Impact of wheat sensitization on wheeze and T2 phenotypes in general population of children

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Background: The association between sensitization to specific aeroallergens and outcomes in patients with asthma is well researched; however, the association between childhood-onset wheeze/asthma and sensitization to various aeroallergens and food allergens in the general pediatric population remains poorly understood.

Objective: We sought to investigate the association between sensitization to common aeroallergens and food allergens with wheeze and type 2 (T2) inflammation in the general pediatric population.

Methods: Specific IgEs against 9 aeroallergens and 4 food allergens were measured in the prospective Hokkaido birth cohort of 428 school-age children (age ~10 years). Wheeze and other allergic symptoms were assessed using the International Study of Asthma and Allergies in Childhood questionnaire. Blood eosinophil count and fractional exhaled nitric oxide level were assessed as T2 biomarkers. The Isle of Wight birth cohort in the United Kingdom was used for replication analysis (n = 1032).

Results: The prevalence of sensitization to at least 1 aeroallergen and food allergen was 70.5% and 22.3%, respectively. A significant association between wheeze and sensitization to aeroallergens such as ragweed, Japanese cedar, mugwort, and pet dander was found. However, the association between wheeze and wheat sensitization was highly significant (Hokkaido birth cohort: odds ratio, 4.67; 95% CI, 1.98-11.01; Isle of Wight birth cohort, odds ratio, 4.01; 95% CI, 1.78-9.07). Sensitization to most aeroallergens, though not any food allergen, was associated with the T2-high phenotype.

Conclusions: Sensitization to wheat may be an important risk factor for wheeze/asthma development, especially the pathogenesis of T2-non/low asthma, independent of aeroallergens, in the general pediatric population. (J Allergy Clin Immunol Global 2024;3:100300.)

Key words: *Sensitization to aeroallergens and food allergens, wheat sensitization, wheeze, blood eosinophil, FENO, T2 phenotype, population-based birth cohort, general population, school-age children*

Allergic diseases are the most common chronic childhood diseases and are a global health problem.[1,2] The global prevalence of childhood allergic diseases has significantly increased in the past decades.[3,4] Therefore, in addition to treatment, the identification of risks and predisposing factors and the pathophysiology of allergic diseases to enhance preventive strategies remains an urgent priority owing to the burgeoning burden of these diseases.[5]

Atopic sensitization is prick test positivity or IgE antibody positivity to common aeroallergens and food allergens.[6] It is a major risk factor for the development of asthma, the most common chronic childhood disease, and other allergic diseases in children.[7-9] Childhood-onset asthma is typically characterized by presence of atopy and type-2 (T2)-mediated inflammation.[10] Previous studies, mainly focused on a single or limited number of aeroallergens such as dust mites and pet (cat and dog) dander, have suggested the possible association between sensitization with other aeroallergens and the risk of allergic diseases,[11-14] albeit with contrasting results.

In children, allergic sensitization is a systemic low-grade inflammatory disorder and early-life sensitization can predict later-life sensitization and consequent asthma.[15,16] Sensitization tests are useful for the diagnosis and management of allergic diseases in addition to recognizing sensitized though clinically asymptomatic children susceptible to allergic diseases in later life. Therefore, extensive studies on common allergen sensitization would help medical staff during assessments in routine clinical settings.

Food allergy modulates allergic airway inflammation via the action of direct and indirect nutritional components on immune cells.[17,18] Patelis et al[19] reported that IgE antibodies against food allergens in adults were independently associated with increased fractional exhaled nitric oxide (FENO) levels and asthma risk in pollen-sensitized individuals. Another study demonstrated the independent effects of IgE sensitization to aero- and food allergens with FENO level and blood eosinophil count in patients with asthma.[20] Recent animal studies have reported that wheat consumption can exacerbate allergen-induced airway responses in addition to intestinal mucosal inflammation in mice.[21,22] However, human studies that have examined the association of food and aeroallergen sensitization with asthma and T2 inflammation, especially in the general pediatric population, are lacking.

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Abbreviations used
aOR: Adjusted odds ratio
ATI: Amylase trypsin inhibitor
FENO: Fractional exhaled nitric oxide
IOW: Isle of Wight
OR: Odds ratio
sIgE: Specific IgE

Recently, we reported a high prevalence of early-life allergic diseases in Japan compared with other Asian and developed countries. We found that approximately one-third of Japanese children have at least 1 allergic symptom, including wheeze, rhinitis, or eczema by the age of 7 years,[23] and that this proportion reaches 50% by the age of 11 years.[24] We hypothesized that such high prevalence could be associated with sensitization to common aeroallergens and food allergens during childhood.

Therefore, in this study, we used data from a population-based prospective birth cohort of the general population and measured the IgE response to 13 common aeroallergens and food allergens in serum, and assessed the association of sensitization to these allergens with wheeze prevalence in the general pediatric population. In addition, we conducted a similar comparative analysis for T2 biomarkers focusing on blood eosinophil count and FENO level.

METHODS

Study participants

Hokkaido birth cohort. This prospective study is part of a large, ongoing birth cohort comprising more than 20,000 mother-child pairs recruited through the Hokkaido Study on the Environment and Children's Health cohort study. Details of this study have been described previously.[23-26] Between September 2017 and March 2020, invitation letters were sent to a total of 1881 eligible children aged approximately 10 years who lived in Sapporo City and its surroundings. Among them, 428 agreed to participate in the present study.[24] The fact that allergic diseases were the outcome of the study was intentionally omitted in the invitation letters to prevent any possible selection bias. Parents and children were requested to visit selected pediatric clinics for physical examination, blood testing, and FENO measurement. At the visit, all parents were asked to answer the International Study of Asthma and Allergies in Childhood questionnaire.[27] Wheeze was defined as a positive answer to the question, "Has your child had wheezing or whistling in the chest in the past 12 months?" The survey objectives and methods were explained in-person, and written informed consent was obtained from all parents. In addition, we explained the study aim and procedures to the children to obtain their assent. The survey was approved by the Research Review Board of the Hokkaido University Center for Environmental and Health Sciences.[21-26]

Isle of Wight birth cohort. The Isle of Wight (IOW) birth cohort is a population-based cohort established on the IOW, United Kingdom, to prospectively study the natural history of allergic diseases among children.[7] wheeze was assessed using the International Study of Asthma and Allergies in Childhood questionnaire.[27] Data of 1032 children at the age of 10 years from the IOW were used for replication analysis of the findings between wheat sensitization and wheeze prevalence.

Measurement of biomarkers and definition of sensitization

Peripheral blood eosinophil counts were collected, and standard complete blood cell counts were performed at SRL, Inc (Tokyo, Japan). Total IgE levels (IU/mL) were measured in serum samples (SRL, Inc). Allergen specific IgE (sIgE) antibodies were measured by the ImmunoCAP system (Thermo Fisher Scientific, Uppsala, Sweden). Totally, 13 common allergens, including 9 aeroallergens and 4 food allergens, were measured. Examined aeroallergens were mites (*Dermatophagoides pteronynissinus*), cat and dog dander, white birch, mugwort, Japanese cedar, *Alternaria*, *Dactylis*, and ragweed. Examined food allergens were peanuts (Ara h2), cow milk, egg (albumen), and wheat. An IgE level of greater than or equal to 0.35 kU/L to specific allergens was considered positive. Sensitization to any aeroallergen or food allergen was defined as multiple antigen simultaneous test scores (≥0.35 lumicount) to at least 1 aeroallergen or food allergen. FENO concentrations were measured with a NIOX VERO (Aerocrine, Stockholm, Sweden) using the single-breath technique according to the American Thoracic Society guidelines.[28] In the IOW cohort, skin prick test assessment had been conducted at the age of 10 years, and allergic sensitization to wheat was defined as a mean wheal size greater than 3 mm compared with that the negative control.

Statistical analysis

Continuous data were presented as total counts, mean ± SD, and median (interquartile range), whereas categorical data were presented as frequencies and proportions. To examine the association of sensitization to aeroallergens or food allergens with wheeze prevalence in school-age children, multivariate logistic regression analyses were performed, adjusted for age, sex, exposure to second-hand smoking, and concurrent rhinitis and eczema. For defining T2 inflammation, the following biomarker cutoff thresholds similar to those described by the Global Initiative for Asthma guidelines were used: blood eosinophil count greater than 300 cells/μL and FENO level greater than 35 parts per billion.[29] Because the maternal history of allergic diseases and the season of the survey could influence children's wheeze prevalence, we conducted a sensitivity analysis and adjusted the models with these potential variables. For possible influence of prescribed drugs, another sensitivity analysis was conducted, and 2 children who were using inhaled corticosteroids and 1 child who was using an oral steroid were excluded. Statistical analyses were performed using the statistical software package JMP version 16 (SAS Institute, Inc, Cary, NC). For all statistical analyses, 2-sided *P* values less than .05 were considered statistically significant.

RESULTS

The characteristics of the 428 study participants in the Hokkaido birth cohort are listed in Table I. Approximately 6.2% of the mothers had a history of active smoking during pregnancy. Maternal and paternal history of allergic diseases was reported by 34.8% and 27.7%, respectively. Approximately 53% of the participants were male. The prevalence of wheeze, rhinitis, and eczema was 7.5%, 46.0%, and 22.4%, respectively. The median (interquartile range) of serum total IgE was 129 (35.6-395.5) IU/mL. In the IOW birth cohort (n = 1032),

TABLE I. Characteristics of the study participants

Characteristics	Total participants (n = 428)
Parental characteristics	
Maternal age at birth (y)	32.0 ± 4.7
Pre-pregnancy maternal body mass index (kg/m^2)	20.9 ± 3.1
Parity, nulliparous	214 (51.8)
Maternal education (≤12 y)	143 (33.9)
Maternal smoking during pregnancy, yes	25 (6.2)
Maternal history of allergic diseases, yes	148 (34.8)
Paternal history of allergic diseases, yes	95 (22.1)
Infant characteristics	
Male	230 (53.7)
Birth weight (g)	2979 ± 444
Child characteristics (age 10)	
BMI (kg/m^2)	17.7 ± 2.9
Age at the survey (mo)	126.9 ± 11.5
Family annual income, <5 million yen	126 (31.1)
Exposure to second-hand smoke	144 (33.6)
Serum total IgE (IU/mL)*	129 (5-1645)
Blood eosinophil number (cells/μL)*	231 (47-1164)
FENO (ppb)*	17 (5-96)
Wheeze	32 (7.5)
Rhinitis	196 (46.0)
Eczema	96 (22.4)

The values are shown in number (%), mean ± SD, or median (5%-95%tile).
ppb, Parts per billion.
*The values are shown in median (5%-95%tile).

49.7% of children were male, and the prevalence of wheeze, rhinitis, and eczema was 20.6%, 20.3%, and 24.8%, respectively (see Table E1 in this article's Online Repository at www.jaci-global.org). In the Hokkaido and IOW birth cohorts, 33.6% and 43.1% of children, respectively, were exposed to second-hand smoking at age 10 years.

In the Hokkaido birth cohort, 70.5% of children were sensitized to at least 1 aeroallergen, with a significantly higher prevalence in males than in females (75.8% vs 64.4%, respectively). Furthermore, 22.3% of children were sensitized to at least 1 food allergen (see Fig E1 in this article's Online Repository at www.jaci-global.org). The most prevalent aeroallergen sensitization was toward mite (*D pteronyssinus*, 58.0%), followed by white birch (33.5%), cat dander (32.6%), dog dander (22.5%), and *Dactylis* (21.8%) (see Fig E2 in this article's Online Repository at www.jaci-global.org). We found a higher prevalence of inhaled allergen sensitizations in males than in females. However, no specific pattern of sex differences was observed for sensitization to food allergens (see Fig E3 in this article's Online Repository at www.jaci-global.org). Moreover, children with wheeze had a higher percentage of sensitization to aeroallergens than to food allergens. Among food allergens, only wheat sensitization was higher than other food allergen sensitization in children with wheeze (see Fig E4 in this article's Online Repository at www.jaci-global.org). Children with wheeze had higher T2 biomarker levels and rhinitis and eczema prevalence, and higher exposure to second-hand smoke than those without wheeze (see Table E2 and Fig E5 in this article's Online Repository at www.jaci-global.org).

Among aeroallergens, children with wheeze had significantly higher sIgE positivity for ragweed, mugwort, Japanese cedar, Alternaria, pet dander, and mite (see Table E3 in this article's Online Repository at www.jaci-global.org). Almost the same aeroallergens had higher IgE positivity in the T2-high group (see Table E4 in this article's Online Repository at www.jaci-global.org). Among food allergens, only wheat, not other food allergens, had significantly higher sIgE positivity in wheezers (Table E4). We did not observe a correlation coefficient (ρ) higher than 0.8 for any correlations. Among food allergens, only the sIgE of wheat showed a relatively high correlation with some aeroallergens as follows: wheat and Japanese cedar (ρ, 0.711); wheat and mugwort (ρ, 0.579); wheat and ragweed; wheat and Dactylis (ρ, 0.553). However, the sIgE for wheat did not have a high correlation with the sIgE of other food allergens. In addition, wheat sensitization was not highly correlated with mite, dog, and cat dander sensitization, which are associated with T2-high phenotypes (see Fig E6 in this article's Online Repository at www.jaci-global.org).

We assessed associations of wheeze with aeroallergen and food allergen sensitization using logistic regression in the Hokkaido birth cohort (Fig 1, *A*; see Tables E5 and E6 in this article's Online Repository at www.jaci-global.org). In crude logistic models, wheeze was associated with sensitization to *Alternaria* (odds ratio [OR], 3.20; 95% CI, 1.00-10.20), mite (OR, 3.26; 95% CI, 1.30-8.12), cat dander (OR, 3.67; 95% CI, 1.72-7.81), dog dander (OR, 3.63; 95% CI, 1.72-7.66), mugwort (OR, 3.73; 95% CI, 1.60-8.69), Japanese cedar (OR, 4.81; 95% CI, 1.86-12.38), and ragweed (OR, 5.33; 95% CI, 2.36-12.00). In adjusted models, associations of wheeze with *Alternaria* (adjusted OR [aOR], 2.83; 95% CI, 0.84-9.52) were attenuated. In addition, a marginal association of any aeroallergen with wheeze was observed in crude (OR, 3.01; 95% CI, 1.03-8.82) and adjusted (aOR, 3.11; 95% CI, 1.05-9.22) models. Sensitization to white birch and *Dactylis* did not exhibit any significant association with wheeze.

In the Hokkaido birth cohort, sensitization to milk, egg, and peanuts was not associated with wheeze (Fig 1, *B*; Table E6). However, children with wheat sensitization had a higher wheeze prevalence than children with other food allergen sensitization (OR, 4.67; 95% CI, 1.98-11.01), and the results did not change in the adjusted model. We performed a replication analysis of the association of wheat sensitization with wheeze among children aged 10 years using the IOW birth cohort. Only 2.3% of 1032 children in the IOW birth cohort had a wheat sensitization; however, our replication analysis revealed a significant association of wheat sensitization with wheeze (OR, 4.01, 95% CI, 1.78-9.07). In the Hokkaido birth cohort, sensitization to any food allergen was associated with wheeze (aOR, 3.78; 95% CI, 1.77-8.08) (Fig 1, *B*; Table E6). As shown in Table II, mutually adjusted association of any aeroallergen and food allergen with wheeze revealed that sensitization to any food allergen was associated with wheeze (Table II). However, the association of sensitization to any aeroallergens with wheeze did not persist after controlling for food allergen sensitization.

In a sensitivity analysis, we additionally adjusted the association of inhaled and food allergen sensitization with wheeze prevalence with history of maternal allergic diseases and season of conducted surveys. However, the results did not change (see Tables E7 and E8 in this article's Online Repository at www.jaci-global.org). Also, excluding 3 children using inhaled and oral corticosteroids did not change the results (data not shown). Because sex may affect wheeze prevalence, we stratified the association of sensitization to examined allergens with wheeze by sex. Boys showed more convincing associations compared with

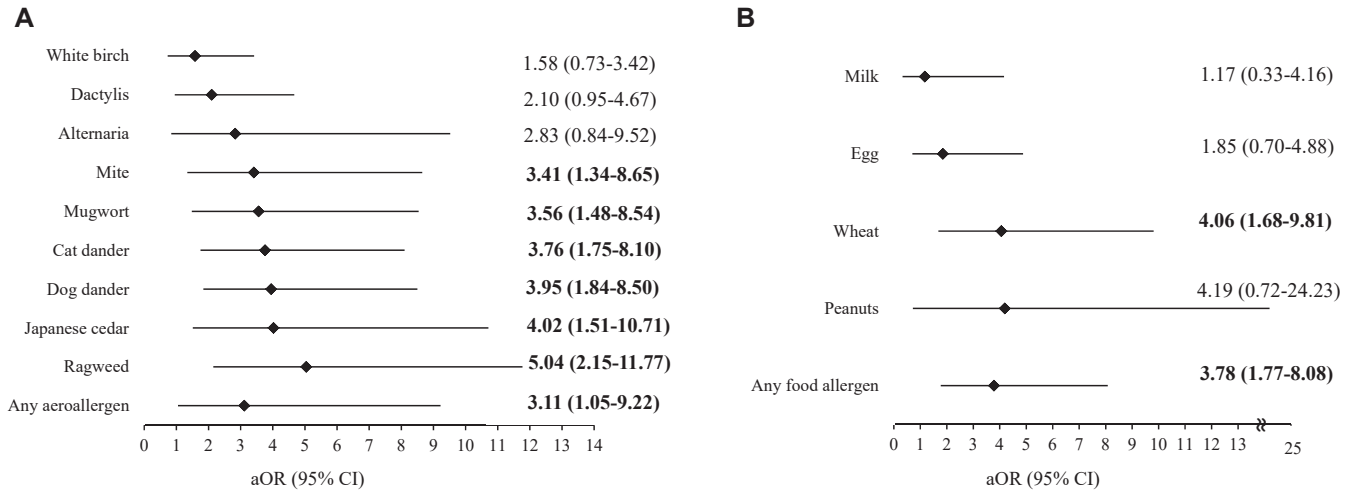

FIG 1. Association of sensitization to individual inhaled (**A**) and food allergen (**B**) with wheeze prevalence in school-age children (n = 428). Adjusted for sex, age (months), and second-hand exposure to tobacco smoke. Bold font indicates significant association.

TABLE II. Mutually adjusted association of any inhaled and food allergen sensitization with wheeze in school-age children (n = 428)

	Model 1		Model 2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Any aeroallergen	2.29 (0.76-6.86)	.136	2.36 (0.77-7.19)	.131
Any food allergen	3.75 (1.75-8.02)	.0006	3.26 (1.50-7.09)	.002

Model 1: Adjusted for any aeroallergen and any food allergen sensitization. Model 2: Adjusted for covariates in model 1 and sex, age (mo), and second-hand smoke exposure.

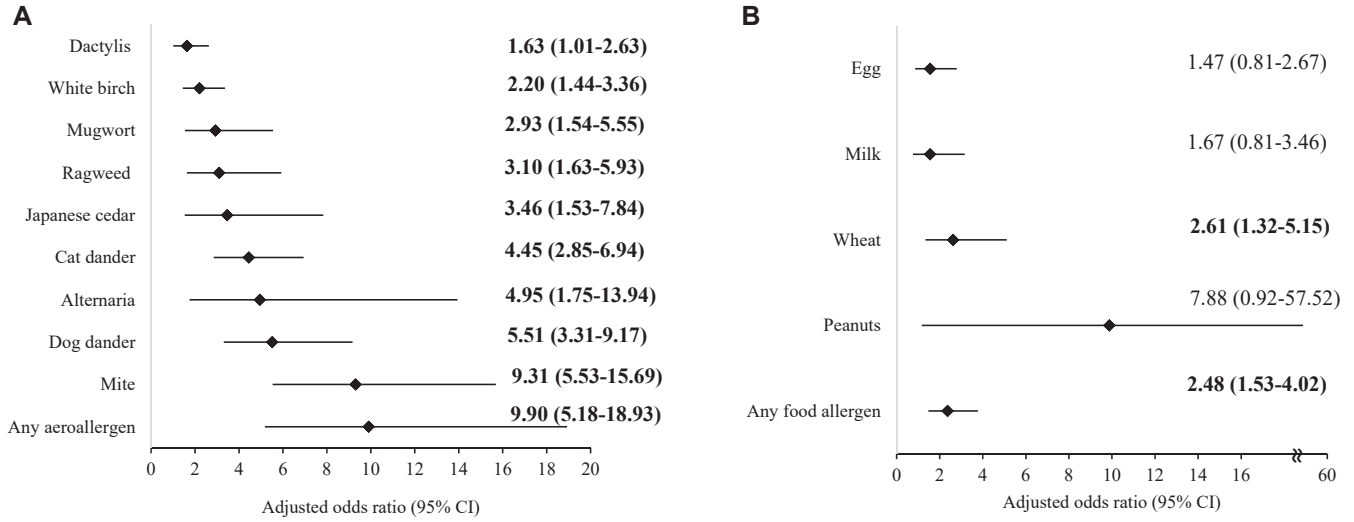

FIG 2. Adjusted logistic regression analysis results for high blood eosinophil (>300 cells/μL) associated with (**A**) inhaled and (**B**) food allergen sensitization (n = 428). Adjusted for sex, age (months), and second-hand exposure to tobacco smoke. Bold font indicates significant association.

girls (see Table E9 in this article's Online Repository at www.jaci-global.org).

To clarify the possible mechanism of aeroallergen and food allergen sensitization with wheeze, we examined the association of sensitization with T2 biomarkers in the Hokkaido birth cohort. We found that sensitization to all aeroallergens was associated with a high blood eosinophil count (≥300 cells/μL) in adjusted models (Fig 2, *A*; see Table E10 in this article's Online Repository at www.jaci-global.org). Most aeroallergens, including ragweed (aOR, 2.34; 1.23-4.42), Japanese cedar (aOR, 2.94, 95% CI, 1.32-6.53), cat dander (aOR, 7.32; 95% CI, 4.50-11.91), dog dander (aOR, 8.26; 95% CI, 4.88-13.97), and mite (aOR, 15.72; 95% CI, 7.36-33.55) were associated with high FENO levels (≥35 parts per billion) (Fig 3, *A*; see Table E11 in this article's Online Repository

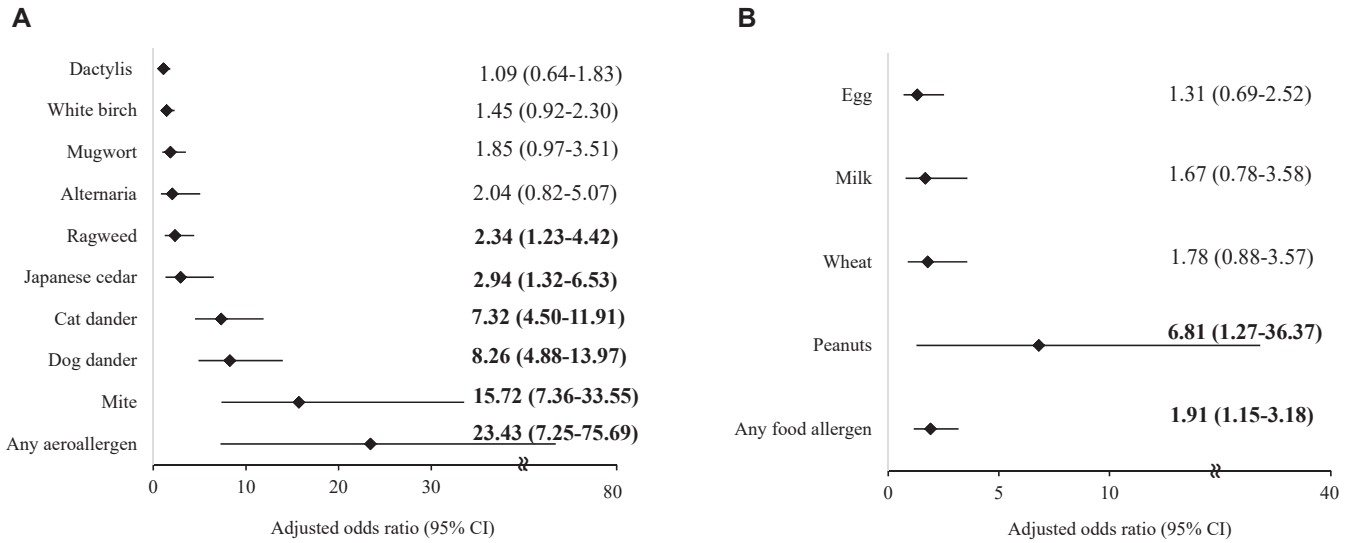

FIG 3. Adjusted logistic regression analysis results for high FENO (>35 ppb) associated with (**A**) inhaled and (**B**) food allergen sensitization (n = 428). *ppb*, Parts per billion. Adjusted for sex, age (months), and second-hand exposure to tobacco smoke. Bold font indicates a significant association. The T2-high phenotype is defined as a blood eosinophil count greater than 300 cells/μL and FENO level greater than 35 ppb.

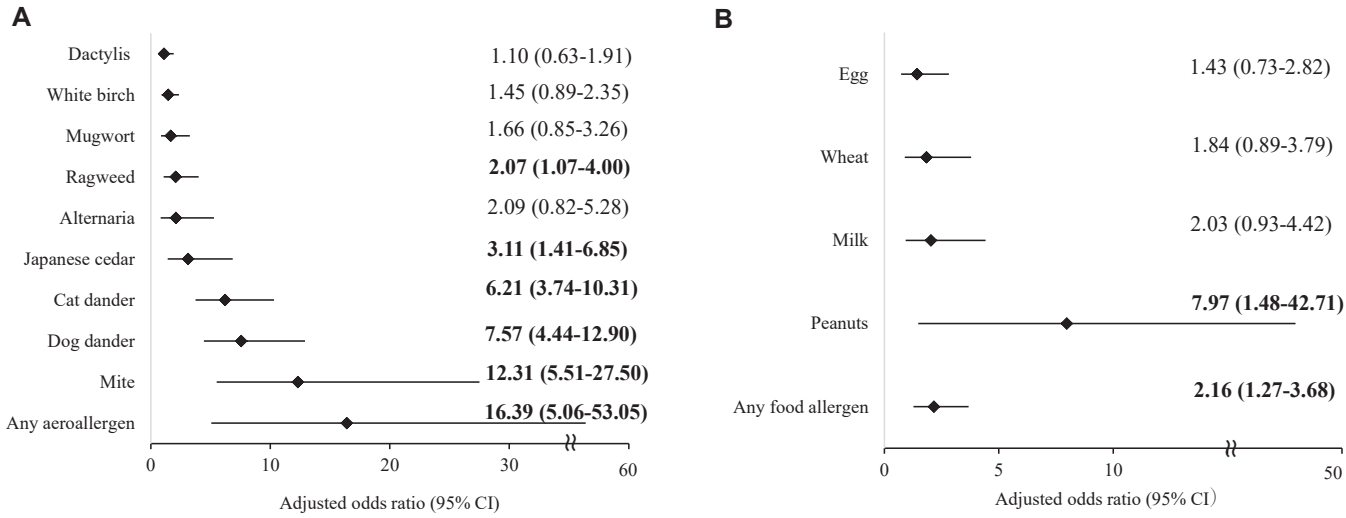

FIG 4. Adjusted logistic regression analysis results for association of (**A**) inhaled and (**B**) food allergen sensitization with the T2-high phenotype (n = 428). Adjusted for sex, age (months), and second-hand exposure to tobacco smoke. Bold font indicates significant association.

at www.jaci-global.org). However, food allergen sensitizations did not exhibit considerable association with T2 biomarkers, except association of wheat sensitization with blood eosinophil count (aOR, 2.61; 95% CI, 1.32-5.15). Also, sensitization to peanuts positively correlated with FENO levels (Fig 2, *B*, and Fig 3, *B*; see Tables E12 and E13 in this article's Online Repository at www.jaci-global.org). T2-high phenotype, defined as blood eosinophil count greater than or equal to 300 cells/μL and FENO greater than or equal to 35 parts per billion, observed in 26.1% of children (n = 92), was associated with aeroallergen sensitization, including ragweed (aOR, 2.07; 95% CI, 1.07-4.00), Japanese cedar (aOR, 3.11; 95% CI, 1.41-6.85), cat dander (aOR, 6.21; 95% CI, 3.74-10.31), dog dander (aOR, 7.57; 95% CI, 4.44-12.90), and mite (aOR, 12.31; 95% CI, 5.51-27.50) (Fig 4, *A*; see Table E14 in this article's Online Repository at www.jaci-global.org). In contrast, we did not observe any association between T2-high phenotype and food allergen sensitization except peanut sensitization (Fig 4, *B*; see Table E15 in this article's Online Repository at www.jaci-global.org). Sensitization to food allergens, though not aeroallergens, was associated with a higher wheeze prevalence in the Hokkaido birth cohort than that in the control group (without any sensitization to aeroallergens and food allergens) (Fig 5, *A*; see Table E16 in this article's Online Repository at www.jaci-global.org). Notably, both aeroallergen and food allergen sensitization did not exhibit any synergic effect on wheeze prevalence. Blood eosinophil counts and FENO levels were higher in the aeroallergen sensitization group than in the food allergen sensitization group (Fig 5, *B* and *C*; Table E16).

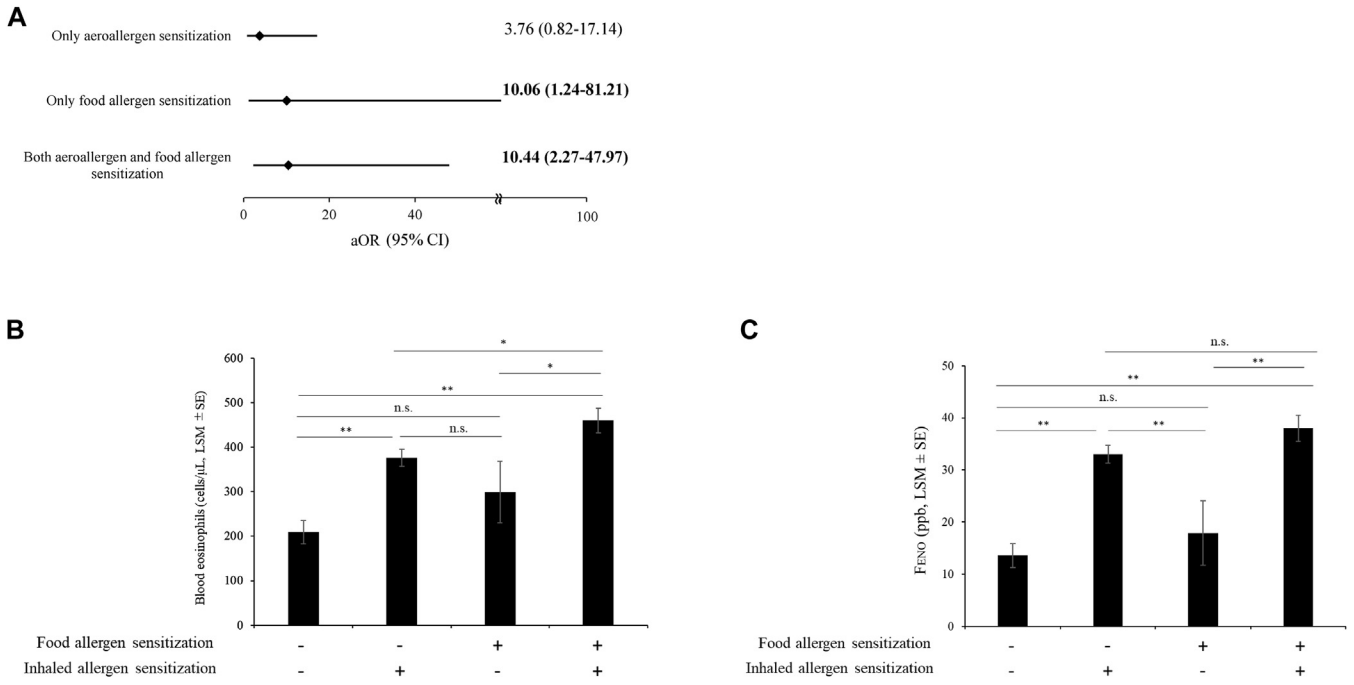

FIG 5. (**A**) Wheeze prevalence and (**B** and **C**) T2 biomarker levels stratified by presence or absence of aeroallergen and food allergen sensitization. *LSM*, Least-square means; *ppb*, parts per billion. Bold font indicates significant association. *Compared with the control group (no aeroallergen and food allergen sensitization), adjusted for sex, age (months), and second-hand exposure to tobacco smoke. No sensitization to inhaled and food allergens was used as a control group.

DISCUSSION

In this study, we measured the IgE response to 13 common allergens (9 aeroallergens and 4 food allergens) in school-age children from a population-based birth cohort. In total, 70.5% and 22.3% of children were sensitized to at least 1 aeroallergen and food allergen, respectively. Sensitization to food allergens, especially wheat, exhibited a higher association with the prevalence of wheeze than did sensitization to aeroallergens. This association of wheat sensitization with wheeze in Asian children was confirmed using replication analysis of the IOW birth cohort, which included European children. In biomarker analysis, we observed that sensitization to only aeroallergens was associated with the T2 phenotype, suggesting that in children, the wheat sensitization may not be associated with the T2-high phenotype.

Previous studies reported that aeroallergen sensitization is associated with an increased risk of wheeze.[7,30] In our study, notably, sensitization to any food allergen exhibited more significant associations with wheeze than that to aeroallergens. This association persisted even in the adjusted models. However, the association of any aeroallergen with wheeze was attenuated after controlling for food allergen sensitization.

The prevalence of wheat sensitization in the Hokkaido birth cohort was higher than that in the IOW birth cohort (9.5% vs 2.3%, respectively). Previous studies revealed that wheat and buckwheat are common food allergens in Japanese and Korean children.[31,32] Notably, we found the same association of wheat sensitization with wheeze in 2 independent pediatric populations with different prevalence of wheat sensitization. Therefore, assessment of food allergen sensitization, in addition to aeroallergens, is required to assess the risk of wheeze and asthma in children regardless of their race and prevalence of sensitization.

The European Community Respiratory Health Survey assessed more than 100 allergens among adults (371 without asthma and 96 with asthma) and found that sensitization to only food allergens (without pollen and perennial allergen sensitization) was not associated with asthma prevalence and FENO levels.[19] However, food allergen sensitization was associated with asthma and FENO levels in participants with pollen sensitization. Although the authors considered a global indicator for more than 20 food allergen sensitizations, data on sensitization to specific food allergens were not provided. Notably, the prevalence of wheat sensitization was zero,[19] which is different in Asian populations.[31,32] Another study reported independent associations of aeroallergens and food allergens (7 allergens, including wheat) with high blood eosinophil count and FENO level in asthma.[20] However, data on the association of individual food allergen sensitization with T2 biomarkers were unavailable. We also found a marginal association of food allergens (sensitization to any examined 4 food allergens) with the T2-high phenotype; however, when we looked at individual food allergens, no association with the T2 phenotype was detected. To our knowledge, our study is the first to demonstrate an association between wheat sensitization and asthma, indicating that individual food allergens may induce wheeze and asthma development.

Wheat is a potent allergen, and baker's asthma in adults is caused by the direct exposure of airways to flour.[33] sIgE antibodies against cereal flours such as wheat, rye, or barley are most often found in baker's asthma. Recent studies demonstrated that nonceliac wheat sensitivity is an innate immune reaction to wheat by amylase trypsin inhibitors (ATIs); however, gluten proteins do not have such activity.[34,35] Wheat ATIs activate myeloid and antigen-presenting cells such as monocytes, macrophages,

and dendritic cells of the intestinal mucosa to produce inflammatory cytokines and chemokines, such as IL-8, TNF-α, or monocyte chemotactic protein-1, via the engagement of Toll-like receptor 4.[34] Two recent murine studies have revealed that dietary wheat ATIs exacerbate allergic airway inflammation and hyperresponsiveness in mice.[21,22] Notably, ATIs exhibited their immunostimulatory potential in PBMC-engrafted mice even in the absence of the respective aeroallergen. This was observed in all humanized mice irrespective of the donor's sensitization status against wheat because most of the donors displayed no or only extremely low IgE titers against wheat or ATIs. Moreover, ATI-induced inflammation was much lower in mice engrafted with PBMCs from healthy donors without allergies than in the control group mice, further supporting the existing evidence that ATIs serve as adjuvants of preexisting T-cell immunity and reduce allergic sensitization rather than functioning as an allergen.

Dietary ATI-induced lung inflammation is dependent on both human IgE and Toll-like receptor 4.[21,22] A gluten-free (ATI-free) diet prevented the recruitment of eosinophils and airway hyperresponsiveness in ovalbumin-sensitized and ovalbumin-challenged mice. This effect could be eliminated via human Toll-like receptor 4 (the ATI receptor on intestinal myeloid cells) blockade and human IgE inactivation using the humanized anti-human IgE mAb omalizumab.[22] Collectively, the findings of the previous animal studies and those of our study suggest the importance of nutritional activation of allergic airway inflammation and exploring preventive strategies for childhood-onset asthma. In contrast to T2-high asthma, for T2-non/low asthma, specific clinically applicable biomarkers have not been identified. These patients have a poor response to corticosteroids, and no targeted biologic agents are available for treatment.[36,37] Therefore, the presence of wheat allergy or wheat sensitization (by measuring sIgE) may help in the prediction, early diagnosis, and management of asthma, especially T2-non/low asthma. Furthermore, omalizumab or ATI-targeting antibodies may improve outcomes in patients with T2-low asthma, who comprise approximately 50% of all patients with asthma.

Hokkaido is the major area in Japan for wheat production, accounting for two-thirds of the domestic wheat production. Wheat is one of the most important cereal crops globally, the second most consumed cereal after rice, and can be grown in various climatic conditions. It is present in many foods and drinks all over the world. China is the largest wheat producer, followed by India, the Russian Federation, the United States, and France, producing several times more wheat than Japan.[38,39] In countries with strong wheat dietary traditions, including those in Northern Africa, West/Central Asia, and Europe, per capita wheat consumption is particularly high.[39] Therefore, the current study's findings may shed light on a new aspect of wheat sensitization's global impact on allergic outcomes, and more studies are necessary to assess such impact in the future.

This study has several strengths. In this study, the results were obtained from the analysis of the Hokkaido birth cohort, which is a well-characterized population-based prospective birth cohort. Furthermore, the association of wheat sensitization with wheeze in the Hokkaido birth cohort was replicated among the general pediatric population with different ethnicity, namely, the IOW birth cohort, another well-characterized birth cohort. To prevent selection bias, we did not inform the study participants and their parents that the focus of the study was on allergic outcomes when requesting their participation. Also, the sociodemographic characteristics of the participants and families in the current analysis were comparable with those of the original cohort.[24] Therefore, we believe that although the present study has a modest sample size, the findings can be extrapolated to the general population. In addition to questionnaire data, all children visited a pediatrician, and a trained nurse collected detailed information on associated diseases and drug history. Among our study participants, 2 children were using inhaled corticosteroids, and 1, an oral steroid. We excluded these children, and the results remained unchanged in the sensitivity analysis. Moreover, sensitization to several common aeroallergens and food allergens was examined in a single laboratory.

This study has some limitations. First, the cross-sectional study design limits the conclusion of a causal relationship between food and aeroallergen sensitization and wheeze. Second, this study has a modest sample size and consequent low number of children with wheeze (n = 32). Such a relatively small number of wheezers may result in a lack of precision in the point estimates with large CIs, and influence the association of some allergen sensitization with the examined outcome. We compared mother-child pairs invited to the current study when children were 10 but did not participate (n = 1453) versus participants in the current analysis (n = 428). We found that participants in the current study had higher maternal education and a lower maternal smoking rate during pregnancy (see Table E17 in this article's Online Repository at www.jaci-global.org). Therefore, we cannot rule out the possibility of selection bias in the current analysis. In our epidemiological study, we cannot clearly demonstrate the differential impact of food versus aeroallergen sensitizations on wheeze prevalence, and there is the possibility of a multisensitization effect on wheeze. Therefore, further studies, including laboratory studies, are necessary to clarify the biological basis of the current findings.

In conclusion, the present study examined the association between sensitization to various aero- and food allergens and wheeze prevalence in a population-based birth cohort of school-age children representative of the general pediatric population. We observed that wheat sensitization had a positive association with wheeze prevalence compared with aeroallergens, which are key etiological factors in asthma pathophysiology. In contrast to aeroallergens, food allergens, including wheat sensitization, were not associated with the T2-high phenotype. The findings highlight our limited understanding of the association between possible food allergens and airway inflammation and diseases. Therefore, more longitudinal studies are required to replicate these findings and provide further insights, and more mechanistic studies are needed to develop effective interventional strategies.

DISCLOSURE STATEMENT

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