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Original Article

Effect of gut microbial composition and diversity on major inhaled allergen sensitization and onset of allergic rhinitis

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ANOSIM, analysis of similarities; FMT, fecal microbiota transplantation; HD, house dust; JCP, Japanese cedar pollen; PC, principal component; PCoA, principal coordinate analysis

ABSTRACT

Background: Decreased gut microbiota diversity is associated with gut dysbiosis and causes various diseases, including allergic diseases. We investigated the relationship between gut microbial diversity and sensitization to major inhaled allergens. Furthermore, the relationship of allergic symptom onset with bacterial composition in sensitized individuals was investigated.

Methods: This study included 1092 local residents who had participated in the Iwaki Health Promotion Project in 2016. Blood samples were analyzed to ascertain specific IgE levels against major inhaled allergens (JCP, HD1, Grass-mix, Weed-mix). Nasal symptoms were estimated by questionnaires. Fecal samples were analyzed for bacterial 16S rRNA using next generation sequencing. The diversity index (α-diversity, β-diversity) and the composition of gut microbes in phylum/order levels were compared between patients sensitized or unsensitized to allergen, and symptomatic and asymptomatic groups.

Results: Some α-diversity metrics were significantly decreased in patients who were sensitized to any/all four allergens compared with the unsensitized group. β-diversity differed significantly between those unsensitized and sensitized to all allergens (aged 20–49 years), and between those unsensitized and sensitized to any/all four allergens (aged ≥50 years). The relative abundance of Bacteroidales was significantly lower in the unsensitized than in the sensitized group. The composition and diversity of gut microbiota were similar between the symptomatic and asymptomatic groups.

Conclusions: Our results suggest that lack of diversity in gut microbiota has an effect on sensitization to allergens. Bacteroidales in order level may affect sensitization; however, the onset of allergy symptoms was not significantly associated with bacterial composition and diversity.

Introduction

Organisms in the gut microbiota exist in a symbiotic relationship with each other. The balance of the microbiome plays an important role in homeostasis in the human body and in the maintenance of the local and systemic immune system. The intestine is indispensable for maintaining normal homeostasis in the host. These bacterial functions include fermentation of non-digestible food residues, production of short-chain fatty acids, vitamin synthesis, inhibition of enterocyte proliferation and differentiation, intestinal hormone production, protection against pathogens, and maturation and homeostasis of the immune system.[1–3] Generally, normal healthy gut flora includes many bacteria enriched in Bacteroidia and Clostridia, is high in diversity, and is functionally excellent.[4] Moreover, it could develop the biological ability to resist changes in community structure under stress (stability), to return to baseline quickly following stress-related changes (resilience), and to maintain the ideal composition and functional bacterial aspects.[5–7]

Recent studies have revealed that decreased microbiome diversity leads to an imbalance in the gut microbiota (dysbiosis). This is associated with a variety of diseases, such as liver disease, colorectal cancer, type 2 diabetes, Alzheimer's disease, inflammatory bowel disease, metabolic syndrome,[8–11] and allergic disease.[12] The association between dysbiosis and atopic dermatitis has been reported for about 20 years.[13–15] In terms of airway allergy, several studies have found that reduced microbiome diversity in infancy

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precedes the development of allergic rhinitis and asthma in early childhood.[16,17] In a study of adult patients with allergic rhinitis, research on the efficacy of probiotics has been preceded by the hygiene hypothesis,[18,19] and the relationship between allergic rhinitis and gut microbiota in adults has recently been reported.[20–22] However, these recent studies were conducted on only a small number of participants.

In our previous study, we investigated the relationship between the bacterial order-level composition of gut microbiota and sensitization to two major inhaled allergens (house dust [HD] and Japanese cedar pollen [JCP]) in the Iwaki Health Promotion Project of 2016, a large-scale epidemiological survey of local residents in the Iwaki area. We found that symbiosis of the order Lactobacillales and Bifidobacteriales suppresses allergen sensitization, while Bacteroidales may promote allergen sensitization.[23]

Although there is no doubt that dysbiosis of gut microbiota plays an important role in allergen sensitization, the effect of gut microbiota diversity on the development of allergic rhinitis in allergen sensitized persons remains obscure. Therefore, the present study explored whether reduced gut microbiota diversity is associated with allergen sensitization and the onset of allergic rhinitis symptoms. In other words, we investigated whether the gut microbiota composition is involved in the induction and effector phases of allergic rhinitis.

Methods

Participants

In the present study, we used the data obtained from the health survey "Iwaki Health Promotion Project 2016," as reported by Nomura *et al.*[23] Briefly, invitation letters for this project were sent by mail to local residents aged ≥20 years, living in the Iwaki District of Hirosaki City, Aomori Prefecture, Japan. Of the 1145 participants, 1092 with no missing data for specific IgE testing, questionnaire, and stool samples were used in the present analysis. Data collection for this study and project was approved by the Ethics Committee of Hirosaki University School of Medicine (authorization number: 2016-028), and all participants gave written informed consent prior to inclusion.

Blood analysis and questionnaire survey

To diagnose sensitization and development of allergic rhinitis, blood samples were obtained and specific IgE for JCP, HD, Grass-mix, and Weed-mix were measured using the ImmunoCAP system (Thermo Fisher Scientific, Waltham, MA, USA). An allergen-specific IgE level ≥0.35 kU/L was considered to indicate sensitization to the allergen.

A questionnaire was used to investigate whether two or more of the symptoms, such as runny nose, paroxysmal sneezing, nasal congestion, and itchy nose had occurred in succession outside the period of contracting cold or influenza. Based on this result, the onset of allergy rhinitis symptoms was estimated. We defined the onset of allergic rhinitis as the presence of the above symptoms in allergen-sensitized participants.

Analysis of gut microbiota

Extraction of DNA from fecal samples

Two to three grams of fresh feces were transferred to a storage container (TechnoSuruga Laboratory, Shizuoka, Japan) containing a stock guanidine thiocyanate solution (100 mM Tris–HCl [pH 9.0], 40 mM Tris–EDTA [pH 8.0], and 4 M guanidine thiocyanate). The fecal sample suspension was milled with zirconia beads at 5 m/s for 2 min using the FastPrep-24 instrument (MP Biomedicals, Santa Ana, CA, USA). DNA was then extracted from 200 μL aliquots of the samples using the automated Magtration System 12GC with Mag-DEA DNA 200 (GC) as the reagent (Precision System Science, Chiba, Japan).

Analysis of gut microbiota by next generation sequencing

The sequence of the V3–V4 region of 16S rDNA was used to identify bacteria. Using an Illumina MiSeq system (Illumina, San Diego, CA, USA), bacterial sequences were detected and identified using Metagenome@KIN (World Fusion, Tokyo, Japan) analysis software. Analysis was conducted to ascertain 97% sequence similarity using the TechnoSuruga Lab Microbial Identification database DB-BA10.0 (TechnoSuruga Laboratory). Proportions of bacterial phyla and orders represented in the gut microbiota are expressed as % relative abundance.

Data analysis

We used the number of observed bacterial species, Chao1, Shannon, and Simpson indices as the α-diversity index. The Chao1 index is based on the number of observed species, with additional weighting for rare species. The Shannon and Simpson indices also consider equality. The Shannon index responds sensitively to the number of rare species, while the Simpson index responds sensitively to the population of dominant species. We also investigated β-diversity, which indicates structural differences in the microbial communities between the two groups. The diversity index (α-diversity, β-diversity) was statistically compared using the R package vegan (version 4.0.3). We investigated the relationship between differences in the status of sensitization to the four major inhaled allergens (unsensitized, sensitized: sensitized to any of them, and sensitization to all of them) and the number of observed species, as well as other α-diversity metrics (Chao1, Shannon, and Simpson). Each α-diversity metric has two components: species richness and equitability indices.[24,25] We also performed a principal coordinate analysis (PCoA) with the top two PCoA scores (principal components PC1 and PC2) and examined their associations with sensitization status, and the onset/non-onset status (symptomatic group/asymptomatic group) in allergen-sensitized participants. β-diversity indices were calculated for the weighted UniFrac distance and were examined using analysis of similarities (ANOSIM).

To assess dysbiosis, we compared the relative abundance at the phylum and order level between sensitized (sensitized to any of the allergens) and unsensitized groups, and between symptomatic and asymptomatic groups. Two-sample *t*-tests and multivariate analysis of factors affecting sensitization to any of the four allergens were performed using SPSS (version. 25.0; IBM Corp., Armonk, NY, USA). Multiple logistic regression analysis was performed using sensitization to any allergen as the dependent variable. The independent variables were age, sex, body mass index, and presence of the four major bacterial orders (Bacteroidales, Bifidobacteriales, Clostridiales, and Lactobacillales). $P < 0.05$ was considered significant for all analyses.

Results

Characteristics of the population

The 1092 participants had a mean age of 54.5 years (range: 20–93 years). The age group with the largest number of participants was 60–69 years. Throughout the age groups, there were more female than male participants (Table 1).

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Table 1
Number of sex-segregated participants, the sensitized/symptomatic rates (%) and specific IgE levels (mean ± SD) of four inhaled allergens by age group.

Age (years)	20–29	30–39	40–49	50–59	60–69	70–79	≥80
Men	23	81	74	80	106	45	17
Women	34	96	112	128	178	94	24
Total	57	177	186	208	284	139	41
(a) JCP							
Participants	31 (54.4%)	100 (56.5%)	101 (54.3%)	116 (55.8%)	89 (31.3%)	32 (23.0%)	3 (7.3%)
sIgE level (kU/L)	8.5 ± 17.2	8.2 ± 17.1	11.2 ± 23.9	8.1 ± 18.6	4.8 ± 14.7	3.3 ± 11.3	0.1 ± 0.2
(b) HD1							
Participants	25 (43.9%)	83 (46.9%)	66 (35.5%)	52 (25.0%)	38 (13.4%)	18 (13.0%)	3 (7.3%)
sIgE level (kU/L)	7.0 ± 16.7	3.7 ± 7.8	2.7 ± 9.2	1.8 ± 6.2	0.8 ± 2.8	0.4 ± 1.3	0.4 ± 1.7
(c) Grass-mix							
Participants	8 (14.0%)	31 (17.5%)	36 (19.4%)	26 (12.5%)	25 (8.8%)	8 (5.8%)	0 (0%)
sIgE level (kU/L)	0.3 ± 0.5	0.4 ± 0.8	0.4 ± 1.1	0.4 ± 1.7	0.4 ± 1.8	0.2 ± 0.4	0.1 ± 0
(d) Weed-mix							
Participants	16 (28.1%)	67 (37.9%)	54 (29.0%)	35 (16.8%)	30 (10.6%)	13 (9.4%)	1 (2.4%)
sIgE level (kU/L)	4.5 ± 15.2	3.4 ± 8.8	2.9 ± 8.8	0.8 ± 2.5	1.2 ± 7.5	0.6 ± 2.2	0.2 ± 0.6
Any sensitized participants	38 (66.7%)	125 (70.6%)	121 (65.1%)	131 (63.0%)	110 (38.7%)	43 (30.9%)	4 (9.8%)
Symptomatic participants	20 (52.6%)	87 (69.6%)	79 (65.3%)	81 (61.8%)	64 (58.2%)	19 (44.2%)	2 (50.0%)

Number of sensitized and symptomatic persons

The number of participants sensitized to the inhaled allergens of JCP, HD, Grass-mix, and Weed-mix was 472 (43.22%), 285 (26.10%), 134 (12.27%), and 216 (19.78%), respectively. The sensitized/symptomatic rates and average allergen-specific IgE levels according to age group are shown in Table 1. Taking into account the overlap in sensitization, 572 (52.38%) participants were sensitized to any one of the four tested allergens, and there was a decrease in the sensitization rate with increasing age. The status of overlapping sensitization by age is shown in Figure 1. As the age group increased, the rate of sensitized persons decreased. The number of participants with nasal symptoms among the sensitized persons was 352 (61.54%). The incidence rate did not vary among the age groups.

The number of gut microbiota species by age group

In this study, the number of leads was set to approximately 10,000 or more, and the number of observed species reached the plateau. Thus, a sufficient number of leads was secured in this diversity analysis, as compared with previous reports.[26–29] The mean number of species by age group is shown in Figure 2. A total of 975 species were detected, with an average of 110.08 species per person (range: 49–221). The number of observed species tended to be slightly higher in women than in men among younger age groups, and increased in the older age group (around 50 years) in both sexes (Fig. 2). In addition, there was also a lower sensitization rate in the older age group than in the younger age group, as mentioned earlier. We have already observed how microbial composition fluctuated greatly after 50 years of age in a previous. Therefore, in order to exclude these effects of aging, we divided the participants into two age groups (20–49 years and ≥50 years) in the subsequent investigations, as we had done in our previous study.

There were significantly more species observed in ≥50 year group than in the 20–49 years group ($P < 0.001$) (Fig. 3a). Moreover, a clear clustering pattern was observed on the PCoA plot, which showed that β-diversity was significantly different between the 20–49 years and ≥50 years age groups ($P = 0.001$) (Fig. 3b).

Relationship between sensitization/onset and diversity in gut microbiota

On comparing the bacterial α-diversity indices in unsensitized participants, participants sensitized to any, and those sensitized to

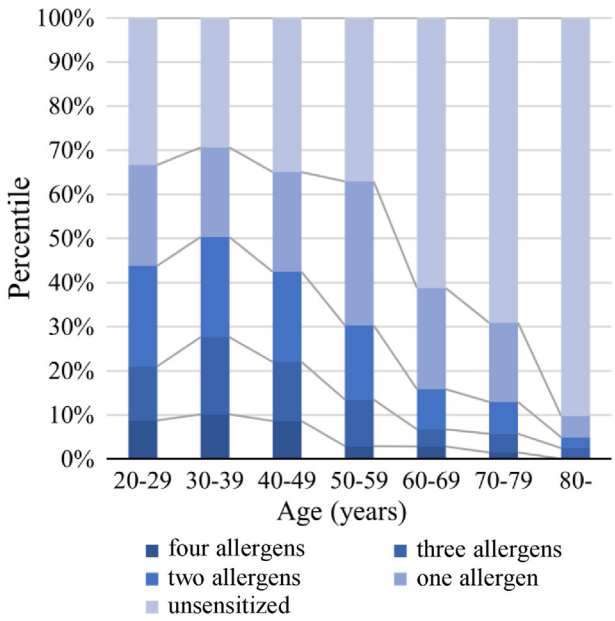

Fig. 1. Percentage of allergen sensitizations by age groups.

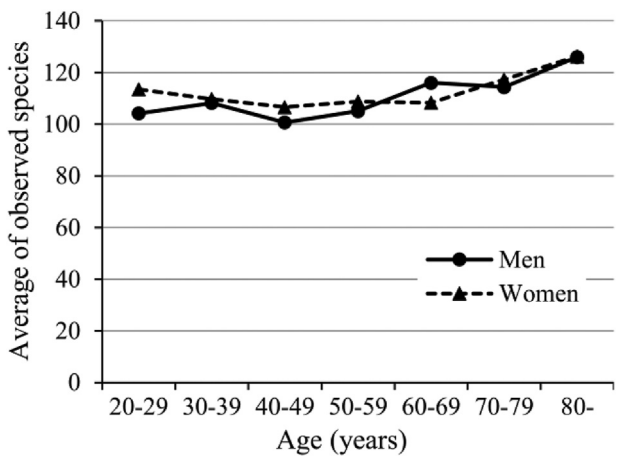

Fig. 2. Average number of observed gut microbiota species by age and sex.

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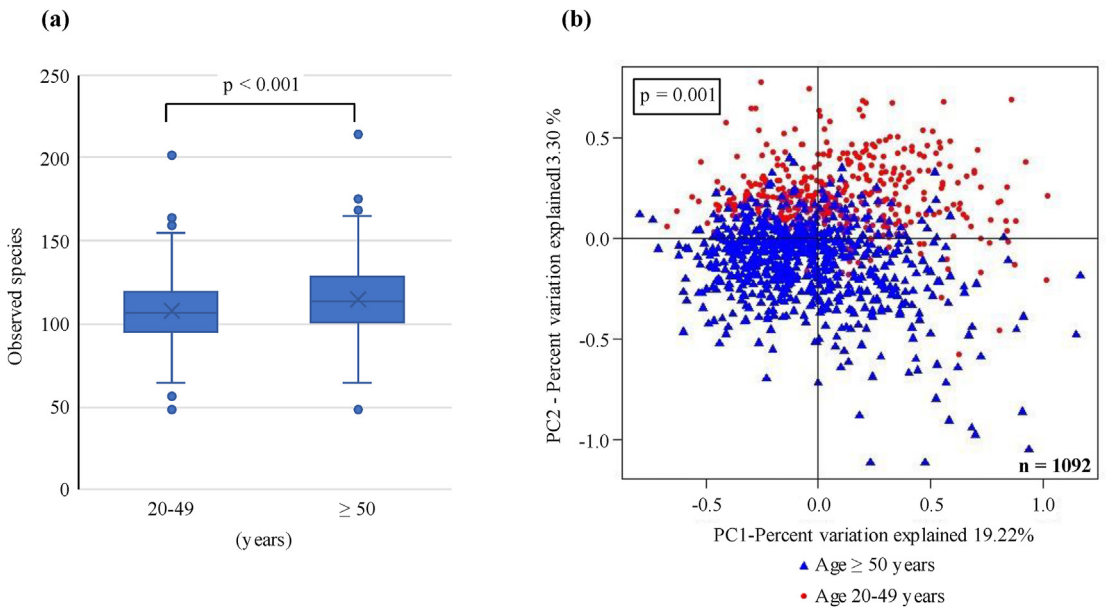

Fig. 3. Comparison of observed species and β-diversity index between participants of 20–49 years and ≥50 years of age. **(a)** Observed species: 114.70 ± 20.49 vs. 107.71 ± 18.84, P < 0.001 **(b)** β-diversity: analysis of similarity [ANOSIM:analysis of similarity] P-value = 0.001.

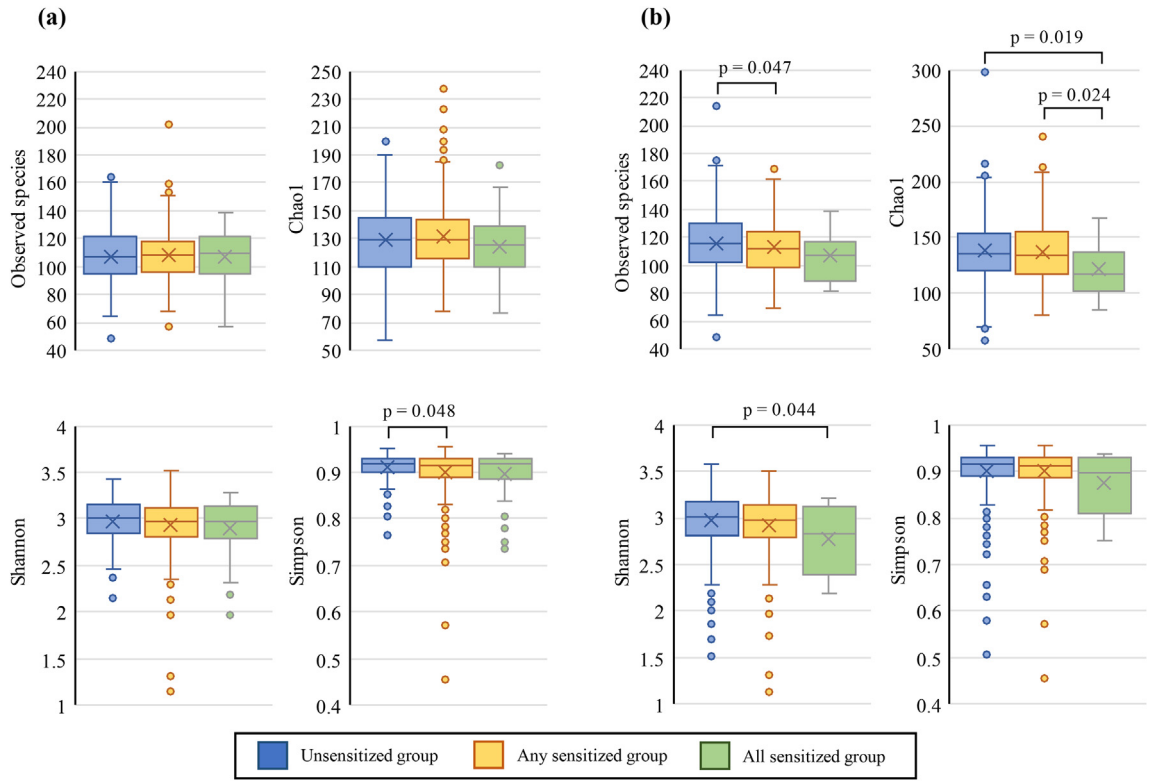

Fig. 4. Comparisons of bacterial diversity between the group sensitized to any/all allergens and the unsensitized group. The bacterial α-diversity indices compared were the number of observed species, Chao1, Simpson, and Shannon indices. **(a)** Age 20–49 years. **(b)** Age ≥50 years.

all four allergens by age 20–49 years (n = 136, 283, and 39, respectively), the Simpson index in the group sensitized to any allergen was significantly decreased compared with that in the unsensitized group (Fig. 4a). In the ≥50 years age group (n = 384, 289, and 16, respectively), some α-diversity metrics (observed species, Chao1, and Shannon indices) were significantly decreased in patients who were sensitized to any/all four allergens compared with the unsensitized group (Fig. 4b).

The PCoA plot analysis (β-diversity) is shown in Figure 5. There was a significant difference between the unsensitized group and the group sensitized to all allergens, among 20–49 years-old participants (ANOSIM P-value 0.018). Similarly, there was a significant

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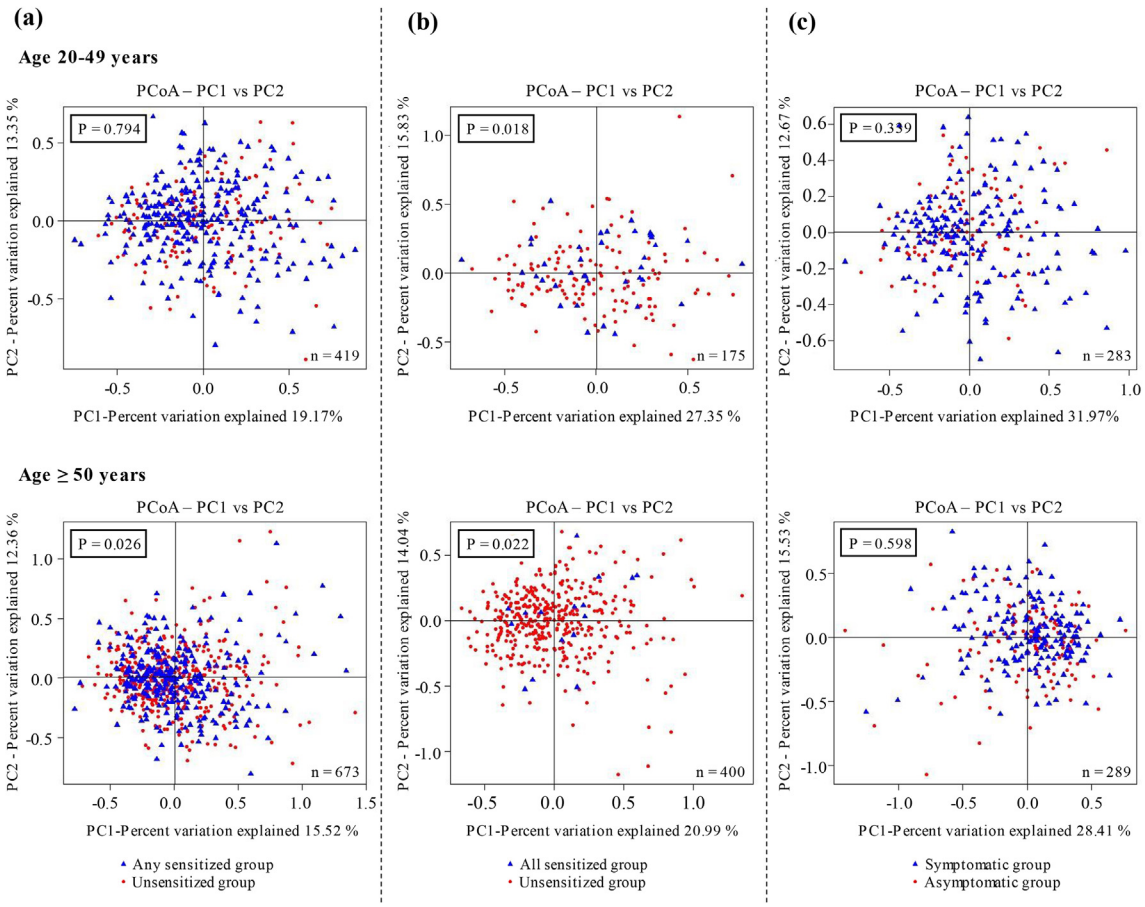

Fig. 5. Principal coordinate analysis (PCoA) plot (β-diversity) of sensitization status and the onset status in allergen-sensitized participants. In the PCoA, no visually obvious clustering was found. However, in the analysis of similarity (ANOSIM), there was a significant difference between the group sensitized to all allergens and the unsensitized group in the principal components PC1 vs. PC2 axis in participants aged 20–49 years. There was a significant difference between the group sensitized to any/all allergens and the unsensitized group in the principal components PC1 vs. PC2 axis among participants aged ≥50 years.

difference between the unsensitized and sensitized groups (any and all four allergens) among participants aged ≥50 years (ANOSIM P-value 0.026 and 0.022, respectively).

On the other hand, there was no statistically significant difference in β-diversity between the symptomatic and asymptomatic groups among the 20–49 year (n = 186 and 97, respectively) and ≥50 year age groups (n = 166 and 123, respectively).

Comparison of relative abundance in bacterial phyla and orders according to sensitization status and onset status

At the phylum level, the relative abundance of Bacteroidetes was lower, and that of Firmicutes was higher, in the unsensitized group than in the sensitized group in both the 20–49 years and ≥50 years age groups (Fig. 6a, b). At the order level, the proportion of Bacteroidales in the unsensitized group was significantly lower than that in the sensitized group across both age groups. Additionally, the relative abundance of Clostridiales in 20–49 year-old participants, and Lactobacillales in both age groups, tended to be higher in the unsensitized group (Fig. 7a, b).

However, there were no marked differences in gut microbiota composition in the symptomatic or asymptomatic groups observed at the phylum (Fig. 6c, d) or order levels (Fig.7c, d). Multivariate analysis also revealed Bacteroidales were significantly high in sensitized to any allergens in 20–49 years compared to the unsensitized group (Supplementary Table 1).

Discussion

A high diversity of gut microbiota is considered to contribute a balanced immune response and be beneficial for health, via mechanisms involving increased metabolites such as anti-inflammatory short-chain fatty acids and decreased production of inflammatory mediators, such as lipopolysaccharides.[2,30] Although *Lactobacillus* and *Bifidobacterium*, which produce lactic acid and acetic acid in the intestines, are well known to be effective for nasal symptoms as typical probiotics in allergic rhinitis,[15,31] no evidence to date has demonstrated that they can prevent the onset of the symptoms.[32,33] Additionally, there is no consensus about the diversity of the gut microbiota in allergic rhinitis. Most reports agree that this diversity is reduced in patients with allergic rhinitis,[1,21,22] but some reports have shown that the diversity was high,[20] or that there was no difference compared to a healthy group.[16,17]

In the present study, we found that the rates of sensitization were decreased, and gut microbial diversity was increased in individuals around the age of 50s. Therefore, this survey was divided into two age groups: 20–49 years and ≥50 years. Consequently, we found a significant difference in some α-diversity indices between the sensitized and unsensitized group, and in the β-diversity between the group sensitized to allergens and the unsensitized group among participants in both age groups. Most studies on gut microbiota diversity in patients with allergic diseases have not

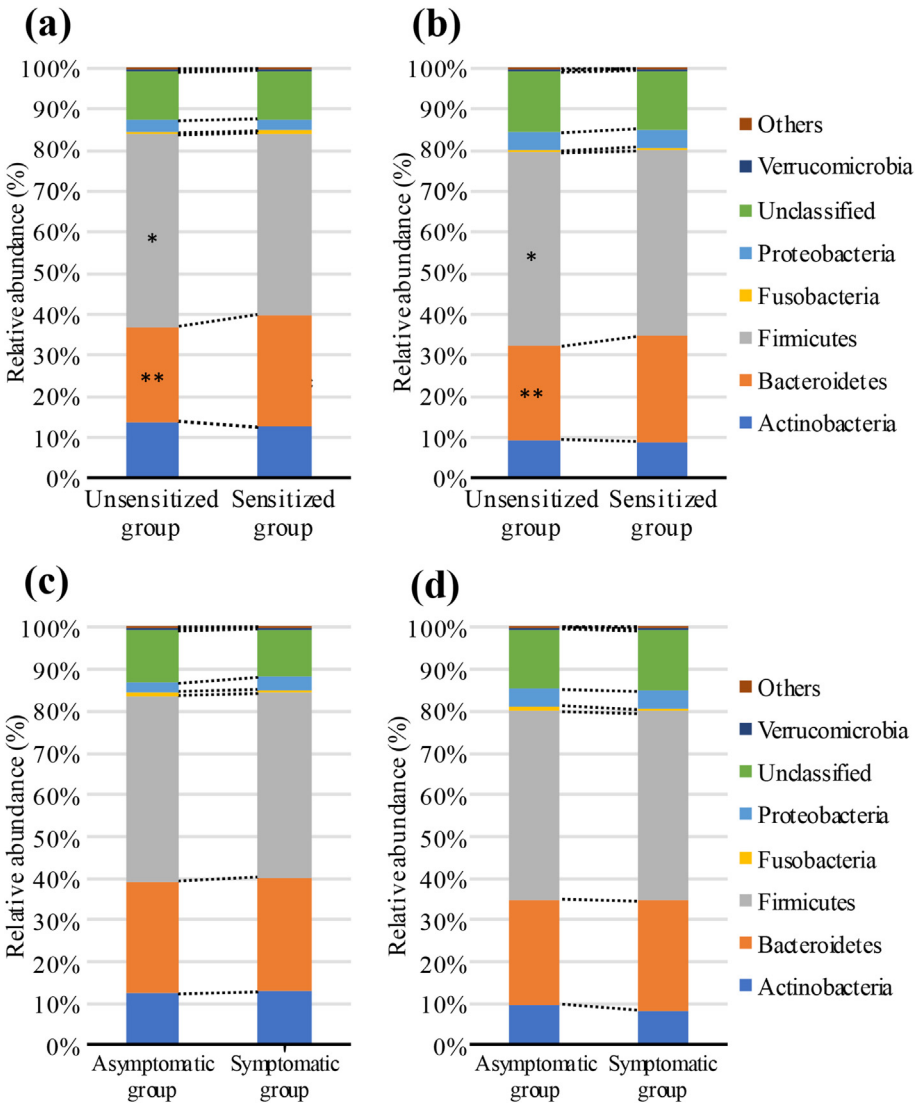

Fig. 6. The relative abundance (%) of bacterial phyla in the sensitized/unsensitized groups aged 20–49 years **(a)** and ≥50 years **(b)**, and in the symptomatic/asymptomatic groups aged 20–49 years **(c)** and ≥50 years **(d)**. *P < 0.05, **P < 0.01.

taken into account the effects of such age-related declines in sensitization rates and increased microbial diversity. Our results suggest that the effects of aging need to be considered when examining allergen sensitization and gut bacterial diversity.

A previous study showed no significant differences in diversity between people who have moderate or severe allergic rhinitis symptoms.[20] Similarly, no apparent effect was seen in either α-diversity or β-diversity indices in terms of the onset of allergic rhinitis symptoms in sensitized groups, regardless of age, in the present study. These results lead us to conclude that decreased diversity in the gut microbiota causes dysbiosis and may affect allergic sensitization, but that this may not be directly associated with the development of allergic rhinitis symptoms.

In a comparison of bacterial composition at the phylum level, the relative abundance of Firmicutes was higher in the unsensitized group, and that of Bacteroidetes was higher in the sensitized group among both 20–49-year-old and ≥50-year-old participants. Firmicutes are associated with butyric acid and lactic acid production. The predominance of Bacteroidetes over Firmicutes (i.e., a lower F/B ratio) reduces the overall lactate production, thereby affecting the intestinal barrier integrity and increasing intestinal permeability in participants with allergic disease.[7,21] The metabolites produced by these phyla are thought to play important roles in colon health and immune regulation. At the order level, the relative abundance of Bacteroidales was significantly lower, while that of Lactobacillales tended to be higher, in the unsensitized group of both age ranges. In addition, Clostridiales were more common in the unsensitized group aged 20–49 years. Similar to the results of this study, a previous study reported that there is decreased diversity and that Bacteroidales is highly abundant in the gut microbiota of allergic patients.[29] Although we previously reported high levels of Bacteroidales in the group sensitized to HD1 and JCP, the effects of this have not been fully elucidated.[23]

Butyrate-producing bacteria, such as Clostridiales, induce regulatory T cells and suppress allergic symptoms by preventing inflammation of the intestinal tract.[21,28,34,35] We have previously reported that the symbiosis of the order Lactobacillales and Bifidobacteriales is useful for suppressing allergen sensitization.[23] Considering the results of the present study, the presence of a varied gut microbiota that produce short-chain fatty acids, such as lactic acid, acetic acid, and butyric acid in the intestine, was effective in preventing sensitization to allergens. On the other hand,

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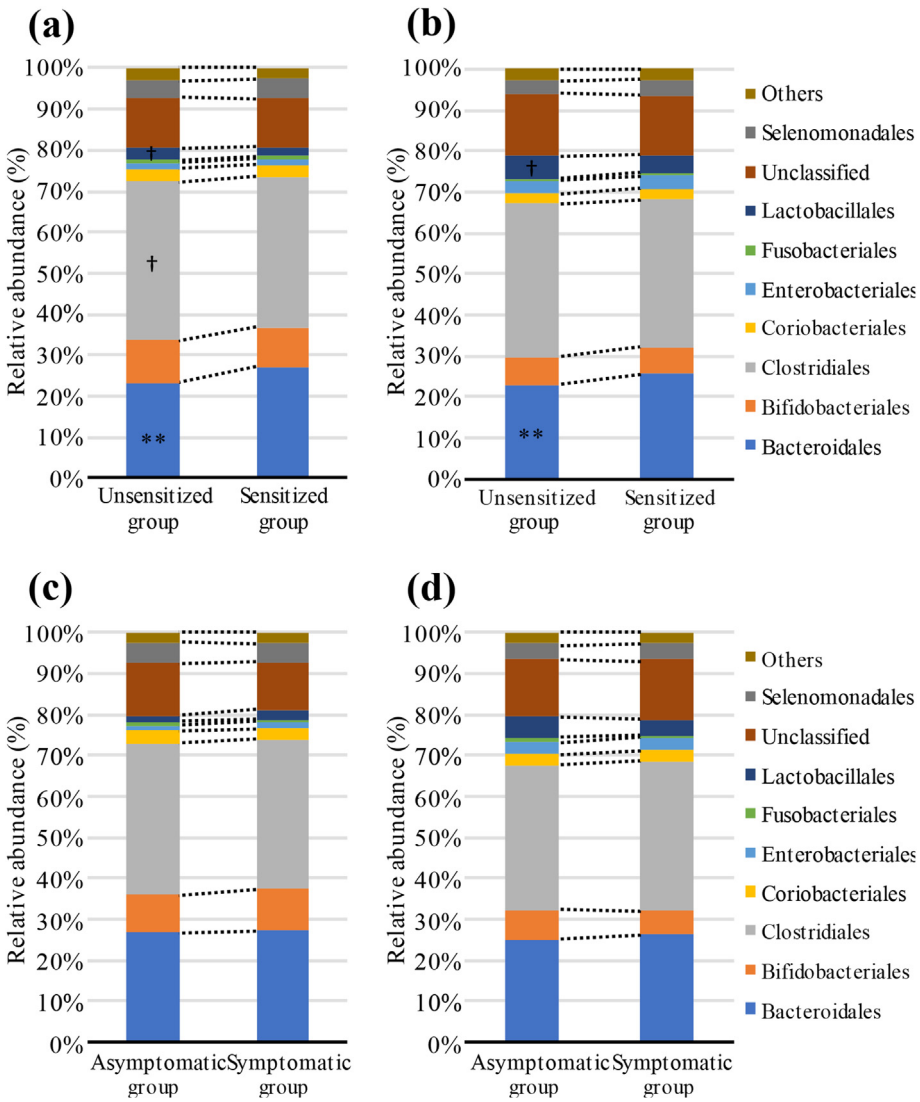

Fig. 7. The relative abundance (%) of bacterial orders in the sensitized/unsensitized group aged 20–49 years **(a)** and ≥50 years **(b)**, and in the symptomatic/asymptomatic group aged 20–49 years **(c)** and ≥50 years **(d)**. †P < 0.1, *P < 0.05, **P < 0.01.

when we assessed the effect in terms of presence or absence of onset of symptoms, no bacterial compositional significant difference was observed between the two groups at phylum or order levels. Our results indicate that there is no strong relationship between gut microbiota at phylum/order levels and the onset of nasal symptoms.

Recently, a marked increase of Japanese cedar pollinosis from childhood has become a serious problem in Japan,[36] and the concept that correcting dysbiosis may lead to the prevention of allergic rhinitis is appealing. Probiotics, such as *Lactobacillus* and *Bifidobacterium*, have been confirmed to reduce rhinitis symptoms, but no evidence has been shown to date in terms of an effect of preventing the onset of symptoms.[32,33] Supplementation with a single bacterial strain alone may not be sufficient to restore the intestinal environment to a good condition, which requires a complex and diverse gut microbiota. Generally, high-quality dietary content, such as fruits and vegetables, high fiber whole grain products, fish, low-fat dairy products, meat, and low-fat foods, has been shown to increase intestinal diversity.[30,37] Various dietary approaches could encourage maintenance of the host's health more effectively. The literature suggests that maternal administration of probiotics failed to increase diversity of the microbiota in the child, and that colonization of more than 40 bacterial strains in sterile mice was necessary to suppress IgE levels.[38] It may be important to emphasize a lifestyle that pays attention to the intestinal environment from childhood.

Fecal microbiota transplantation (FMT) for *Clostridium difficile* enteritis has achieved good results.[39–42] This condition is the result of dysbiosis. Clinically, FMT has been used to increase intestinal microbiota diversity, with the concept that returning the original healthy intestinal environment (rebiosis) can be used to treat the disease.[9] Although the application of FMT to allergic rhinitis may be difficult, we believe that the concept of rebiosis may be important in allergy treatment in the future.

This study has a limitation. Various complex genetic, environmental, and dietary factors may cause new onset of allergies. Since the survey employed for local residents who participated in this study may have similar demographic characteristics, the effect of these factors cannot be ruled out completely. Therefore, we would like to conduct a longitudinal study in the future to confirm the effect of these factors on sensitization and progression of symptoms.

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In conclusion, reduced diversity and dysbiosis are associated with allergen sensitization, as an induction phase. Nevertheless, gut microbiota do not seem to be involved in the onset of symptomatic nasal allergy. As the metabolites and mechanisms that support the relationship between gut microbiota and host become more apparent, it is likely that more research on rebiosis will be carried out as a therapeutic strategy to improve the quality of life of allergic patients. We believe that the knowledge gained through our study's findings could be used to prevent and reduce sensitization prophylactically.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2022.06.005.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

TY and AM designed the study and wrote the manuscript. AN and TH contributed to the analysis of the data. YT, TM, and MI performed data collection. All authors have read this paper and agreed to submit the manuscript.

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