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

Satoshi Takasugi[1]*, Shuhei Iimura[2], Miyabi Yasuda[3], Yoshie Saito[3], Masashi Morifuji[3]

*Corresponding author: Satoshi Takasugi
[1] Meiji Co., Ltd., R&D Division, 1-29-1 Nanakuni, Hachioji, Tokyo 192-0919, Japan
[2] Soka University; 1-236 Tangi-machi, Hachioji-shi, Tokyo 192-8577, Japan
[3] Meiji Holdings Co., Ltd., Wellness Science Labs, 1-29-1 Nanakuni, Hachioji, Tokyo 192-0919, Japan

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*) or the family *Akkermansiace* (genus *Akkermansia*) 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 analyzed using QIIME2 (https://qiime2.org/) to calculate the ratio of each family and genus, as well as the alpha diversity indices. For richness, observed operational taxonomic units (OTUs; observed species), and for biodiversity, Faith's phylogenetic diversity (PD) [33] were calculated as alpha diversity indices. 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].

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 level 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 only for those bacterial taxa that exhibited significant interactions at the family 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 at the family level, along with the correlations between alpha diversity indices and bacterial taxa at the family level

The relative abundance and prevalence of gut microbiome taxa at the family level are presented in Table 2, which excludes taxa with a prevalence of less than 5%. 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*, *MollicutesRF39 uncultured bcterium* and *Akkermansiaceae*.

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	*
MollicutesRF39 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, ** $p < 0.01$; * $p < 0.05$; † $p < 0.10$.

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 3). 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 3. 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 4). 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 5), family *Marinifilaceae* ($\Delta R^2 = 0.030$, $p = 0.062$) (Table 6), family *Defluviitaleaceae* ($\Delta R^2 = 0.027$, $p < 0.05$) (Table 7), and family *XIII* ($\Delta R^2 = 0.023$, $p = 0.099$) (Table 8). The p-values for the interaction between environmental sensitivity and the other bacterial taxa were > 0.1 in relation to LBP.

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

	Log-normalized LBP			
	Step1		Step2	
Predictors	β	p	β	p
Age	0.042		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 6. 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 7. 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 8. 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 exclusively for the gut microbiome taxa (genus) within the family where a significant interaction effect was observed (family *Marinifilaceae*). Among the two taxa, genus *Butyricimonas* and genus *Odoribacter*, the interaction term between environmental sensitivity and genus *Butyricimonas* emerged as a significant predictor for CRP ($\beta = -0.218$, $p < 0.05$) (Table 9). 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 genus *Odoribacter* did not show a significant association with CRP.

Table 9. 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*). Among the four taxa, genus *Barnesiella*, genus *Coprobacter*, genus *Barnesiellaceae_uncultured bacterium* and genus *Akkermansia*, the interaction between environmental sensitivity and genus *Coprobacter* was found to be a significant predictor for LBP ($\beta = -0.233$, $p < 0.05$) (Table 10). The coefficient of determination, R^2, increased from that in Step 1 when the interaction term between environmental sensitivity and genus *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 11) and genus *Akkermansia* ($\Delta R^2 = 0.035$, $p < 0.05$) (Table 12).

Table 10. 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 11. 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 12. 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.

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*, and genus *Akkermansia* (associated with LBP).

For individuals with high environmental sensitivity, there was no significant association with CRP when family *Marinifilaceae* abundance was high (M+1SD; β = -0.110, p = 0.496). However, CRP levels were significantly elevated when the abundance of family *Marinifilaceae* was low (M-1SD; β = 0.434, p = 0.008) (Figure 1A). Similar results were observed for other taxa. When genus *Butyricimonas* abundance was high (M+1SD; β = -0.020, p = 0.855), no significant association with CRP was found, but when its abundance was low (M-1SD; 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+1SD; β = -0.127, p = 0.419), but LBP levels were significantly elevated when the abundance of family *Barnesiellaceae* was low (M-1SD; 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).

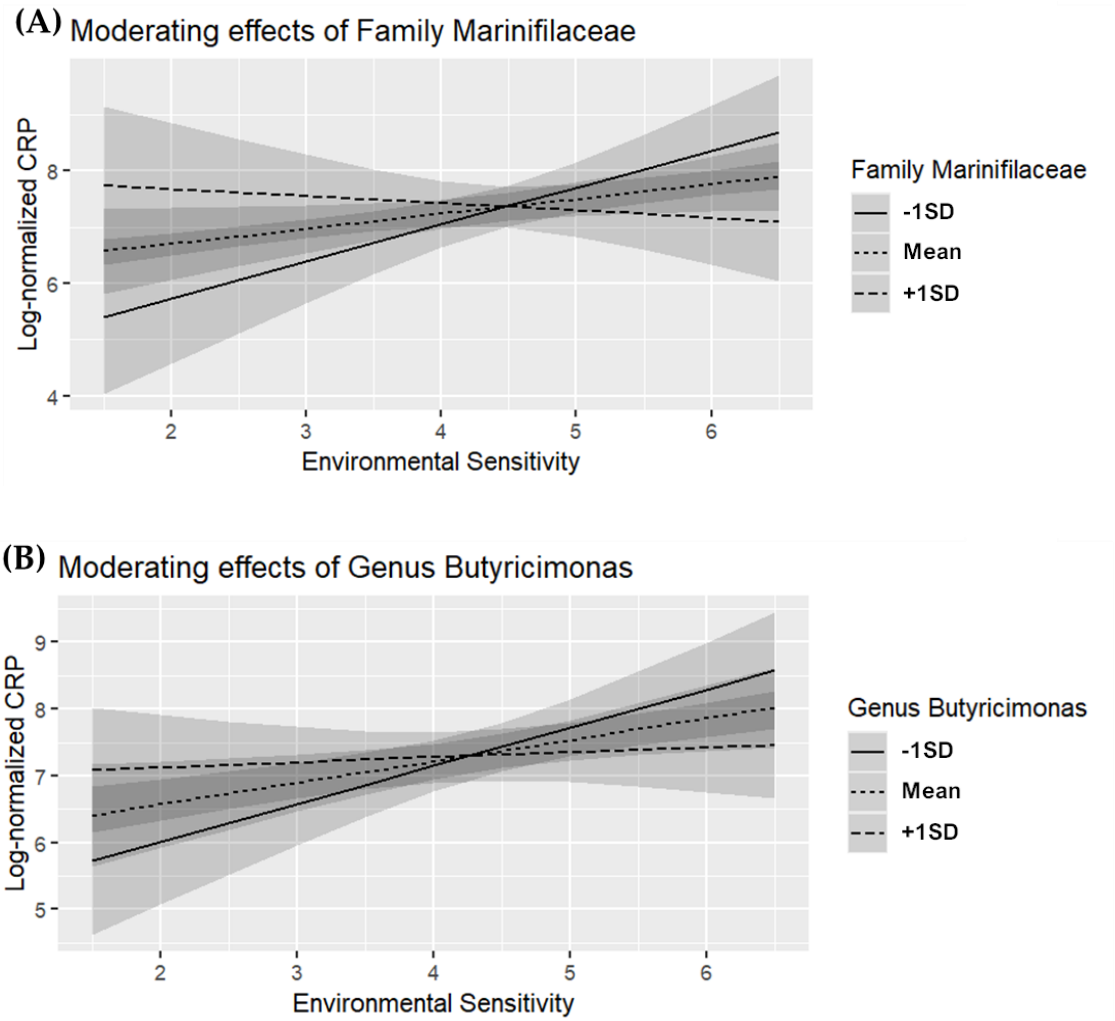
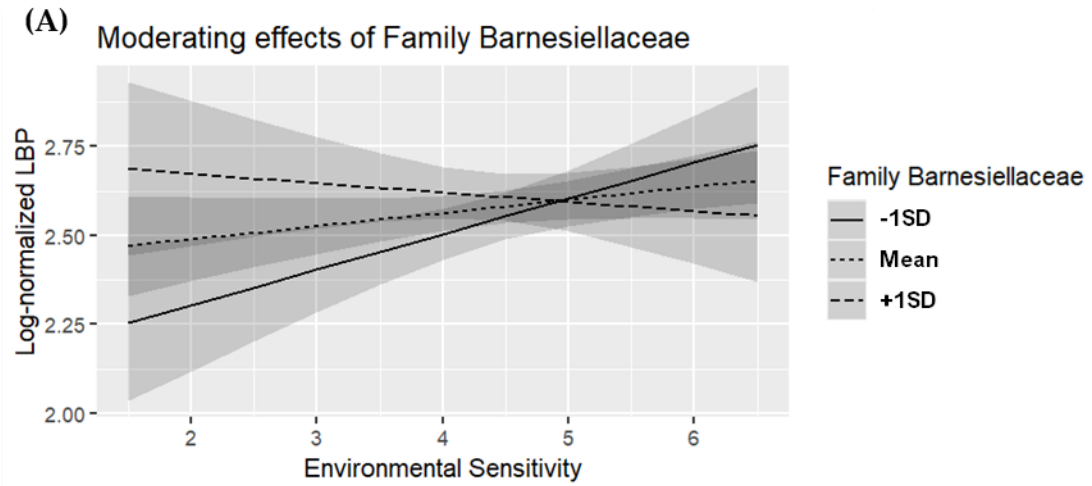
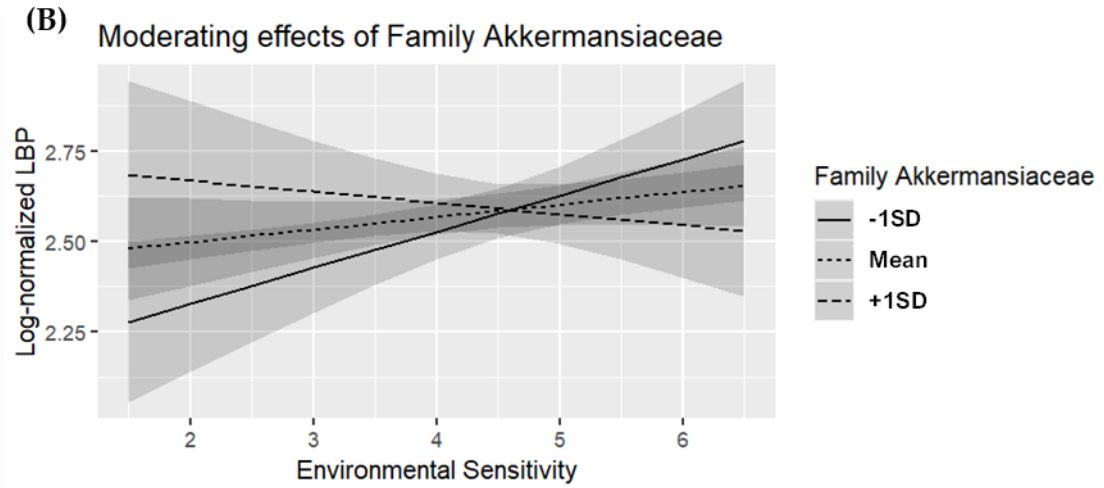
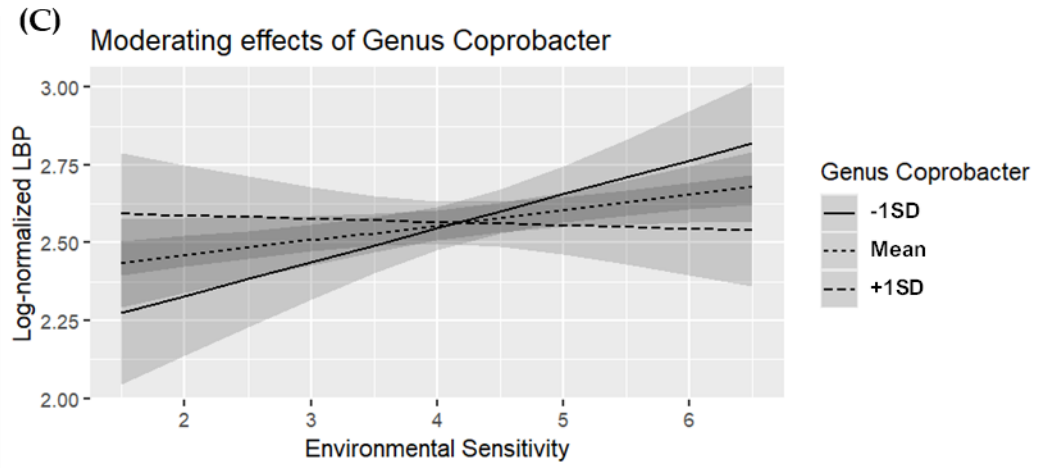


Figure 1. Moderating effects of gut microbiome taxa on the relationship between environmental sensitivity and C-reactive protein (CRP) (n = 88). (A) Family *Marinifilaceae*, (B) Genus *Butyricimonas*.


(A)
Moderating effects of Family Barnesiellaceae
Log-normalized LBP
2.75
2.50
2.25
2.00
2
3
4
5
6
Environmental Sensitivity
Family Barnesiellaceae
-1SD
Mean
+1SD


(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

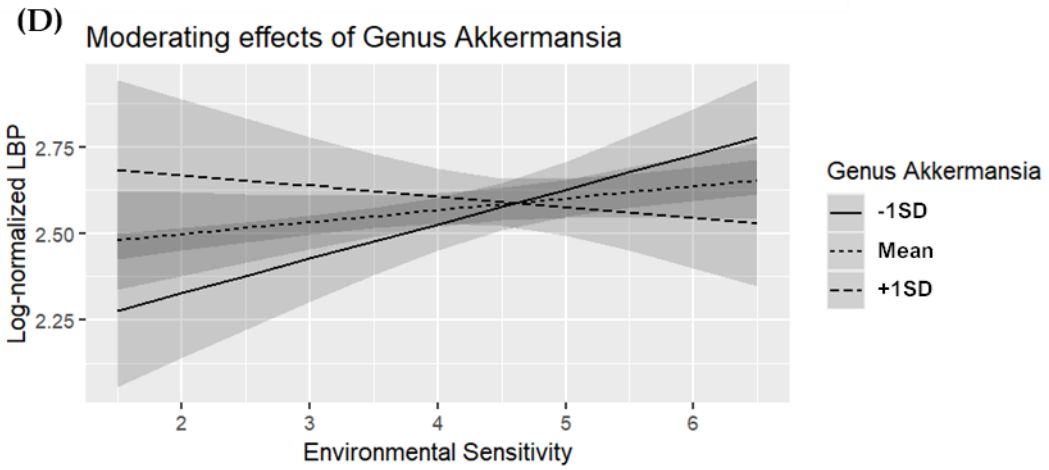


Figure 2. Moderating effects of gut microbiome taxa on the relationship between environmental sensitivity and lipopolysaccharide-binding protein (LBP) (n = 88). (A) Family *Barnesiellaceae*, (B) Family *Akkermansiace*, (C) Genus *Coprobacter*, (D) Genus *Akkermansia*.

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*), as well as the family *Akkermansiace* (genus *Akkermansia*), both 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. First, butyrate acts as a ligand for G-protein-coupled receptors on intestinal epithelial cells, leading to the regulation of inflammatory responses [61]. Second, it modulates the immune responses of intestinal macrophages by inhibiting histone deacetylase, resulting in the downregulation of pro-inflammatory mediators [62]. Third, butyrate help maintain the intestinal epithelial barrier, which leads to the reduction of inflammation [55,63]. Fourth, butyrate improves inflammation through the gut-brain axis [64]; it can cross the blood-brain barrier and activate the vagus nerve. Activation of the vagal efferent pathway improves the inflammation [64,65] as well as gut permeability [66]. Fifth, short-chain fatty acids (SCFAs) including butyrate can attenuate the HPA axis response [42], leading to the decrease in the gut permeability and inflammation. 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. Consequently, these taxa may contribute to gut integrity through these mechanisms in individuals with high environmental sensitivity.

Clinical implications

This study suggests that high environmental sensitivity can be a risk factor for inflammation and gut permeability when specific taxa of the gut microbiota are low. Elevated levels of CRP or LBP are linked to increased stress-related psychiatric symptoms, such as depression and anxiety [37-39], as well as physical symptoms, including IBS [23]. Therefore, enhancing the abundance of family *Marinifilaceae* (genus *Butyricimonas*), family *Barnesiellaceae* (genus *Coprobacter*), and family *Akkermansiace* (genus *Akkermansia*) through the use of prebiotics and/or probiotics may represent an effective strategy for treating and/or preventing various symptoms associated with inflammation and/or gut barrier dysfunction 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 [73] or evaluations of neurophysiological reactivity during stressful tasks [74], 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 [75-77], 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 [78], lower risk of IBD [79] and gut bacterial composition and diversity [80]. 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 2-7 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*), and family *Akkermansiace* (genus *Akkermansia*) 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.

Author Contributions: Conceptualization, S.T. and S.I.; Formal Analysis, S.T., S.I., M.Y. and Y.S.; Data Curation, S.T., S.I., M.Y. and Y.S.; Writing – Original Draft Preparation, S.T. and S.I.; Writing – Review & Editing, S.T, S.I. and M.M.; Visualization, S.I.; Supervision, S.T. and M.M.

Funding: This research received no external funding.

Conflicts of Interest: S. Takasugi is full-time employee of Meiji Co., Ltd. M. Yasuda, Y. Saito, and M. Morifuji are full-time employees of Meiji Holdings Co., Ltd. This study was conducted without external funding and was self-funded.

References

1. Pluess, M. Individual Differences in Environmental Sensitivity. *Child Development Perspectives* **2015**, *9*, 138-143, doi:https://doi.org/10.1111/cdep.12120.
2. Belsky, J.; Pluess, M. Beyond diathesis stress: differential susceptibility to environmental influences. *Psychol Bull* **2009**, *135*, 885-908, doi:10.1037/a0017376.
3. Boyce, W.T.; Ellis, B.J. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Dev Psychopathol* **2005**, *17*, 271-301, doi:10.1017/s0954579405050145.
4. Greven, C.U.; Lionetti, F.; Booth, C.; Aron, E.N.; Fox, E.; Schendan, H.E.; Pluess, M.; Bruining, H.; Acevedo, B.; Bijttebier, P., et al. Sensory Processing Sensitivity in the context of Environmental Sensitivity: A critical review and development of research agenda. *Neurosci Biobehav Rev* **2019**, *98*, 287-305, doi:10.1016/j.neubiorev.2019.01.009.
5. Iimura, S.; Takasugi, S. Sensory Processing Sensitivity and Gastrointestinal Symptoms in Japanese Adults. *Int J Environ Res Public Health* **2022**, *19*, doi:10.3390/ijerph19169893.
6. Baliatsas, C.; van Kamp, I.; Hooiveld, M.; Lebret, E.; Yzermans, J. The relationship of modern health worries to non-specific physical symptoms and perceived environmental sensitivity: A study combining self-reported and general practice data. *Journal of Psychosomatic Research* **2015**, *79*, 355-361, doi:https://doi.org/10.1016/j.jpsychores.2015.09.004.
7. Le, T.L.; Geist, R.; Hunter, J.; Maunder, R.G. Relationship between insecure attachment and physical symptom severity is mediated by sensory sensitivity. *Brain Behav* **2020**, *10*, e01717, doi:10.1002/brb3.1717.
8. Benham, G. The Highly Sensitive Person: Stress and physical symptom reports. *Personality and Individual*

Differences **2006**, *40*, 1433-1440, doi:https://doi.org/10.1016/j.paid.2005.11.021.

9. Takahashi, T.; Kawashima, I.; Nitta, Y.; Kumano, H. Dispositional Mindfulness Mediates the Relationship Between Sensory-Processing Sensitivity and Trait Anxiety, Well-Being, and Psychosomatic Symptoms. *Psychol Rep* **2020**, *123*, 1083-1098, doi:10.1177/0033294119841848.
10. Listou Grimen, H.; Diseth, Å. Sensory Processing Sensitivity: Factors of the Highly Sensitive Person Scale and Their relationships to Personality and Subjective Health Complaints. *Percept Mot Skills* **2016**, *123*, 637-653, doi:10.1177/0031512516666114.
11. Belsky, J.; Bakermans-Kranenburg, M.J.; van IJzendoorn, M.H. For Better and For Worse:Differential Susceptibility to Environmental Influences. *Current Directions in Psychological Science* **2007**, *16*, 300-304, doi:10.1111/j.1467-8721.2007.00525.x.
12. Belsky, J.; Jonassaint, C.; Pluess, M.; Stanton, M.; Brummett, B.; Williams, R. Vulnerability genes or plasticity genes? *Molecular Psychiatry* **2009**, *14*, 746-754, doi:10.1038/mp.2009.44.
13. Ellis, B.J.; Boyce, W.T.; Belsky, J.; Bakermans-Kranenburg, M.J.; van Ijzendoorn, M.H. Differential susceptibility to the environment: An evolutionary–neurodevelopmental theory. *Development and Psychopathology* **2011**, *23*, 7-28, doi:10.1017/S0954579410000611.
14. Song, I.U.; Chung, S.W.; Kim, Y.D.; Maeng, L.S. Relationship between the hs-CRP as non-specific biomarker and Alzheimer's disease according to aging process. *Int J Med Sci* **2015**, *12*, 613-617, doi:10.7150/ijms.12742.
15. Tegeler, C.; O'Sullivan, J.L.; Bucholtz, N.; Goldeck, D.; Pawelec, G.; Steinhagen-Thiessen, E.; Demuth, I. The inflammatory markers CRP, IL-6, and IL-10 are associated with cognitive function--data from the Berlin Aging Study II. *Neurobiol Aging* **2016**, *38*, 112-117, doi:10.1016/j.neurobiolaging.2015.10.039.
16. Baysak, E.; Guden, D.S.; Aricioglu, F.; Halaris, A. C-reactive protein as a potential biomarker in psychiatric practice: Are we there yet? *World J Biol Psychiatry* **2022**, *23*, 243-256, doi:10.1080/15622975.2021.1961502.
17. Cesari, M.; Penninx, B.W.; Newman, A.B.; Kritchevsky, S.B.; Nicklas, B.J.; Sutton-Tyrrell, K.; Tracy, R.P.; Rubin, S.M.; Harris, T.B.; Pahor, M. Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition [Health ABC] Study). *Am J Cardiol* **2003**, *92*, 522-528, doi:10.1016/s0002-9149(03)00718-5.
18. Danesh, J.; Whincup, P.; Walker, M.; Lennon, L.; Thomson, A.; Appleby, P.; Gallimore, J.R.; Pepys, M.B. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *Bmj* **2000**, *321*, 199-204, doi:10.1136/bmj.321.7255.199.
19. Makita, S.; Nakamura, M.; Hiramori, K. The association of C-reactive protein levels with carotid intima-media complex thickness and plaque formation in the general population. *Stroke* **2005**, *36*, 2138-2142, doi:10.1161/01.STR.0000181740.74005.ee.
20. Ridker, P.M. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* **2001**, *103*, 1813-1818, doi:10.1161/01.cir.103.13.1813.
21. Ridker, P.M. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation* **2003**, *107*, 363-369, doi:10.1161/01.cir.0000053730.47739.3c.
22. Tracy, R.P.; Lemaitre, R.N.; Psaty, B.M.; Ives, D.G.; Evans, R.W.; Cushman, M.; Meilahn, E.N.; Kuller, L.H. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol* **1997**, *17*, 1121-1127, doi:10.1161/01.atv.17.6.1121.
23. Hod, K.; Dickman, R.; Sperber, A.; Melamed, S.; Dekel, R.; Ron, Y.; Halpern, Z.; Berliner, S.; Maharshak, N. Assessment of high-sensitivity CRP as a marker of micro-inflammation in irritable bowel syndrome. *Neurogastroenterol Motil* **2011**, *23*, 1105-1110, doi:10.1111/j.1365-2982.2011.01788.x.
24. Iimura, S.; Takasugi, S.; Yasuda, M.; Saito, Y.; Morifuji, M. Interactions between environmental sensitivity and gut microbiota are associated with biomarkers of stress-related psychiatric symptoms. *J Affect Disord* **2023**, *339*,

136-144, doi:10.1016/j.jad.2023.07.016.
25. Iimura, S.; Yano, K.; Ishii, Y. Environmental Sensitivity in Adults: Psychometric Properties of the Japanese Version of the Highly Sensitive Person Scale 10-Item Version. *J Pers Assess* **2023**, *105*, 87-99, doi:10.1080/00223891.2022.2047988.
26. Iimura, S. Highly sensitive adolescents: The relationship between weekly life events and weekly socioemotional well-being. *Br J Psychol* **2021**, *112*, 1103-1129, doi:10.1111/bjop.12505.
27. Costa, P.T., Jr.; McCrae, R.R. Personality in adulthood: a six-year longitudinal study of self-reports and spouse ratings on the NEO Personality Inventory. *J Pers Soc Psychol* **1988**, *54*, 853-863, doi:10.1037//0022-3514.54.5.853.
28. Canipe, A.; Chidumayo, T.; Blevins, M.; Bestawros, M.; Bala, J.; Kelly, P.; Filteau, S.; Shepherd, B.E.; Heimburger, D.C.; Koethe, J.R. A 12 week longitudinal study of microbial translocation and systemic inflammation in undernourished HIV-infected Zambians initiating antiretroviral therapy. *BMC Infectious Diseases* **2014**, *14*, 521, doi:10.1186/1471-2334-14-521.
29. Stehle, J.R., Jr; Leng, X.; Kitzman, D.W.; Nicklas, B.J.; Kritchevsky, S.B.; High, K.P. Lipopolysaccharide-Binding Protein, a Surrogate Marker of Microbial Translocation, Is Associated With Physical Function in Healthy Older Adults. *The Journals of Gerontology: Series A* **2012**, *67*, 1212-1218, doi:10.1093/gerona/gls178.
30. Gonzalez-Quintela, A.; Alonso, M.; Campos, J.; Vizcaino, L.; Loidi, L.; Gude, F. Determinants of Serum Concentrations of Lipopolysaccharide-Binding Protein (LBP) in the Adult Population: The Role of Obesity. *PLOS ONE* **2013**, *8*, e54600, doi:10.1371/journal.pone.0054600.
31. Taylor, S.E.; Lehman, B.J.; Kiefe, C.I.; Seeman, T.E. Relationship of Early Life Stress and Psychological Functioning to Adult C-Reactive Protein in the Coronary Artery Risk Development in Young Adults Study. *Biological Psychiatry* **2006**, *60*, 819-824, doi:10.1016/j.biopsych.2006.03.016.
32. Costea, P.I.; Zeller, G.; Sunagawa, S.; Pelletier, E.; Alberti, A.; Levenez, F.; Tramontano, M.; Driessen, M.; Hercog, R.; Jung, F.-E., et al. Towards standards for human fecal sample processing in metagenomic studies. *Nature Biotechnology* **2017**, *35*, 1069-1076, doi:10.1038/nbt.3960.
33. Faith, D.P. Conservation evaluation and phylogenetic diversity. *Biological Conservation* **1992**, *61*, 1-10, doi:https://doi.org/10.1016/0006-3207(92)91201-3.
34. RCoreTeam *R: A Language and Environment for Statistical Computing.*, R Foundation for Statistical Computing: Vienna, Austria, 2022.
35. RStudioTeam *RStudio: Integrated Development for R.*, Boston, MA., 2020.
36. Aiken, L.S.; West, S.G. *Multiple regression: Testing and interpreting interactions*; Sage Publications, Inc: Thousand Oaks, CA, US, 1991; pp. xi, 212-xi, 212.
37. Copeland, W.E.; Shanahan, L.; Worthman, C.; Angold, A.; Costello, E.J. Generalized anxiety and C-reactive protein levels: a prospective, longitudinal analysis. *Psychological Medicine* **2012**, *42*, 2641-2650, doi:10.1017/S0033291712000554.
38. Gimeno, D.; Kivimäki, M.; Brunner, E.J.; Elovainio, M.; De Vogli, R.; Steptoe, A.; Kumari, M.; Lowe, G.D.O.; Rumley, A.; Marmot, M.G., et al. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychological Medicine* **2009**, *39*, 413-423, doi:10.1017/S0033291708003723.
39. Iordache, M.M.; Tocia, C.; Aschie, M.; Dumitru, A.; Manea, M.; Cozaru, G.C.; Petcu, L.; Vlad, S.E.; Dumitru, E.; Chisoi, A. Intestinal Permeability and Depression in Patients with Inflammatory Bowel Disease. *Journal of Clinical Medicine* **2022**, *11*, 5121.
40. Alexander, N.; Wankerl, M.; Hennig, J.; Miller, R.; Zänkert, S.; Steudte-Schmiedgen, S.; Stalder, T.; Kirschbaum, C. DNA methylation profiles within the serotonin transporter gene moderate the association of 5-HTTLPR and cortisol stress reactivity. *Translational Psychiatry* **2014**, *4*, e443-e443, doi:10.1038/tp.2014.88.

41. Miller, R.; Wankerl, M.; Stalder, T.; Kirschbaum, C.; Alexander, N. The serotonin transporter gene-linked polymorphic region (5-HTTLPR) and cortisol stress reactivity: a meta-analysis. *Molecular Psychiatry* **2013**, *18*, 1018-1024, doi:10.1038/mp.2012.124.
42. Misiak, B.; Łoniewski, I.; Marlicz, W.; Frydecka, D.; Szulc, A.; Rudzki, L.; Samochowiec, J. The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota? *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **2020**, *102*, 109951, doi:https://doi.org/10.1016/j.pnpbp.2020.109951.
43. Vicario, M.; Alonso, C.; Guilarte, M.; Serra, J.; Martínez, C.; González-Castro, A.M.; Lobo, B.; Antolín, M.; Andreu, A.L.; García-Arumí, E., et al. Chronic psychosocial stress induces reversible mitochondrial damage and corticotropin-releasing factor receptor type-1 upregulation in the rat intestine and IBS-like gut dysfunction. *Psychoneuroendocrinology* **2012**, *37*, 65-77, doi:https://doi.org/10.1016/j.psyneuen.2011.05.005.
44. Vanuytsel, T.; van Wanrooy, S.; Vanheel, H.; Vanormelingen, C.; Verschueren, S.; Houben, E.; Salim Rasoel, S.; Tóth, J.; Holvoet, L.; Farré, R., et al. Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. *Gut* **2014**, *63*, 1293-1299, doi:10.1136/gutjnl-2013-305690.
45. Mukherji, A.; Kobiita, A.; Ye, T.; Chambon, P. Homeostasis in Intestinal Epithelium Is Orchestrated by the Circadian Clock and Microbiota Cues Transduced by TLRs. *Cell* **2013**, *153*, 812-827, doi:https://doi.org/10.1016/j.cell.2013.04.020.
46. Desbonnet, L.; Garrett, L.; Clarke, G.; Kiely, B.; Cryan, J.F.; Dinan, T.G. Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. *Neuroscience* **2010**, *170*, 1179-1188, doi:https://doi.org/10.1016/j.neuroscience.2010.08.005.
47. Eutamene, H.; Lamine, F.; Chabo, C.; Theodorou, V.; Rochat, F.; Bergonzelli, G.E.; Corthésy-Theulaz, I.; Fioramonti, J.; Bueno, L. Synergy between Lactobacillus paracasei and Its Bacterial Products to Counteract Stress-Induced Gut Permeability and Sensitivity Increase in Rats1,2. *The Journal of Nutrition* **2007**, *137*, 1901-1907, doi:https://doi.org/10.1093/jn/137.8.1901.
48. Gareau, M.G.; Jury, J.; MacQueen, G.; Sherman, P.M.; Perdue, M.H. Probiotic treatment of rat pups normalises corticosterone release and ameliorates colonic dysfunction induced by maternal separation. *Gut* **2007**, *56*, 1522, doi:10.1136/gut.2006.117176.
49. Clarke, G.; Stilling, R.M.; Kennedy, P.J.; Stanton, C.; Cryan, J.F.; Dinan, T.G. Minireview: Gut Microbiota: The Neglected Endocrine Organ. *Molecular Endocrinology* **2014**, *28*, 1221-1238, doi:10.1210/me.2014-1108.
50. Crumeyrolle-Arias, M.; Jaglin, M.; Bruneau, A.; Vancassel, S.; Cardona, A.; Daugé, V.; Naudon, L.; Rabot, S. Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats. *Psychoneuroendocrinology* **2014**, *42*, 207-217, doi:https://doi.org/10.1016/j.psyneuen.2014.01.014.
51. Sudo, N. Role of microbiome in regulating the HPA axis and its relevance to allergy. *Chem Immunol Allergy* **2012**, *98*, 163-175, doi:10.1159/000336510.
52. Schmidt, K.; Cowen, P.J.; Harmer, C.J.; Tzortzis, G.; Errington, S.; Burnet, P.W.J. Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. *Psychopharmacology* **2015**, *232*, 1793-1801, doi:10.1007/s00213-014-3810-0.
53. Zijlmans, M.A.C.; Korpela, K.; Riksen-Walraven, J.M.; de Vos, W.M.; de Weerth, C. Maternal prenatal stress is associated with the infant intestinal microbiota. *Psychoneuroendocrinology* **2015**, *53*, 233-245, doi:https://doi.org/10.1016/j.psyneuen.2015.01.006.
54. Di Vincenzo, F.; Del Gaudio, A.; Petito, V.; Lopetuso, L.R.; Scaldaferri, F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. *Internal and Emergency Medicine* **2024**, *19*, 275-293, doi:10.1007/s11739-023-03374-w.
55. de Punder, K.; Pruimboom, L. Stress Induces Endotoxemia and Low-Grade Inflammation by Increasing Barrier

Permeability. *Frontiers in Immunology* **2015**, *6*, doi:10.3389/fimmu.2015.00223.
56. Sakamoto, M.; Takagaki, A.; Matsumoto, K.; Kato, Y.; Goto, K.; Benno, Y. Butyricimonas synergistica gen. nov., sp. nov. and Butyricimonas virosa sp. nov., butyric acid-producing bacteria in the family 'Porphyromonadaceae' isolated from rat faeces. *Int J Syst Evol Microbiol* **2009**, *59*, 1748-1753, doi:10.1099/ijs.0.007674-0.
57. Resende, W.R.; Valvassori, S.S.; Réus, G.Z.; Varela, R.B.; Arent, C.O.; Ribeiro, K.F.; Bavaresco, D.V.; Andersen, M.L.; Zugno, A.I.; Quevedo, J. Effects of sodium butyrate in animal models of mania and depression: implications as a new mood stabilizer. *Behav Pharmacol* **2013**, *24*, 569-579, doi:10.1097/FBP.0b013e32836546fc.
58. Valvassori, S.S.; Resende, W.R.; Budni, J.; Dal-Pont, G.C.; Bavaresco, D.V.; Réus, G.Z.; Carvalho, A.F.; Gonçalves, C.L.; Furlanetto, C.B.; Streck, E.L., et al. Sodium Butyrate, a Histone Deacetylase Inhibitor, Reverses Behavioral and Mitochondrial Alterations in Animal Models of Depression Induced by Early- or Late-life Stress. *Curr Neurovasc Res* **2015**, *12*, 312-320, doi:10.2174/1567202612666150728121121.
59. Soret, R.; Chevalier, J.; De Coppet, P.; Poupeau, G.; Derkinderen, P.; Segain, J.P.; Neunlist, M. Short-Chain Fatty Acids Regulate the Enteric Neurons and Control Gastrointestinal Motility in Rats. *Gastroenterology* **2010**, *138*, 1772-1782.e1774, doi:10.1053/j.gastro.2010.01.053.
60. Mowat, A.M.; Agace, W.W. Regional specialization within the intestinal immune system. *Nat Rev Immunol* **2014**, *14*, 667-685, doi:10.1038/nri3738.
61. Kim, M.H.; Kang, S.G.; Park, J.H.; Yanagisawa, M.; Kim, C.H. Short-chain fatty acids activate GPR41 and GPR43 on intestinal epithelial cells to promote inflammatory responses in mice. *Gastroenterology* **2013**, *145*, 396-406.e391-310, doi:10.1053/j.gastro.2013.04.056.
62. Chang, P.V.; Hao, L.; Offermanns, S.; Medzhitov, R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *Proc Natl Acad Sci U S A* **2014**, *111*, 2247-2252, doi:10.1073/pnas.1322269111.
63. Chen, T.; Kim, C.Y.; Kaur, A.; Lamothe, L.; Shaikh, M.; Keshavarzian, A.; Hamaker, B.R. Dietary fibre-based SCFA mixtures promote both protection and repair of intestinal epithelial barrier function in a Caco-2 cell model. *Food Funct* **2017**, *8*, 1166-1173, doi:10.1039/c6fo01532h.
64. Okumura, T.; Nozu, T.; Ishioh, M.; Igarashi, S.; Kumei, S.; Ohhira, M. Centrally administered butyrate improves gut barrier function, visceral sensation and septic lethality in rats. *J Pharmacol Sci* **2021**, *146*, 183-191, doi:10.1016/j.jphs.2021.04.005.
65. Borovikova, L.V.; Ivanova, S.; Zhang, M.; Yang, H.; Botchkina, G.I.; Watkins, L.R.; Wang, H.; Abumrad, N.; Eaton, J.W.; Tracey, K.J. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* **2000**, *405*, 458-462, doi:10.1038/35013070.
66. Ishioh, M.; Nozu, T.; Igarashi, S.; Tanabe, H.; Kumei, S.; Ohhira, M.; Okumura, T. Ghrelin acts in the brain to block colonic hyperpermeability in response to lipopolysaccharide through the vagus nerve. *Neuropharmacology* **2020**, *173*, 108116, doi:10.1016/j.neuropharm.2020.108116.
67. Di Vincenzo, F.; Del Gaudio, A.; Petito, V.; Lopetuso, L.R.; Scaldaferri, F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. *Intern Emerg Med* **2024**, *19*, 275-293, doi:10.1007/s11739-023-03374-w.
68. Zhu, M.; Song, Y.; Xu, Y.; Xu, H. Manipulating Microbiota in Inflammatory Bowel Disease Treatment: Clinical and Natural Product Interventions Explored. *Int J Mol Sci* **2023**, *24*, doi:10.3390/ijms241311004.
69. Okuma, K.; Hatayama, K.; Tokuno, H.; Ebara, A.; Odachi, A.; Masuyama, H.; Hoshiko, N.; Tanaka, N. A risk estimation method for depression based on the dysbiosis of intestinal microbiota in Japanese patients. *Front Psychiatry* **2024**, *15*, 1382175, doi:10.3389/fpsyt.2024.1382175.
70. Shkoporov, A.N.; Khokhlova, E.V.; Chaplin, A.V.; Kafarskaia, L.I.; Nikolin, A.A.; Polyakov, V.Y.; Shcherbakova,

V.A.; Chernaia, Z.A.; Efimov, B.A. Coprobacter fastidiosus gen. nov., sp. nov., a novel member of the family Porphyromonadaceae isolated from infant faeces. *Int J Syst Evol Microbiol* **2013**, *63*, 4181-4188, doi:10.1099/ijs.0.052126-0.

71. Yang, R.; Hu, X.; Xie, X.; Chen, H.; Fang, H.; Zhu, L.; Li, Z. Propionic Acid Targets the TLR4/NF-κB Signaling Pathway and Inhibits LPS-Induced Intestinal Barrier Dysfunction: In Vitro and In Vivo Studies. *Front Pharmacol* **2020**, *11*, 573475, doi:10.3389/fphar.2020.573475.
72. Deleu, S.; Arnauts, K.; Deprez, L.; Machiels, K.; Ferrante, M.; Huys, G.R.B.; Thevelein, J.M.; Raes, J.; Vermeire, S. High Acetate Concentration Protects Intestinal Barrier and Exerts Anti-Inflammatory Effects in Organoid-Derived Epithelial Monolayer Cultures from Patients with Ulcerative Colitis. *Int J Mol Sci* **2023**, *24*, doi:10.3390/ijms24010768.
73. Keers, R.; Coleman, J.R.I.; Lester, K.J.; Roberts, S.; Breen, G.; Thastum, M.; Bögels, S.; Schneider, S.; Heiervang, E.; Meiser-Stedman, R., et al. A Genome-Wide Test of the Differential Susceptibility Hypothesis Reveals a Genetic Predictor of Differential Response to Psychological Treatments for Child Anxiety Disorders. *Psychotherapy and Psychosomatics* **2016**, *85*, 146-158, doi:10.1159/000444023.
74. Weyn, S.; Van Leeuwen, K.; Pluess, M.; Goossens, L.; Claes, S.; Bosmans, G.; Van Den Noortgate, W.; Lutin, E.; Bröhl, A.S.; Chubar, V., et al. Individual differences in environmental sensitivity at physiological and phenotypic level: Two sides of the same coin? *International Journal of Psychophysiology* **2022**, *176*, 36-53, doi:https://doi.org/10.1016/j.ijpsycho.2022.02.010.
75. Saji, N.; Niida, S.; Murotani, K.; Hisada, T.; Tsuduki, T.; Sugimoto, T.; Kimura, A.; Toba, K.; Sakurai, T. Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in Japan. *Scientific Reports* **2019**, *9*, 1008, doi:10.1038/s41598-018-38218-7.
76. Vu Thi Ngoc, B.; Ho Bich, H.; Galazzo, G.; Vu Tien Viet, D.; Oomen, M.; Nghiem Nguyen Minh, T.; Tran Huy, H.; van Doorn, H.R.; Wertheim, H.F.L.; Penders, J. Cross-Sectional Analysis of the Microbiota of Human Gut and Its Direct Environment in a Household Cohort with High Background of Antibiotic Use. *Microorganisms* **2021**, *9*, doi:10.3390/microorganisms9102115.
77. Kashtanova, D.A.; Klimenko, N.S.; Strazhesko, I.D.; Starikova, E.V.; Glushchenko, O.E.; Gudkov, D.A.; Tkacheva, O.N. A Cross-Sectional Study of the Gut Microbiota Composition in Moscow Long-Livers. *Microorganisms* **2020**, *8*, 1162.
78. Esmaillzadeh, A.; Kimiagar, M.; Mehrabi, Y.; Azadbakht, L.; Hu, F.B.; Willett, W.C. Fruit and vegetable intakes, C-reactive protein, and the metabolic syndrome. *Am J Clin Nutr* **2006**, *84*, 1489-1497, doi:10.1093/ajcn/84.6.1489.
79. Milajerdi, A.; Ebrahimi-Daryani, N.; Dieleman, L.A.; Larijani, B.; Esmaillzadeh, A. Association of Dietary Fiber, Fruit, and Vegetable Consumption with Risk of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Advances in Nutrition* **2021**, *12*, 735-743, doi:https://doi.org/10.1093/advances/nmaa145.
80. Frankenfeld, C.L.; Hullar, M.A.J.; Maskarinec, G.; Monroe, K.R.; Shepherd, J.A.; Franke, A.A.; Randolph, T.W.; Wilkens, L.R.; Boushey, C.J.; Le Marchand, L., et al. The Gut Microbiome Is Associated with Circulating Dietary Biomarkers of Fruit and Vegetable Intake in a Multiethnic Cohort. *J Acad Nutr Diet* **2022**, *122*, 78-98, doi:10.1016/j.jand.2021.05.023.

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* (ΔR^2 = 0.031, p = 0.056), as well as for the genus *Coprobacter*, genus *Barnesiella*, and genus *Akkermansia.*

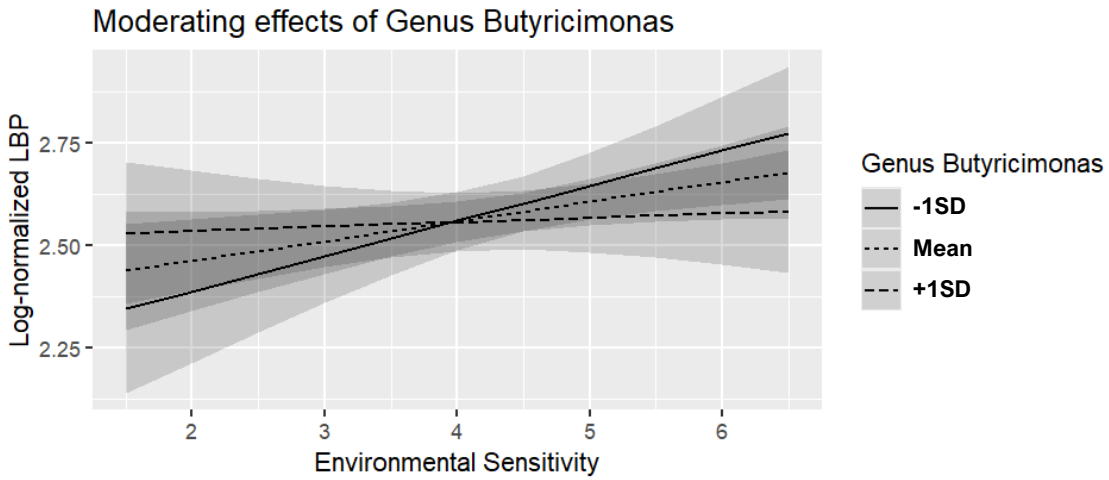
Supplementary Table 1. Interaction effects between environmental sensitivity and the genus *Butyricimonas* predicting LBP (n = 88).

	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+1SD; β = -0.004, p = 0.969). In contrast, LBP levels were significantly elevated when the abundance of *Butyricimonas* was low (M-1SD; β = 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* (ΔR^2 = 0.026, p = 0.071) and genus *Butyricimonas* (ΔR^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* (ΔR^2 = 0.030, p = 0.057) (Supplementary Table 4), the family *Akkermansiace* (ΔR^2 = 0.029, p = 0.063) (Supplementary Table 5), the genus *Coprobacter* (ΔR^2 = 0.030, p = 0.056) (Supplementary Table 6), and the genus *Akkermansia* (ΔR^2 = 0.029, p = 0.063) (Supplementary Table 7).

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.