

**Supplementary Table 1.** The Descriptions of 13 Cytokines Investigated in This Study

Cytokine	Description
IFN- $\gamma$	A cytokine associated innate and adopted immune response. IFN- $\gamma$ activates antigen presenting cells such as macrophage and promotes Th1 cell differentiation.
MIP-1 $\alpha$	A chemokine produced by macrophage. MIP-1 $\alpha$ activates granulocytes and promotes pro-inflammatory cytokine production.
Eotaxin	One of a major chemokine that induces recruitment of eosinophils and is involved allergic responses.
IL-1 $\beta$	A pro-inflammatory cytokine mainly produced by macrophages. IL-1 $\beta$ promotes activation of inflammatory cells and production of acute-phase proteins.
IL-4	A Th2 cytokine that induces differentiation and proliferation of Th2 cells. IL-4 promotes antibody production and class switching.
IL-5	A Th2 cytokine associated with allergic diseases. IL-5 is involved in differentiation, proliferation and activation of eosinophils.
IL-6	A pro-inflammatory cytokine detected acute and chronic inflammatory states. IL-6 induces differentiation and proliferation of Th17 cells.
IL-8	A chemokine that induces chemotaxis mainly in neutrophils. IL-8 is one of the major mediators of inflammation.
IL-10	An anti-inflammatory cytokine to suppress differentiation of Th1 cell, activation of macrophages and promote pro-inflammatory cytokines.
IL-12p70	A cytokine that induces differentiation of Th1 cells and stimulates secretion of Th1 cytokines such as IFN- $\gamma$ .
IL-13	One of a Th2 cytokine that promotes proliferation of B cells and IgE production. IL-13 regulates goblet cells functions in lung and gut.
IL-17	A cytokine secreted Th17 cells. It promotes inflammatory response through enhancing production of pro-inflammatory cytokines and chemokines.
TNF- $\alpha$	TNF- $\alpha$ is one of the major pro-inflammatory cytokine involved local and systemic inflammation. TNF- $\alpha$ is mainly produced by macrophages and induces fever, activation of macrophages, neutrophils, T cells and endothelial cells.

Th, T helper cells; MIP-1 $\alpha$ , macrophage inflammatory protein-1 alpha.

**Supplementary Table 2.** Gastrointestinal Symptom Rating Scale Scores Obtained by Bootstrapping in Patients With Irritable Bowel Syndrome With Diarrhea

(mean [95% CI])	IgE-mediated serological food hypersensitivity		P-value
	Negative (n = 40)	Positive (n = 20)	
Reflux	1.78 (1.5-2.1)	2.06 (1.6-2.5)	0.303
Abdominal pain	2.43 (2.0-2.8)	2.34 (1.9-2.8)	0.787
Indigestion	2.31 (2.0-2.6)	2.21 (1.9-2.4)	0.669
Diarrhea	4.28 (3.8-4.7)	4.35 (3.8-4.8)	0.866
Constipation	2.31 (2.1-2.6)	2.12 (1.8-2.5)	0.431

The subject who has at least one food allergen with class 2 or above was considered as being positive for IgE-mediated serological food hypersensitivity. Mean, 95% confidence intervals and P-value were obtained by Bootstrapping and student t test.

**Supplementary Table 3.** Correlations Provided as *r* Value Between Serum Cytokine Levels and Gastrointestinal Symptom Scores in Patients With Irritable Bowel Syndrome With Diarrhea

Serum cytokine	Reflux	Abdominal pain	Indigestion	Diarrhea	Constipation
IL-1 $\beta$	-0.035	0.115	-0.022	0.211	-0.198
MIP-1 $\alpha$	-0.025	-0.013	-0.066	0.090	-0.096
IL-6	-0.068	0.054	-0.154	0.154	-0.011
IL-8	0.054	0.173	-0.101	0.095	-0.136
TNF- $\alpha$	-0.132	-0.041	-0.055	0.023	-0.116

MIP-1 $\alpha$ , macrophage inflammatory protein-1alpha.

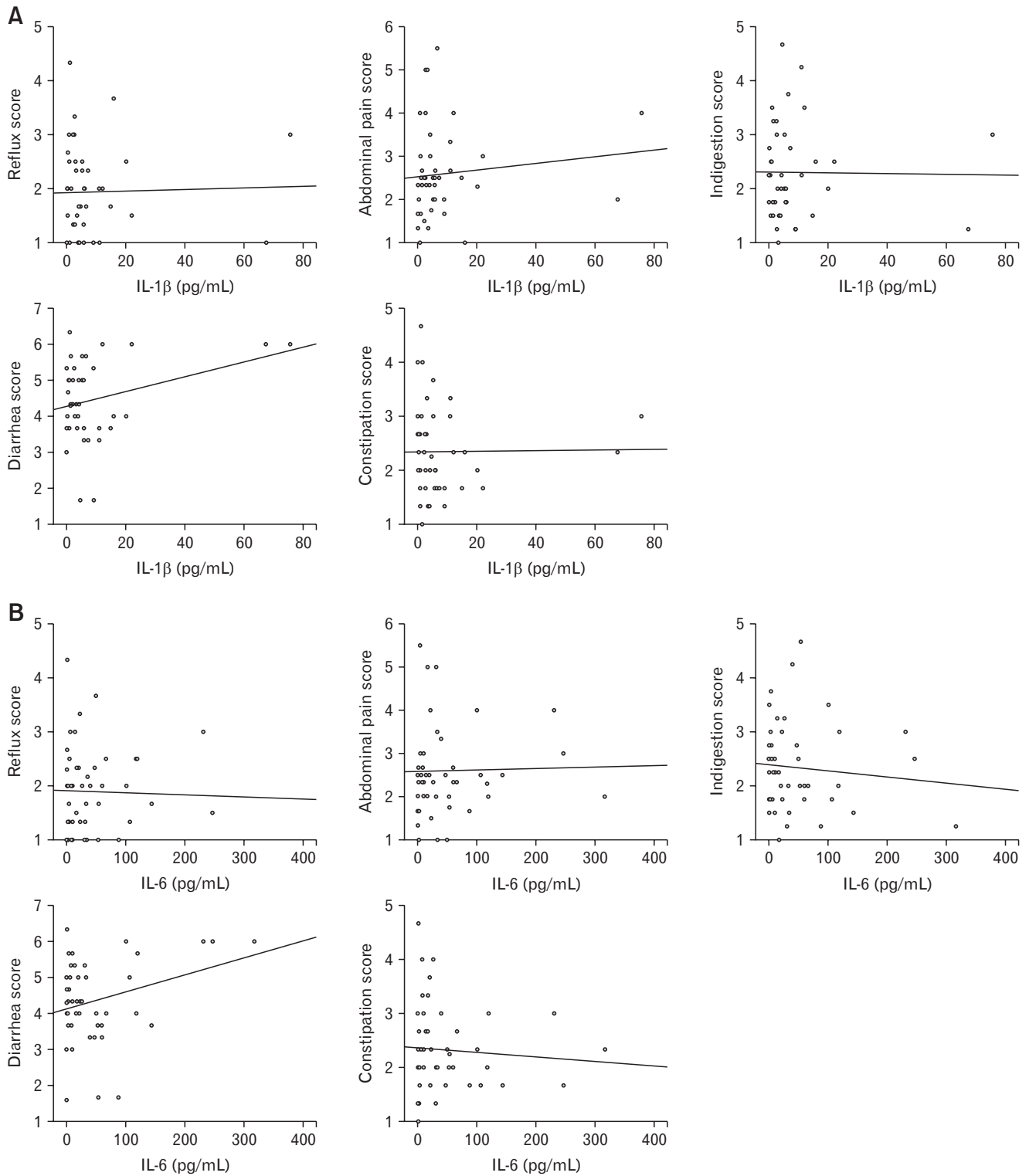
*P*-value and *r* value was calculated by the Spearman test. *P* < 0.05.

**Supplementary Table 4.** Comparison of Serum Cytokine Profile Obtained by Bootstrapping Between IgE-mediated Serological Food Hypersensitivity Negative and Positive in Patients With Irritable Bowel Syndrome With Diarrhea

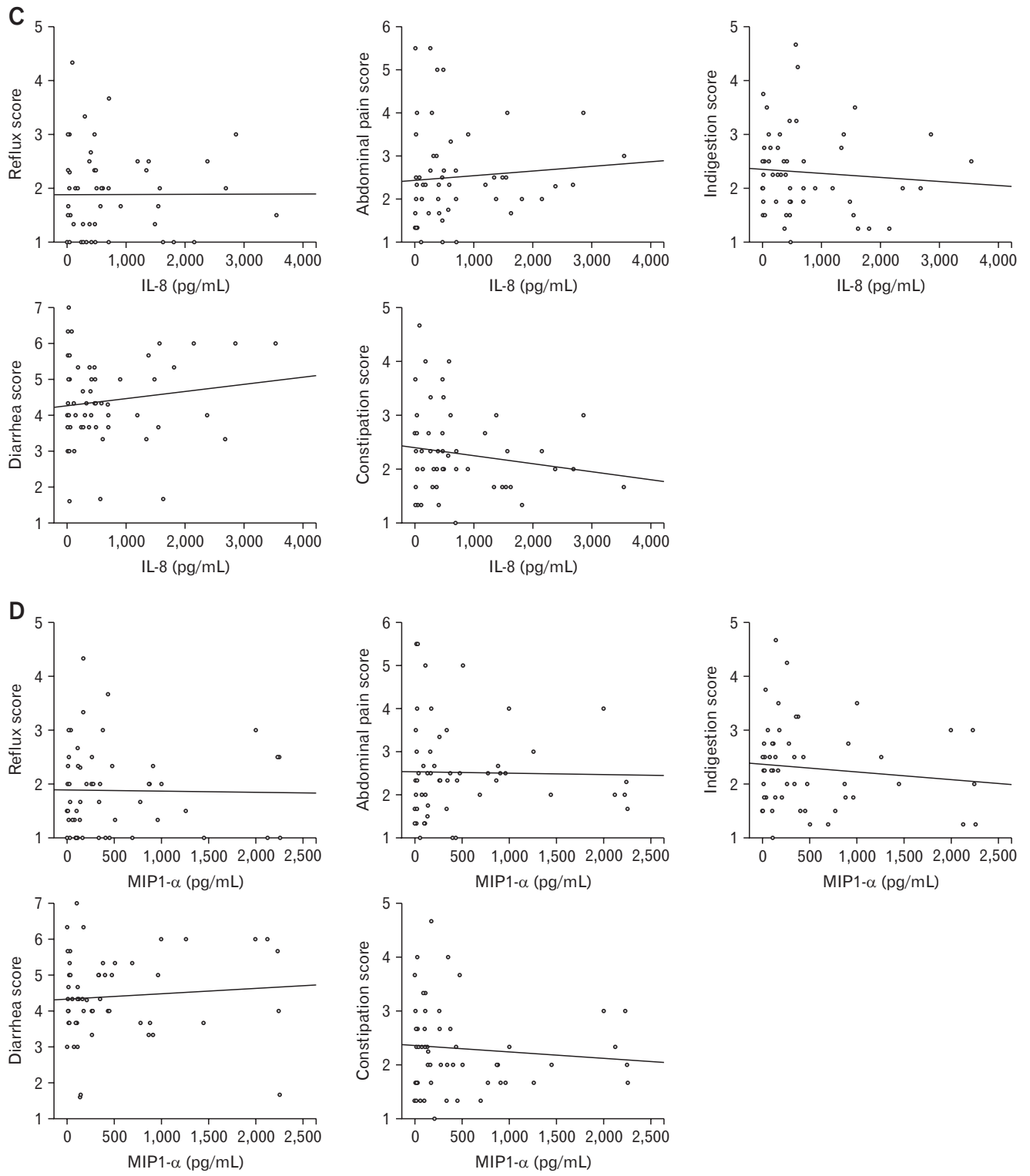
Serum cytokine level (mean [CI], pg/mL)	IgE-mediated serological food hypersensitivity		<i>P</i> -value
	Negative (n = 40)	Positive (n = 20)	
IL-1 $\beta$	8.6 (4.3-14.4)	5.7 (2.2-9.3)	0.392
IFN- $\gamma$	27.7 (18.4-39.7)	20.1 (11.6-31.1)	0.342
MIP-1 $\alpha$	538.8 (362.1-758.8)	331.3 (135.1-612.7)	0.196
Eotaxin	166.3 (143.1-189.7)	164.6 (120.1-211.4)	0.939
IL-6	53.7 (35.5-79.1)	33.3 (10.5-70.1)	0.300
IL-8	788.8 (525.5-1049.5)	593.9 (266.1-1010.5)	0.416
IL-10	15.9 (4.7-36.7)	8.3 (3.9-13.8)	0.512
IL-12p70	26.0 (10.7-47.9)	14.1 (4.1-25.3)	0.349
IL-13	53.3 (26.6-83.1)	61.9 (16.3-128.1)	0.793
IL-17	11.3 (7.1-16.2)	5.6 (3.2-8.4)	0.057
TNF- $\alpha$	71.6 (50.7-96.1)	35.5 (21.3-53.4)	0.031

MIP-1 $\alpha$ , macrophage inflammatory protein-1alpha.

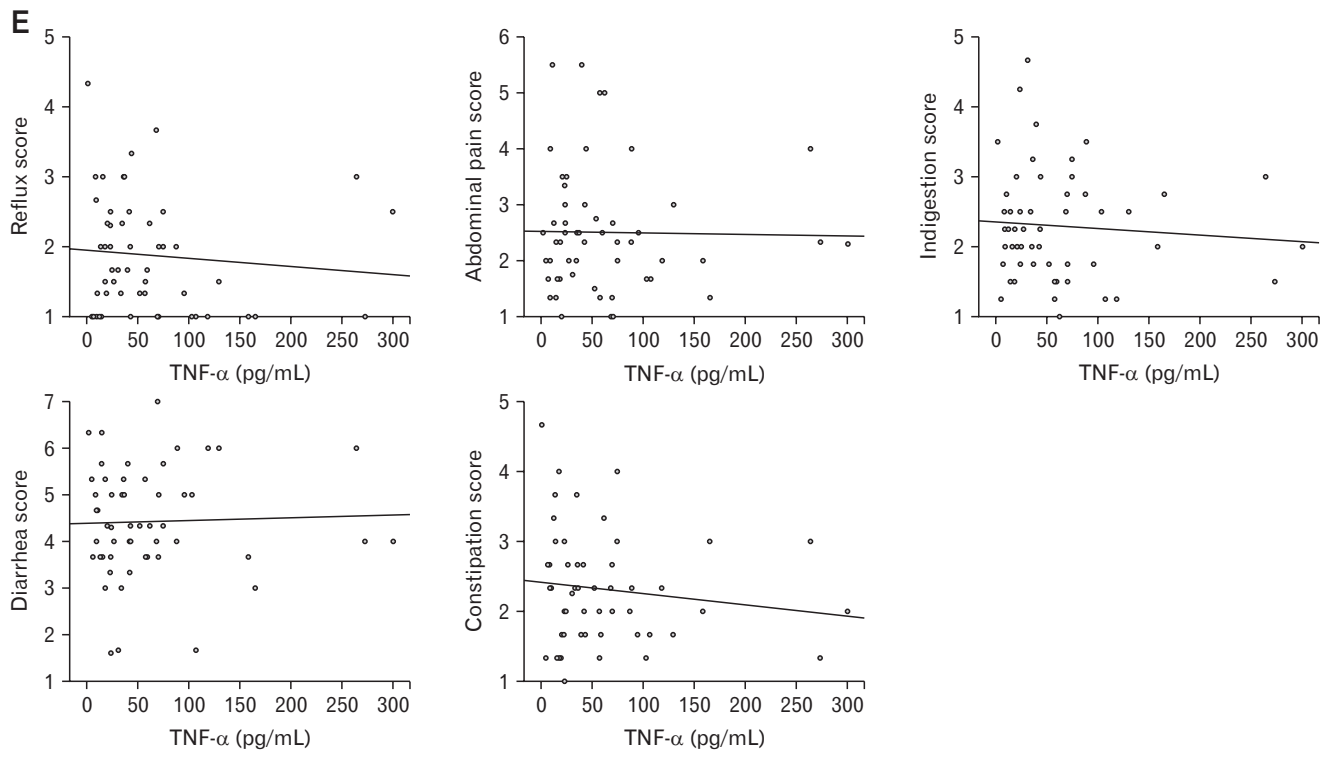
The subject who has at least one food allergen with class 2 or above was considered as being positive for IgE-mediated serological food hypersensitivity. mean, 95% confidence intervals and *P*-value were obtained by Bootstrapping and student *t* test.



**Supplementary Figure.** Correlations presented as  $r$  value between serum cytokine levels and gastrointestinal symptom scores in patients with irritable bowel syndrome with diarrhea (IBS-D). MIP-1 $\alpha$ , macrophage inflammatory protein-1alpha. (A) Correlations between serum IL-1 $\beta$  levels and gastrointestinal symptom scores. (B) Correlations between serum IL-6 levels and gastrointestinal symptom scores. (C) Correlations between serum IL-8 levels and gastrointestinal symptom scores. (D) Correlations between serum MIP-1 $\alpha$  levels and gastrointestinal symptom scores. (E) Correlations between serum TNF- $\alpha$  levels and gastrointestinal symptom scores.



**Supplementary Figure.** Continued.



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