Coprobacter*, genus *Akkermansia,* genus *Family XIII AD3011 group,* genus *GCA-900066225,* and genus *Ruminiclostridium 1* (associated with LBP).

For individuals with high environmental sensitivity, there was no significant association with CRP when family *Marinifilaceae* abundance was high (*M*+1*SD*; β = -0.110, p = 0.496). However, CRP levels were significantly elevated when the abundance of family *Marinifilaceae* was low (*M*-1*SD*; β = 0.434, p = 0.008) (Figure 1A). Similar results were observed for other taxa. When genus *Butyricimonas* abundance was high (*M*+1*SD*; β = -0.020, p = 0.855), no significant association with CRP was found, but when its abundance was low (*M*-1*SD*; β = 0.392, p = 0.003), CRP levels were significantly higher (Figure 1B).

For LBP, individuals with high environmental sensitivity showed no association when family *Barnesiellaceae* was abundant (*M*+1*SD*; β = -0.127, p = 0.419), but LBP levels were significantly elevated when the abundance of family *Barnesiellaceae* was low (*M*-1*SD*; β = 0.371, p = 0.011) (Figure 2A). Similarly, in individuals with high environmental sensitivity, no association with LBP was found when family *Akkermansiace* abundance was high (*M*+1*SD*; β = -0.143, p = 0.386), but LBP levels were elevated when its abundance was low (*M*-1*SD*; β = 0.362, p = 0.015) (Figure 2B). Individuals with high environmental sensitivity showed no association with LBP when genus *Coprobacter* abundance was high (*M*+1*SD*; β = -0.077, p = 0.560), but LBP levels were significantly higher when its abundance was low (*M*-1*SD*; β = 0.402, p = 0.009) (Figure 2C). Similarly, individuals with high environmental sensitivity showed no association with LBP when genus *Akkermansia* abundance was high (*M*+1*SD*; β = -0.143, p = 0.386), but LBP was elevated when genus *Akkermansia* abundance was low (*M*-1*SD*; β = 0.362, p = 0.015) (Figure 2D). Individuals with high environmental sensitivity showed no association with LBP when genus *Family XIII AD3011 group* abundance was high (*M*+1*SD*; β = -0.126, p = 0.376), but LBP was elevated when genus *Family XIII AD3011 group* abundance was low (*M*-1*SD*; β = 0.393, p = 0.004) (Figure 2E). Individuals with high environmental sensitivity showed no association with LBP when genus *GCA-900066225* abundance was high (*M*+1*SD*; β = -0.238, p = 0.218), but LBP was elevated when genus *GCA-900066225* abundance was low (*M*-1*SD*; β = 0.420, p = 0.006) (Figure 2F). Furthermore, individuals with high environmental sensitivity showed no association with LBP when genus *Ruminiclostridium 1* abundance was high (*M*+1*SD*; β = -0.140, p = 0.396), but LBP was elevated when genus *Ruminiclostridium 1* abundance was low (*M*-1*SD*; β = 0.370, p = 0.015) (Figure 2G).

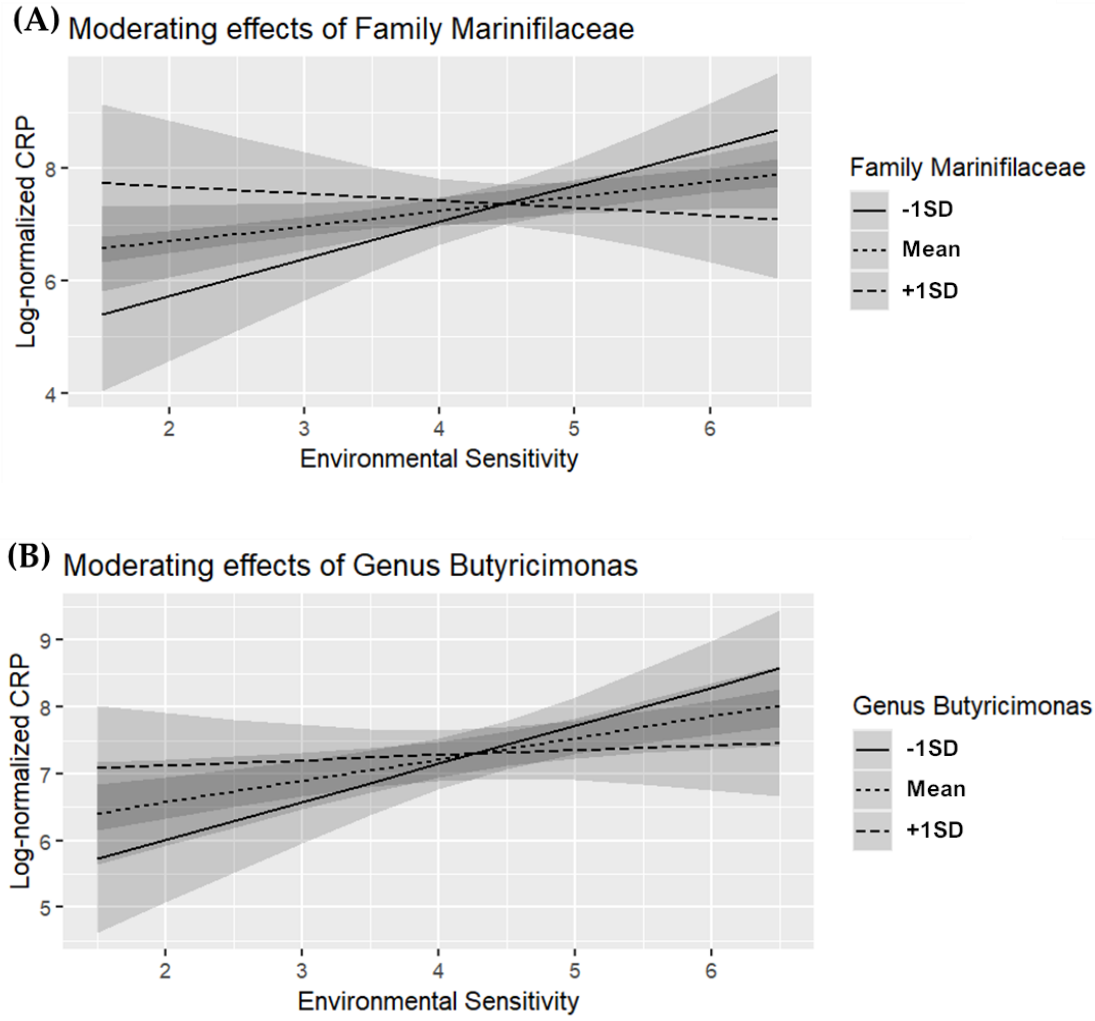
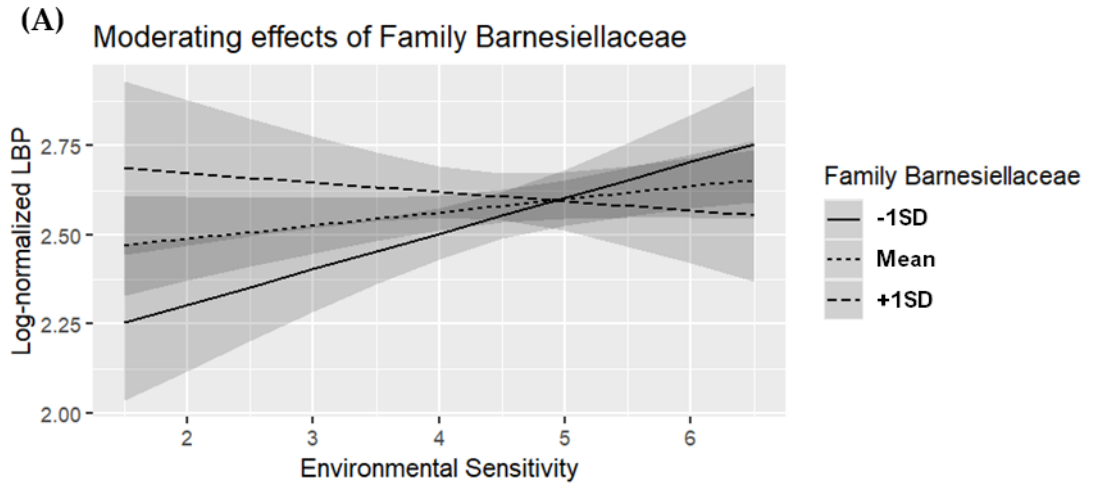
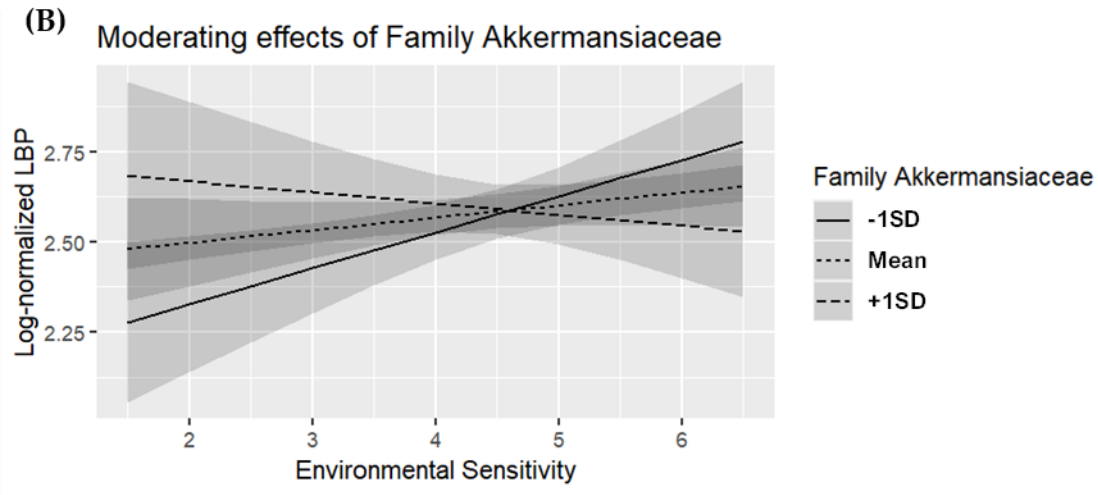
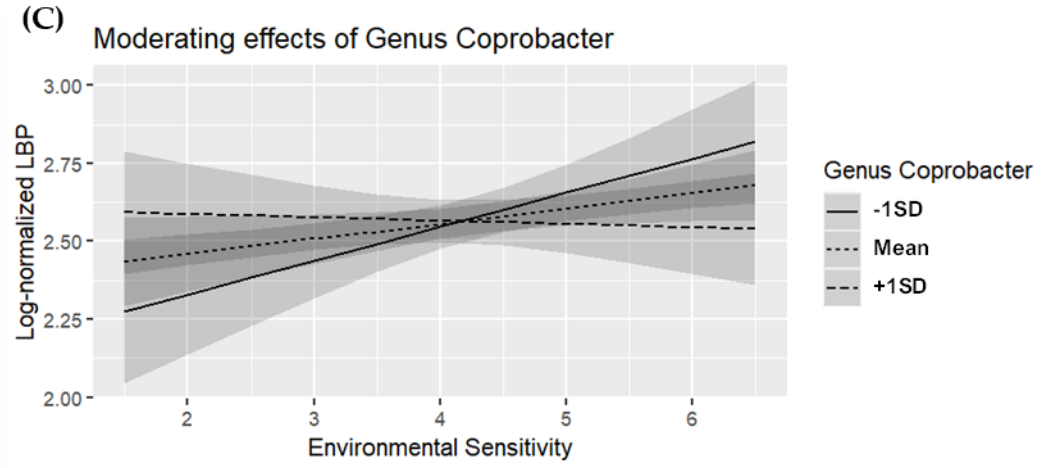
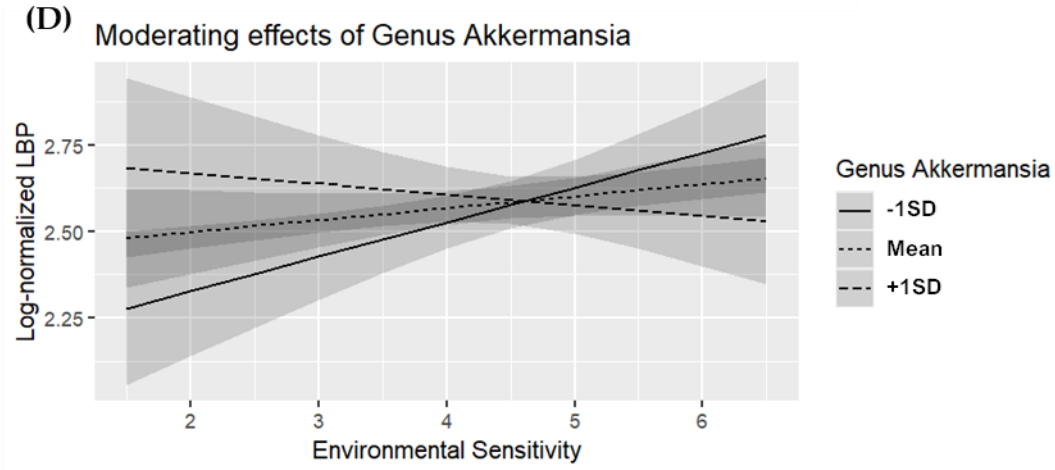


Figure 1. Moderating effects of gut microbiome taxa on the relationship between environmental sensitivity and C-reactive protein (CRP) (n = 88). (A) Family *Marinifilaceae*, (B) Genus *Butyricimonas*.




(B)
Moderating effects of Family Akkermansiaceae
Log-normalized LBP
2.75
2.50
2.25
2
3
4
5
6
Environmental Sensitivity
Family Akkermansiaceae
-1SD
Mean
+1SD


(C)
Moderating effects of Genus Coprobacter
Log-normalized LBP
3.00
2.75
2.50
2.25
2.00
2
3
4
5
6
Environmental Sensitivity
Genus Coprobacter
-1SD
Mean
+1SD


(D)
Moderating effects of Genus Akkermansia
Log-normalized LBP
2.75
2.50
2.25
2
3
4
5
6
Environmental Sensitivity
Genus Akkermansia
-1SD
Mean
+1SD

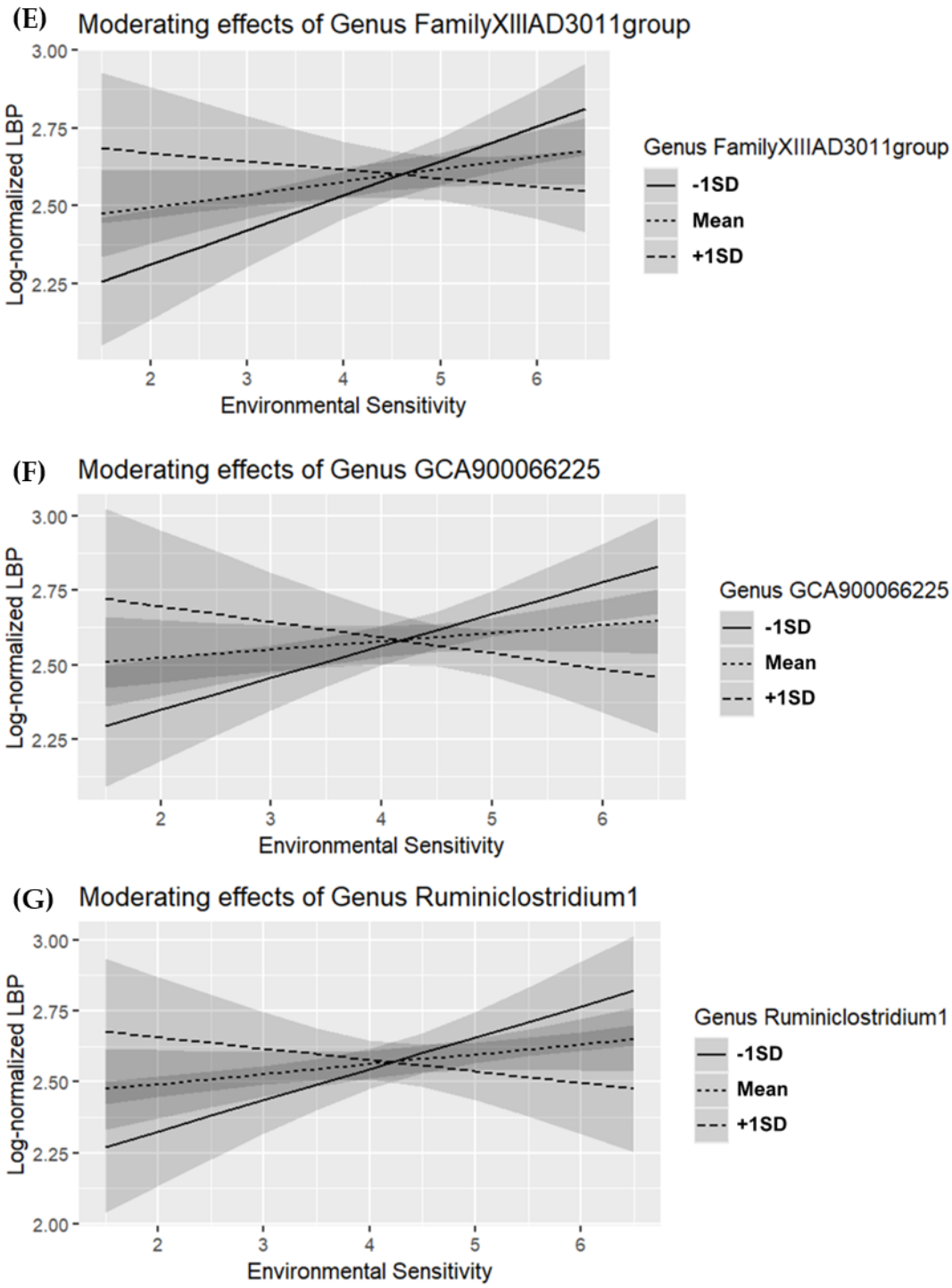


Figure 2. Moderating effects of gut microbiome taxa on the relationship between environmental sensitivity and lipopolysaccharide-binding protein (LBP) (n = 88). (A) Family *Barnesiellaceae*, (B) Family *Akkermansiace*, (C) Genus *Coprobacter*, (D) Genus *Akkermansia*, (E) Genus *Family XIII AD3011 group*, (F) Genus *GCA-900066225*, (G) Genus *Ruminiclostridium 1*.

Discussion

This study aimed to investigate the key taxa of the gut microbiome associated with the interaction between environmental sensitivity and inflammation biomarkers. We identified an interaction between environmental sensitivity and the family *Marinifilaceae* (genus *Butyricimonas*), which was associated with CRP, an inflammation biomarker.

Additionally, we found interactions between environmental sensitivity and the family *Barnesiellaceae* (genus *Coprobacter*), the family *Akkermansiace* (genus *Akkermansia*), genus *Family XIII AD3011 group*, genus *GCA-900066225*, and genus *Ruminiclostridium 1*, all of which are associated with LBP (a gut permeability biomarker). Simple slope tests on these taxa indicated that individuals with high environmental sensitivity did not exhibit significant associations with CRP or LBP when the abundance of these taxa was high. Conversely, elevated levels of these biomarkers were observed when the abundance of the taxa was low. These findings suggest that these taxa play a protective role in moderating inflammation and gut permeability, acting as key components of the gut microbiome that are associated with the interaction between environmental sensitivity and biomarkers of inflammation or gut permeability. Given existing reports linking higher levels of CRP or LBP to increased stress-related psychiatric symptoms, such as depression and anxiety [37-39], as well as physical symptoms including IBS [23], these taxa may play a crucial role in the development or worsening of these symptoms among individuals with high environmental sensitivity.

This study indicated that individual differences in environmental sensitivity may result in different levels of inflammation and gut permeability, depending on the gut microbiome. The serotonin transporter gene polymorphism (5-HTTLPR), one of the genes related to environmental sensitivity, is associated with cortisol responsiveness to acute psychosocial stress [40,41], which suggests that hypothalamic-pituitary-adrenal (HPA) axis responsiveness to the internal and/or external environmental stimuli is involved in individual differences in environmental sensitivity. Several animal and human studies indicate that overactivation of HPA axis in response to chronic stressful stimuli increases gut permeability [42-44] and that the gut microbiome can affect the HPA axis [45-53], which suggests that the gut microbiome can affect gut permeability through the HPA axis. In contrast, gut microbiome can also affect gut permeability independently of the HPA axis [54]. With high gut permeability, lipopolysaccharide (endotoxin) derived from bacteria enters the bloodstream through the intestinal tract, and induces inflammation [55]. Therefore, the plausible mechanisms of the interaction between environmental sensitivity and the gut microbiome are as follows: first, the gut microbiome may influence gut permeability and inflammation through the HPA axis as an internal environmental factor; second, the gut microbiome may act as a moderating factor and influence the gut permeability and inflammation caused by HPA axis activation in response to other stressful stimuli.

The genus *Butyricimonas* is a well-known butyrate-producing bacterium in the intestinal tract [56]. Butyrate has been shown to have beneficial effects on both psychological and physical health. In animal models of depression induced by chronic mild stress or maternal deprivation, butyrate exhibited antidepressant effects [57,58]. *In vitro* and *in vivo* studies suggest that butyrate may play a significant role in regulating neuromediator gene expression within the enteric nervous system and in gastrointestinal functions, such as motility [59]. Furthermore, butyrate possesses anti-inflammatory properties [60], which operate through several mechanisms [42,55,61-66] including maintenance of the intestinal barrier [55,66] and attenuation of the HPA axis [42]. Indeed, the present study demonstrated a tendency for an interaction between environmental sensitivity and the genus *Butyricimonas*, which is associated with the gut permeability biomarker LBP (Supplementary Table 1, Supplementary Figure 1). Therefore, the various functions of butyrate may help explain how the family *Marinifilaceae* (genus *Butyricimonas*) plays a protective role in inflammation among individuals with high environmental sensitivity.

The genus *Akkermansia* is recognized for its ability to enhance intestinal barrier integrity by stimulating mucin production in both human and animal models [67,68]. Okuma et al. [69] reported that several taxa, including the genera *Coprobacter* and *Butyricimonas*, were found to be less abundant in the male depression group compared to the male control group. The genus *Coprobacter* produces propionic and acetic acids [70]. Both propionic [71] and acetic acids [72] also exhibit protective effects on the intestinal barrier. There are limited reports on genus *Family XIII AD3011 group*, genus *GCA-900066225*, and genus *Ruminiclostridium 1*. However, Shang et al. [73] reported that the gut microflora including

some taxa such as *Family XIII AD3011 group* was conducive to improving disease resistance in pigs. Mao et al. [74] reported that the relative abundance of *GCA-900066225* was positively associated with the cecal short-chain fatty acids levels and colonic gut integrity-related marker in mice. Cao et al. [75] reported that *Ruminiclostridium 1* was negatively correlated with inflammation markers and positively correlated with acetic acid and propionic acid in the ileum of mice. Consequently, these taxa might contribute to gut integrity through these mechanisms in individuals with high environmental sensitivity.

Possible limitations and future directions

This study has several possible limitations. First, environmental sensitivity was assessed using a questionnaire. Although HSP-J10 is a well-validated scale by using a large sample size and experimental manipulation [25], integration of alternative measurement methods, such as polygenic scores derived from genome-wide analysis [76] or evaluations of neurophysiological reactivity during stressful tasks [77], could provide comprehensive insights and strengthen our findings. Second, the study utilized a cross-sectional design. Generally, cross-sectional study design has been often used to evaluate the associations between variables in the microbiome research [78-80], as it is technically difficult to reproduce a specific gut microbiome through interventions in human. Future longitudinal studies would allow for better exploration of the causal relationships. Third, several factors, such as diet, might affect the results as confounding factors. Especially, higher intakes of fruit and vegetable were reported to be associated with lower CRP levels [81], lower risk of IBD [82] and gut bacterial composition and diversity [83]. In contrast, in the interaction effect analysis, even when frequencies of fruit and vegetable intakes were added as independent variables, the similar interaction effects between environmental sensitivity and the specific taxa in the gut microbiome were observed (see Supplementary Table 2-10 for details). Finally, we could not explore the precise mechanism involved due to the nature of cross-sectional study. However, based on our results, we speculated that short-chain fatty acids (such as butyric, propionic, and acetic acids) produced by gut microbiome and/or the factors involved in the HPA axis, such as cortisol, might be involved in the interaction. Future studies could strengthen our findings by measuring levels of short-chain fatty acids (such as butyric, propionic, and acetic acids) in fecal samples and/or cortisol levels in samples such as hair.

Conclusions

The present study suggests that the family *Marinifilaceae* (genus *Butyricimonas*), family *Barnesiellaceae* (genus *Coprobacter*), family *Akkermansiace* (genus *Akkermansia*), genus *Family XIII AD3011 group*, genus *GCA-900066225*, and genus *Ruminiclostridium 1* are key taxa in the gut microbiome associated with the relationship between environmental sensitivity and biomarkers of inflammation or gut permeability. Specifically, for individuals with high environmental sensitivity, these taxa might serve as one of the protective factors against inflammation and intestinal permeability. Further studies are required to elucidate the underlying mechanisms.

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Supplementary materials

The genus *Butyricimonas* is the only taxa for which a significant interaction effect was observed in relation to CRP. Additionally, for the family, *Marinifilaceae*, which includes the genus *Butyricimonas*, a trend toward an interaction effect ($p = 0.062$) was noted in association with LBP. Therefore, we conducted a hierarchical multiple regression analysis focused on LBP for this taxon. As indicated in supplementary Table 1, we observed similar results for the genus *Butyricimonas* ($\Delta R^2 = 0.031$, $p = 0.056$), as well as for the genus *Coprobacter*, genus *Barnesiella*, genus *Akkermansia*, genus *Family XIII AD3011 group*, genus *GCA-900066225*, and genus *Ruminiclostridium 1*.

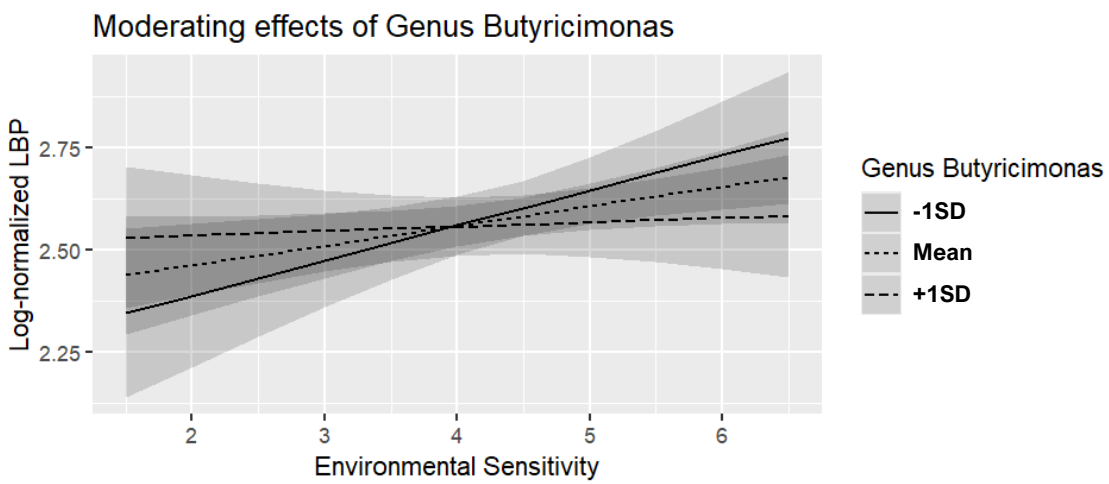
Supplementary Table 1. Interaction effects between environmental sensitivity and the genus *Butyricimonas* predicting LBP ($n = 88$).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.034		0.043	
Sex	0.003		-0.012	
BMI	0.509	**	0.488	**
HSP-J10	0.128		0.162	†
Genus *Butyricimonas*	-0.039		-0.074	
HSP-J10 × Genus *Butyricimonas*			-0.185	†
R^2	0.290	**	0.322	**
ΔR^2			0.031	†

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$

LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Next, we conducted simple slope tests on the genus *Butyricimonas* in relation to LBP. Individuals with high environmental sensitivity exhibited no association with LBP when the abundance of *Butyricimonas* was high (*M*+1*SD*; $\beta = -0.004$, $p = 0.969$). In contrast, LBP levels were significantly elevated when the abundance of *Butyricimonas* was low (*M*-1*SD*; $\beta = 0.320$, $p = 0.022$) (Supplementary Figure 1).



Supplementary Figure 1. Moderating effects of the genus *Butyricimonas* on the relationship between environmental sensitivity and lipopolysaccharide-binding protein (LBP) ($n = 88$).

As an exploratory analysis, we examined interaction effects between environmental sensitivity and the specific taxa using hierarchical multiple regression analysis in a similar manner by adding frequencies of vegetable and fruit intakes as independent variables. Frequencies of vegetable and fruit intakes were assessed by using a food frequency questionnaire, respectively. As indicated in Supplementary Table 2 and 3, for CRP, similar results were observed for the family *Marinifilaceae* ($\Delta R^2 = 0.026$, $p = 0.071$) and genus *Butyricimonas* ($\Delta R^2 = 0.037$, $p < 0.05$), even when the frequencies of vegetable and fruit intakes were entered as independent variables. For LBP, similar results were observed for the family *Barnesiellaceae* ($\Delta R^2 = 0.030$, $p = 0.057$) (Supplementary Table 4), the family *Akkermansiace* ($\Delta R^2 = 0.029$, $p = 0.063$) (Supplementary Table 5), the genus *Coprobacter* ($\Delta R^2 = 0.030$, $p = 0.056$) (Supplementary Table 6), the genus *Akkermansia* ($\Delta R^2 = 0.029$, $p = 0.063$) (Supplementary Table 7), the genus *Family XIII AD3011 group* ($\Delta R^2 = 0.050$, $p < 0.05$) (Supplementary Table 8), the genus *GCA-900066225* ($\Delta R^2 = 0.044$, $p < 0.05$) (Supplementary Table 9) , and the genus *Ruminiclostridium 1* ($\Delta R^2 = 0.028$, $p = 0.066$) (Supplementary Table 10).

Supplementary Table 2. Interaction effects between environmental sensitivity and family *Marinifilaceae* predicting CRP ($n = 88$).

	Log-normalized CRP			
	Step1		Step2	
Predictors	β	p	β	p
Age	-0.148		-0.161	†
Sex	-0.125		-0.140	
BMI	0.557	**	0.550	**
Vegetable intake	0.130		0.116	
Fruit intake	-0.113		-0.080	
HSP-J10	0.196	*	0.187	*
Family *Marinifilaceae*	0.011		0.026	
HSP-J10 × Family *Marinifilaceae*			-0.166	†
R^2	0.361	**	0.387	**
ΔR^2			0.026	†

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. CRP: C-reactive protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Supplementary Table 3. Interaction effects between environmental sensitivity and genus *Butyricimonas* predicting CRP ($n = 88$).

	Log-normalized CRP			
	Step1		Step2	
Predictors	β	p	β	p
Age	-0.147		-0.137	
Sex	-0.129		-0.138	
BMI	0.556	**	0.530	**
Vegetable intake	0.132		0.107	
Fruit intake	-0.114		-0.099	
HSP-J10	0.197	*	0.230	*
Genus *Butyricimonas*	0.018		-0.022	
HSP-J10 × Genus *Butyricimonas*			-0.204	*
R^2	0.361	**	0.399	**
ΔR^2			0.037	*

Note. ** $p < 0.01$; * $p < 0.05$. CRP: C-reactive protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Supplementary Table 4. Interaction effects between environmental sensitivity and family *Barnesiellaceae* predicting LBP (n = 88).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.067		0.082	
Sex	-0.035		-0.038	
BMI	0.515	**	0.455	**
Vegetable intake	0.038		0.027	
Fruit intake	-0.204	*	-0.186	†
HSP-J10	0.166	†	0.146	
Family *Barnesiellaceae*	0.112		0.123	
HSP-J10 × Family *Barnesiellaceae*			-0.183	†
R^2	0.342	**	0.371	**
ΔR^2			0.030	†

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Supplementary Table 5. Interaction effects between environmental sensitivity and family *Akkermansiace* predicting LBP (n = 88).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.071		0.061	
Sex	-0.037		-0.042	
BMI	0.515	**	0.532	**
Vegetable intake	0.064		0.050	
Fruit intake	-0.218	*	-0.202	*
HSP-J10	0.166	†	0.141	
Family *Akkermansiace*	0.044		0.070	
HSP-J10 × Family *Akkermansiace*			-0.175	†
R^2	0.332	**	0.360	**
ΔR^2			0.029	†

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Supplementary Table 6. Interaction effects between environmental sensitivity and genus *Coprobacter* predicting LBP (n = 88).

	Log-normalized LBP			
	Step1		Step2	
Variables	β	p	β	p
Age	0.065		0.018	
Sex	-0.021		-0.030	
BMI	0.520	**	0.500	**
Vegetable intake	0.062		0.078	
Fruit intake	-0.214	*	-0.183	†

HSP-J10	0.165	†	0.188	†
Genus *Coprobacter*	0.006		-0.079	
HSP-J10 × Genus *Coprobacter*			-0.203	†
R^2	0.330	**	0.361	**
ΔR^2			0.030	†

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Supplementary Table 7. Interaction effects between environmental sensitivity and genus *Akkermansia* predicting LBP (n = 88).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.071		0.061	
Sex	-0.037		-0.042	
BMI	0.515	**	0.532	**
Vegetable intake	0.064		0.050	
Fruit intake	-0.218	*	-0.202	*
HSP-J10	0.166	†	0.141	
Genus *Akkermansia*	0.044		0.070	
HSP-J10 × Genus *Akkermansia*			-0.175	†
R^2	0.332	**	0.360	**
ΔR^2			0.029	†

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Supplementary Table 8. Interaction effects between environmental sensitivity and genus *Family XIII AD3011 group* predicting LBP (n = 88).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.071		0.012	
Sex	0.009		0.010	
BMI	0.503	**	0.566	**
Vegetable intake	0.045		0.056	
Fruit intake	-0.210	*	-0.202	*
HSP-J10	0.175	†	0.162	†
Genus *Family XIII AD3011 group*	-0.094		0.071	
HSP-J10 × Genus *Family XIII AD3011 group*			-0.276	*
R^2	0.337	**	0.387	**
ΔR^2			0.050	*

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Supplementary Table 9. Interaction effects between environmental sensitivity and genus *GCA-900066225* predicting LBP (n = 88).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.057		0.027	
Sex	-0.006		-0.033	
BMI	0.511	**	0.532	**
Vegetable intake	0.063		0.056	
Fruit intake	-0.215	*	-0.219	*
HSP-J10	0.180	†	0.122	
Genus *GCA-900066225*	-0.121		-0.049	
HSP-J10 × Genus *GCA-900066225*			-0.233	*
R^2	0.344	**	0.388	**
ΔR^2			0.044	*

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.

Supplementary Table 10. Interaction effects between environmental sensitivity and genus *Ruminiclostridium 1* predicting LBP (n = 88).

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.064		0.069	
Sex	-0.015		-0.038	
BMI	0.520	**	0.517	**
Vegetable intake	0.066		0.062	
Fruit intake	-0.221	*	-0.204	*
HSP-J10	0.163	†	0.145	
Genus *Ruminiclostridium 1*	-0.028		-0.101	
HSP-J10 × Genus *Ruminiclostridium 1*			-0.189	†
R^2	0.331	**	0.359	**
ΔR^2			0.028	†

Note. ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$. LBP: lipopolysaccharide-binding protein; BMI: body mass index; HSP-J10: environmental sensitivity.