

Patterns in the Development of Pediatric Allergy

Stanislaw J. Gabryszewski, MD, PhD,^a Jesse Dudley, MS,^b Di Shu, PhD,^{b,c} Jennifer A. Faerber, PhD,^b Robert W. Grundmeier, MD,^b Alexander G. Fiks, MD, MSCE,^b David A. Hill, MD, PhD^{a,d}

abstract

OBJECTIVES: Describe clinical and epidemiologic patterns of pediatric allergy using longitudinal electronic health records (EHRs) from a multistate consortium of US practices.

METHODS: Using the multistate Comparative Effectiveness Research through Collaborative Electronic Reporting EHR database, we defined a cohort of 218 485 children (0–18 years) who were observed for ≥ 5 years between 1999 and 2020. Children with atopic dermatitis (AD), immunoglobulin E–mediated food allergy (IgE-FA), asthma, allergic rhinitis (AR), and eosinophilic esophagitis (EoE) were identified using a combination of diagnosis codes and medication prescriptions. We determined age at diagnosis, cumulative incidence, and allergic comorbidity.

RESULTS: Allergic disease cumulative (and peak age of) incidence was 10.3% (4 months) for AD, 4.0% (13 months) for IgE-FA, 20.1% (13 months) for asthma, 19.7% (26 months) for AR, and 0.11% (35 months) for EoE. The most diagnosed IgE-FAs were peanut (1.9%), egg (0.8%), and shellfish (0.6%). A total of 13.4% of children had ≥ 2 allergic conditions, and respiratory allergies (ie, asthma, AR) were commonly comorbid with each other, and with other allergic conditions.

CONCLUSIONS: We detail pediatric allergy patterns using longitudinal, health care provider-based data from EHR systems across multiple US states and varied pediatric practice types. Our results support the population-level allergic march progression and indicate high rates of comorbidity among children with food and respiratory allergies.



^aDivision of Allergy and Immunology, and ^bClinical Futures, Department of Biomedical and Health Informatics, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and ^cDepartment of Biostatistics, Epidemiology and Informatics, and ^dDepartment of Pediatrics and Institute for Immunology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

Drs Gabryszewski and Hill conceptualized the study, performed data analysis, drafted the initial manuscript, and reviewed and revised the manuscript; Ms Dudley and Drs Shu, Faerber, Grundmeier, and Fiks were involved in study design, data collection and analysis, and review and revision of the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Address correspondence to David A. Hill, MD, PhD, Division of Allergy and Immunology, Children's Hospital of Philadelphia, Abramson Research Building, 1208B, 3615 Civic Center Blvd, Philadelphia, PA 19104. E-mail: hilld3@chop.edu

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WHAT'S KNOWN ON THIS SUBJECT: Analysis of electronic health record–based clinical cohorts is an emerging approach for the longitudinal study of disease patterns that has not been previously applied to broadly study US patterns of pediatric allergy.

WHAT THIS STUDY ADDS: Our study uses data from a multistate electronic health record consortium to describe patterns of health care provider–diagnosed pediatric allergy. Our results support the population-level allergic march paradigm and indicate marked comorbidity among children with food and/or respiratory allergies.

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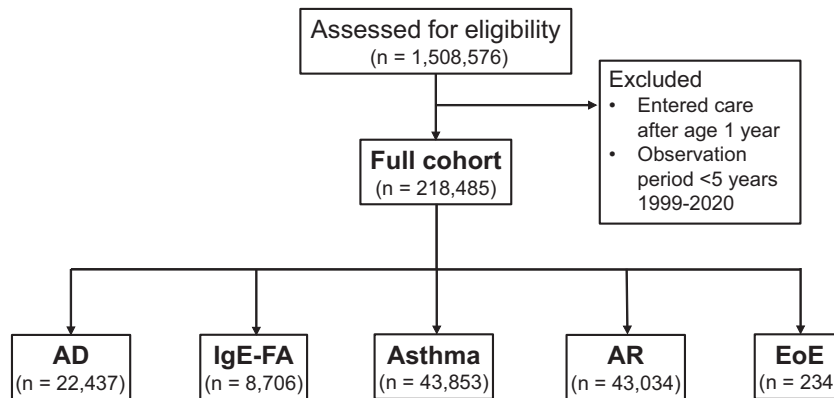


FIGURE 1

Summary flow diagram of full cohort and allergic disease subcohorts and exclusions. Consort diagram of the generation of the full and disease cohorts. AD, atopic dermatitis; AR, allergic rhinitis; EoE, eosinophilic esophagitis; IgE-FA, immunoglobulin E-mediated food allergy.

Pediatric allergic diseases are associated with impaired quality of life, absenteeism, and significant health care expenses.¹⁻⁴ The most common allergic manifestations in children include atopic dermatitis (AD), systemic (ie, anaphylactic) immunoglobulin E-mediated food allergy (IgE-FA), asthma, allergic rhinitis (AR), and eosinophilic esophagitis (EoE).⁵ Together, these conditions are among the most common chronic diseases of childhood, affecting approximately 1 in 5 children.⁶

Assessing allergic disease patterns is necessary to identify risk factors, detect disparate health outcomes, and inform clinical and research efforts.⁷⁻⁹ To date, allergic disease epidemiology in the United States has been measured largely via retrospective surveys.¹⁰⁻¹⁴ A methodologic strength of survey-based approaches is the ability to construct nationally representative cohorts. However, surveys are also subject to reporting bias.¹⁵⁻¹⁷ An emerging and complementary strategy is analysis of electronic health record (EHR)-based clinical cohorts. Strengths of EHR-based analyses include their use of provider-based diagnosis and prescription data and their longitudinal nature, enabling examinations of disease onset, risk factors, and comorbidities over time.¹⁸⁻²⁰ To date, EHR-based studies of US pediatric allergy patterns have not been performed using multistate cohorts.^{5,6,21,22}

To address this need, we conducted a detailed examination of pediatric allergy patterns using the Comparative Effectiveness Research through Collaborative Electronic Reporting (CER²) Consortium database, comprising more than 1 million children across multiple independent primary care practices and health systems within the United States.²³ For each allergic disease, we determined age at diagnosis, cumulative incidence, and allergic disease comorbidities. Our study details clinical and epidemiologic features of pediatric allergy as managed by a consortium of primary care practices and health systems across the United States.

METHODS

Subject Identification and Study Design

Using the American Academy of Pediatrics CER² EHR database, a Health Insurance Portability and Accountability Act-limited database, we defined a retrospective birth cohort of 218 485 US children who established care before their first birthday and were observed for at least 5 years between their first and last office visits through age 18 years, between 1999 and 2020. Diagnosis codes and medication prescriptions were used to identify children with AD, IgE-FA, asthma, AR, and EoE. Additional clinical descriptors were used to identify individual IgE-FAs, as detailed later. In addition to abstracting birth year and sex (a separate variable for gender was not available), we abstracted data on self-reported racial/ethnic designations to assess for factors that might influence disease rates.²⁴ The race category “Unknown” includes subjects with self-identified unknown race, whereas “Other” comprises all other entries including “American Indian or Alaska native,” “Mixed racial group,” and “Race not available.” Geographic distribution (Supplemental Table 7) was determined using subject’s ZIP codes. Urbanicity (Supplemental Table 8) was determined by merging subject’s ZIP codes with 2010 Rural-Urban Commuting Area codes.²⁵ Statistical analyses were performed using multivariable logistic regression with membership in the allergic disease subgroup of interest as the outcome. The study was approved by the American Academy of Pediatrics institutional review board and deemed not to be human subjects research by the Children’s Hospital of Philadelphia institutional review board.

Disease Definitions and Epidemiologic Analyses

To identify children with AD, IgE-FA, asthma, AR, and EoE (Fig 1), the CER² database was queried for the presence of relevant International Classification of Diseases Ninth Revision

TABLE 1 Demographic Features of Total and Allergic Disease-Specific Cohorts

Variable	All		AD			IgE-FA			Asthma			AR			EoE		
	<i>n</i>	%	<i>n</i>	%	<i>P</i>	<i>n</i>	%	<i>P</i>	<i>n</i>	%	<i>P</i>	<i>n</i>	%	<i>P</i>	<i>n</i>	%	<i>P</i>
Sex ^a																	
Male	111 577	51.1	11 983	53.4	—	5100	58.6	—	26 015	59.3	—	24 002	55.8	—	166	70.9	—
Female	106 907	48.9	10 454	46.6	<.0001	3606	41.4	<.0001	17 837	40.7	<.0001	19 031	44.2	<.0001	68	29.1	<.0001
Race ^b																	
White	103 942	47.6	6 778	30.2	—	4234	48.6	—	17 141	39.1	—	18 725	43.5	—	141	60.3	—
Black	69 796	31.9	11 489	51.3	<.0001	2861	32.9	<.01	19 477	44.4	<.0001	18 200	42.3	<.0001	54	23.1	<.01
Asian or Pacific Islander	6210	2.8	908	4.0	<.0001	513	5.9	<.0001	1098	2.5	NS	1092	2.5	NS	13	5.5	NS
Unknown	14 393	6.6	1439	6.4	<.0001	577	6.6	<.0001	2761	6.3	NS	2457	5.7	<.0001	14	6.0	<.05
Other	24 144	11.1	1823	8.1	<.0001	521	6.0	NS	3376	7.7	NS	2560	6.0	<.0001	12	5.1	NS
Ethnicity																	
Non-Hispanic	166 521	76.2	18 074	80.5	—	7657	88.0	—	35 125	80.1	—	36 463	84.7	—	202	86.3	—
Hispanic	22 195	10.2	2102	9.4	<.0001	516	5.9	<.0001	4497	10.3	<.0001	3871	9.0	<.0001	24	10.3	NS
Other	29 769	13.6	2261	10.1	<.0001	533	6.1	<.0001	4231	9.6	<.0001	2700	6.3	<.0001	8	3.4	<.01
Birth year																	
Pre-2000	3337	1.5	187	0.8	—	36	0.4	—	676	1.5	—	505	1.2	—	2	0.9	—
2000–2004	41 898	19.2	5226	23.3	<.0001	1294	14.9	<.05	9877	22.5	<.0001	9417	21.9	NS	30	12.8	NS
2005–2009	94 489	43.3	10 562	47.1	<.0001	4139	47.5	<.01	20 074	45.8	<.0001	21 023	48.8	<.0001	127	54.3	NS
2010–2014	76 919	35.2	6286	28.0	NS	3156	36.3	NS	12 988	29.6	<.0001	11 915	27.7	<.0001	74	31.6	NS
2015 or later	1842	0.8	176	0.8	NS	81	0.9	NS	238	0.6	<.0001	174	0.4	<.0001	1	0.4	NS
Total	218 485	100.0	22 437	100.0	—	8706	100.0	—	43 853	100.0	—	43 034	100.0	—	234	100.0	—

Race was not available for 20 343 (9.3% of total) subjects. *P* value presented in boldface if $<.05$. AD, atopic dermatitis; AR, allergic rhinitis; EoE, eosinophilic esophagitis; IgE-FA, immunoglobulin E-mediated food allergy; NS, not significant.

^aIn the full cohort and asthma and AR subcohorts, sex was unknown for 1 subject.

^bThe race category “Unknown” represents subjects with self-identified unknown race, whereas “Other” comprises all other entries including “American Indian or Alaska Native,” “Mixed racial group,” and “Race not available.”

or Tenth Revision diagnosis codes and/or Systematized Nomenclature of Medicine codes (Supplemental Table 9). Search terms were specified to identify individual IgE-FAs (Supplemental Table 10). Disease-specific diagnosis codes were required during at least 2 clinical visits separated by at least 6 months, with the exception of EoE, for which only 1 visit was required as this condition is commonly managed by specialists following initial diagnosis. Codes corresponding to “reactive airway disease” and asthma diagnosis before age 1 year were not included in our asthma subcohort definition (Supplemental Table 9).^{5,6} Similarly, to define IgE-FA, we did not include diagnosis codes related to lactose intolerance, celiac disease, or milk protein sensitivity (Supplemental Table 9). Finally, we required presence of relevant prescriptions for the asthma (asthma medications on at least 2 separate calendar days) and IgE-FA (epinephrine on at least 1 calendar day) subcohorts (Supplemental Table 9). Similar disease criteria showed concordance with established practice parameters on chart review in a regional EHR-based analysis.^{5,6} R software (version 3.6) was used to determine incidence rate (ie, new cases per given age range) and cumulative incidence (ie, total cases per given age range). Descriptive statistics were also obtained in a sensitivity analysis with a minimum observation period of 2 years rather than 5 years.

RESULTS

Birth and Disease Cohort Demographic Features

Generation of disease cohorts is illustrated in Fig 1. Demographics and geographic distribution of subjects are detailed in Table 1 and Supplemental Table 7, respectively. A total of 78.5% of children were born between 2005 and 2014 (Table 1). The sex breakdown of the total cohort was approximately equal (51.1% male vs. 48.9% female), with a slight male predominance in allergic subcohorts, most notably for EoE (70.9% male vs. 29.1% female). The total cohort was 47.6% White, 31.9% Black, 2.8% Asian or Pacific Islander, and 17.7% Other or Unknown. Regarding ethnicity, the cohort was 10.2% Hispanic, 76.2% non-Hispanic, and 13.6% Other. In allergic subcohorts, compared with the full cohort, there was significantly higher representation of Black children for AD and asthma, significantly higher representation of White children for EoE, and significantly lower representation of Hispanic children for IgE-FA. Most subjects (89.5%) were located in metropolitan cores, a proxy for urbanized areas (Supplemental Table 8).²⁵ The mean observation period for the cohort was 9.3 years (Supplemental Table 11).

TABLE 2 Age at Diagnosis of Allergic Conditions

Age Range (mo)	AD		IgE-FA		Asthma		AR		EoE	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
0–<6	8029	35.8	510	5.9	0	0.0	302	0.7	1	0.4
6–<12	4216	18.8	1199	13.8	0	0.0	2031	4.7	5	2.1
12–<18	2659	11.9	1819	20.9	13 143	30.0	3231	7.5	14	6.0
18–<24	1540	6.9	883	10.1	4914	11.2	3284	7.6	11	4.7
24–<30	1188	5.3	726	8.3	4272	9.7	3910	9.1	16	6.8
30–<36	704	3.1	437	5.0	3165	7.2	3214	7.5	17	7.3
36–<42	741	3.3	479	5.5	3247	7.4	3885	9.0	15	6.4
42–<48	466	2.1	283	3.3	2400	5.5	2898	6.7	15	6.4
48–<54	559	2.5	371	4.3	2512	5.7	3505	8.1	9	3.8
54–<60	303	1.4	225	2.6	1747	4.0	2297	5.3	10	4.3
≥60	2032	9.1	1774	20.4	8453	19.3	14 479	33.6	121	51.7
Total	22 437	100.0	8706	100.0	43 853	100.0	43 034	100.0	234	100.0

AD, atopic dermatitis; AR, allergic rhinitis; EoE, eosinophilic esophagitis; IgE-FA, immunoglobulin E-mediated food allergy.

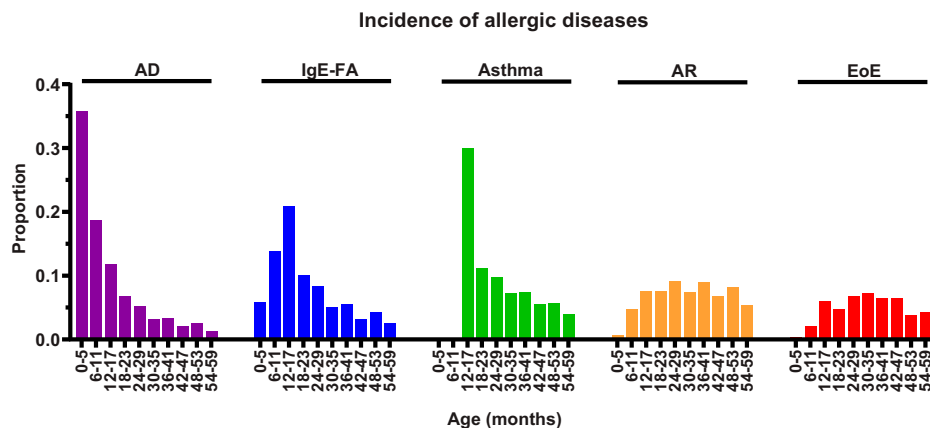
Age at Diagnosis, Incidence, and Cumulative Incidence of Allergic Diseases

For each allergic manifestation, we determined age at diagnosis (Table 2), distribution of incidence rates (Fig 2), and cumulative incidence (Table 3). The median (and interquartile range) age at diagnosis was 10 (4–25) months for AD, 23 (13–50) months for IgE-FA, 29 (16–52) months for asthma, 45 (27–69) months for AR, and 62 (33–97) months for EoE. The peak incidence for AD, IgE-FA, asthma, AR, and EoE occurred at 4 months, 13 months, 13 months, 26 months, and 35 months, respectively (Fig 2; Table 2). We also determined the cumulative incidence, a proxy for disease prevalence, for each allergic manifestation (Table 3). For all children (0–18 years), the cumulative incidence was 10.3% for AD, 4.0% for IgE-FA, 20.1% for asthma, 19.7% for AR, and 0.11% for EoE (Table 3). A total of 61.1% (26 800 of 43 853) of children with asthma retained their diagnosis in the last year of their observation period. We note that a sensitivity analysis

with a minimum observation period of 2 rather than 5 years ($n = 366\,056$ subjects) yielded comparable results for cumulative incidences and peak age of onset (data not shown).

Age at Diagnosis, Incidence, and Cumulative Incidence of IgE-Mediated Food Allergies

We next determined age at diagnosis (Table 4; Supplemental Table 13), distribution of incidence rates (Fig 3), and cumulative incidence (Table 5; Supplemental Table 14) for individual IgE-FA allergens. The median (and interquartile range) age at diagnosis was 12 (7–19) months for milk, 16 (12–34) months for egg, 18 (11–49) months for wheat, 25 (15–49) months for peanut, 26 (13–65) months for soy, 40 (22–72) months for fish, 52 (28–83) months for sesame, 54 (30–86) months for shellfish, and 58 (34–86) months for tree nuts. The peak age of incidence was 12 months for milk, 13 months for egg and wheat, 15 months for peanut

**FIGURE 2**

Distribution of allergic condition incidence by age. Proportions of initial diagnoses of atopic dermatitis (AD), immunoglobulin E-mediated food allergy (IgE-FA), asthma, allergic rhinitis (AR), or eosinophilic esophagitis (EoE) by age intervals (months). For asthma, incidence before age 1 year was excluded as per the disease definition criteria.

TABLE 3 Cumulative Incidence of Allergic Conditions

Age Range (y)	AD		IgE-FA		Asthma		AR		EoE	
	n	%	n	%	n	%	n	%	n	%
0-<3	19 543	8.9	6336	2.9	31 141	14.3	22 753	10.4	94	0.04
0-<5	21 051	9.6	7412	3.4	38 312	17.5	32 982	15.1	139	0.06
0-<11	22 264	10.2	8500	3.9	43 219	19.8	42 154	19.3	210	0.10
0-<14	22 415	10.3	8665	4.0	43 778	20.0	42 930	19.6	229	0.10
0-18	22 437	10.3	8706	4.0	43 853	20.1	43 034	19.7	234	0.11

All reported percentages indicate the percentage of total subjects in the full cohort (n = 218 485) with the stated allergic disease. AD, atopic dermatitis; AR, allergic rhinitis; EoE, eosinophilic esophagitis; IgE-FA, immunoglobulin E-mediated food allergy.

and soy, 22 months for fish, 26 months for sesame, 28 months for shellfish, and 52 months for tree nuts (Fig 3).

During the first year of life, the most frequently diagnosed IgE-FA allergens were milk, egg, and peanut (45.6%, 23.9%, and 11.3% of initial diagnoses, respectively) (Table 4). Peanut, egg, and milk were the most prevalent food allergens during the first 5 years of life (cumulative incidences of 1.7%, 0.7%, and 0.4%, respectively) (Table 5). For children older than age 5 years, the most frequently diagnosed food allergens were peanut, tree nuts, and shellfish (18.7%, 48.5%, and 45.1% of initial diagnoses, respectively). The food allergens with the highest cumulative incidence overall were peanut (1.9%), egg (0.8%), and shellfish (0.6%). Of children with documented food allergens, 37.4% had allergy to two or more distinct foods (Table 6; Supplemental Table 12). Age at diagnosis and cumulative incidence data for individual tree nuts are shown in Supplemental Table 13 and Supplemental Table 14, respectively.

Allergic Comorbidities

Because a personal history of atopy is a risk factor for allergy progression in children, we next determined the portion of children with a specific allergy who were diagnosed with a comorbid allergic manifestation during the observation

period (Fig 4). We found that the respiratory allergies (ie, asthma and AR) were markedly comorbid with each other (43.9% of asthma subjects had AR, and 44.8% of AR subjects had asthma) as well as with other allergic manifestations (38.3%–39.7% of AD subjects, 46.9%–49.6% of IgE-FA subjects, and 54.7%–64.1% of EoE subjects had asthma and/or AR). Of subjects with IgE-FA, 33.1% were also diagnosed with AD. Furthermore, comorbidity with EoE was notably higher in subjects with IgE-FA (1.1%) compared with other allergic subcohorts (0.3% for AD, asthma, and AR). Notably, 40.6% of those with EoE were also diagnosed with IgE-FA. In the entire birth cohort, 23.3%, 9.9%, 2.8%, 0.6%, and 0.01% of children had 1, 2, 3, 4, or 5 allergic manifestations, respectively (Supplemental Figure 5). Allergic multimorbidity for each allergic subcohort is shown in Supplemental Figure 5.

DISCUSSION

Our analysis uses health care provider diagnosis data to inform our understanding of patterns of pediatric allergic disease across a multistate network of practices and health systems.²³ As practices and health systems shift to exclusive electronic documentation, the EHR represents a compendium of medical data that can be leveraged to define large patient cohorts, detect disease patterns, and identify disease-related risk factors to guide clinical and public health interventions.^{18,19} To our knowledge, our study is the first to determine pediatric allergic disease patterns across multiple US pediatric practices and health systems. This cohort is also unique in that it includes longitudinal data entered by primary care providers including pediatricians, family physicians, and advanced practice providers practicing in urban, suburban, and rural sites.²³ In using exclusively health care provider-based diagnostic data, our study minimizes bias (eg, recall bias) that is inherent to survey-based analyses, which rely on caregiver or patient-reported data.

TABLE 4 Age at Diagnosis of IgE-Mediated Food Allergies by Food Allergen

Age Range (mo)	Egg		Milk		Soy		Wheat		Fish		Shellfish		Peanut		Tree Nut		Sesame	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0-<6	62	3.6	196	19.3	21	7.9	2	1.6	12	1.6	24	1.8	109	2.6	33	2.7	1	0.2
6-<12	346	20.3	267	26.3	37	13.9	30	23.8	19	2.6	14	1.1	364	8.7	15	1.2	7	1.6
12-<18	510	29.9	266	26.2	40	15.0	30	23.8	88	12.0	96	7.3	930	22.1	56	4.5	44	10.2
18-<24	190	11.1	65	6.4	22	8.3	6	4.8	87	11.9	101	7.7	548	13.0	57	4.6	32	7.4
24-<30	109	6.4	34	3.4	21	7.9	10	7.9	70	9.6	92	7.0	447	10.6	95	7.6	38	8.8
30-<36	81	4.7	24	2.4	9	3.4	2	1.6	46	6.3	90	6.9	226	5.4	71	5.7	22	5.1
36-<42	78	4.6	24	2.4	7	2.6	9	7.1	53	7.3	89	6.8	295	7.0	90	7.2	33	7.6
42-<48	44	2.6	14	1.4	7	2.6	2	1.6	39	5.3	72	5.5	187	4.4	57	4.6	15	3.5
48-<54	58	3.4	21	2.1	21	7.9	6	4.8	48	6.6	79	6.0	208	4.9	105	8.4	28	6.5
54-<60	30	1.8	12	1.2	4	1.5	5	4.0	31	4.2	64	4.9	104	2.5	61	4.9	25	5.8
≥60	199	11.7	91	9.0	77	28.9	24	19.0	238	32.6	592	45.1	785	18.7	603	48.5	187	43.3
Total	1707	100.0	1014	100.0	266	100.0	126	100.0	731	100.0	1313	100.0	4203	100.0	1243	100.0	432	100.0

IgE, immunoglobulin E.

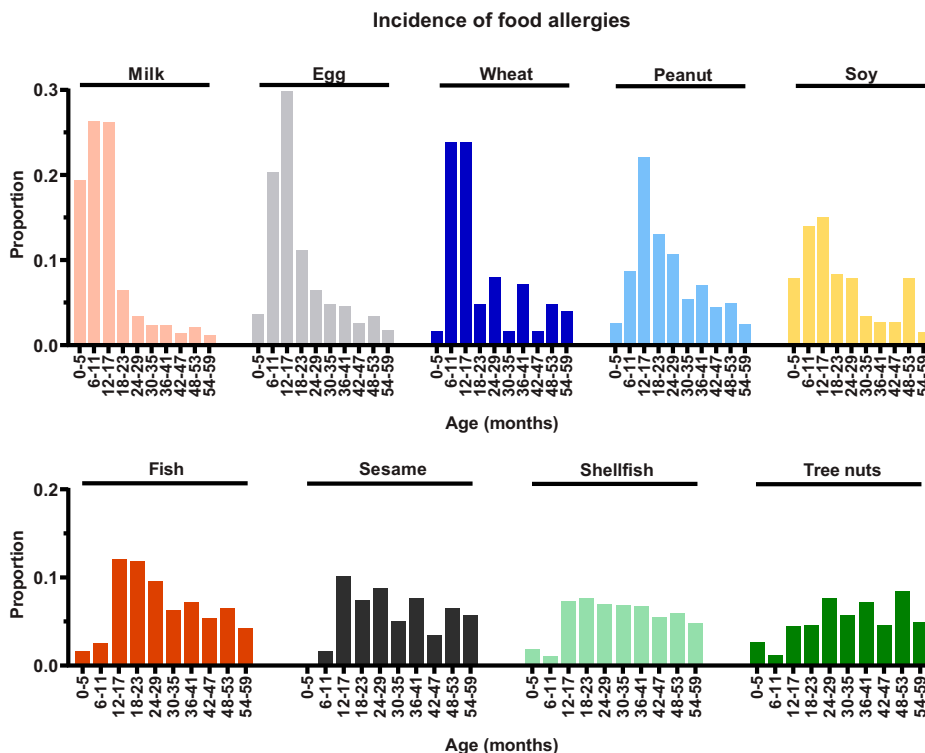


FIGURE 3 Distribution of individual immunoglobulin E–mediated food allergy incidence by age. Proportions of initial diagnoses of individual food allergies for milk, egg, wheat, peanut, soy, fish, sesame, shellfish, and tree nuts by age intervals (months).

The CER² database represents a nonrandom sample of health systems making comparisons with nationally representative surveys challenging. However, the allergic disease rates we measured are in general agreement with previously reported rates. For example, the overall cumulative incidence of AD in our study is in line with previous reports,^{5,10,26,27} and the cumulative incidence of IgE-FA is within the lower end of previously reported rates.^{6,10,11,12} We speculate that the latter finding reflects our intentional exclusion of multiple non-IgE-mediated (nonanaphylactic) food allergies. These are sometimes conflated with IgE-FAs, which are the primary cause of anaphylaxis in the pediatric population and that necessitate treatment with epinephrine in the case of systemic reactions.^{12,28} For individual food allergens, our reported rates were dependent on a child’s age, consistent with

the known natural histories of specific food allergies.²⁹ In our cohort, peanut, egg, and shellfish were the most common food allergens overall. Of note, although milk was recently reported as the second most common allergen using survey-based methods,²⁸ milk was fifth most common in our analysis, possibly because of our exclusion of non-IgE-mediated cow’s milk allergies and intolerances from our IgE-FA disease subcohort.

The cumulative incidence for asthma and AR aligns with figures reported in recent regional, EHR-based studies.^{5,6} Although the 2018 National Health Interview Survey estimates for the prevalence of hay fever, asthma, or respiratory allergy are 7.2% to 9.6%,¹⁰ considerably higher rates have been reported elsewhere, likely because of differences in definitions and populations studied. For example, studies of predominantly urban cohorts, like ours, have reported asthma

Age Range (y)	Egg		Milk		Soy		Wheat		Fish		Shellfish		Peanut		Tree Nut		Sesame	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0-<3	1420	0.65	890	0.41	164	0.07	91	0.04	414	0.19	578	0.26	3106	1.42	474	0.22	192	0.09
0-<5	1567	0.71	953	0.43	211	0.10	108	0.05	546	0.25	860	0.39	3666	1.67	789	0.36	287	0.13
0-<11	1685	0.77	1001	0.46	261	0.12	125	0.06	695	0.32	1220	0.56	4136	1.89	1151	0.52	399	0.18
0-<14	1702	0.78	1013	0.46	265	0.12	126	0.06	725	0.33	1294	0.59	4190	1.91	1236	0.56	427	0.19
0-18	1707	0.78	1014	0.46	266	0.12	126	0.06	731	0.33	1313	0.60	4205	1.92	1244	0.57	432	0.20

All reported percentages (%) indicate the percentage of total subjects in the full cohort (n = 218 485) with the stated food allergy. IgE, immunoglobulin E.

Food Allergen(s) (n)	Subjects	
	n	%
1	4290	62.6
2	1546	22.5
3	638	9.3
4	227	3.3
≥5	155	2.3
Total	6856	100.0

rates as high as 25%.³⁰ Likewise, AR prevalence as high as 43% has been reported.^{31,32} We note that the peak incidence of asthma in our cohort occurs during a period when 50% or more children may experience the clinically distinct and transient entity of reactive airway disease.³³⁻³⁵ Further, the majority of children with asthma in our cohort retained their asthma diagnosis in the last year of their observation period; however, the possibility that some subjects experienced transient wheeze cannot be excluded. With regard to rhinitis, given the common occurrence of rhinitis symptoms in children, it is possible that some clinicians might not

formally code cases of mild disease. Last, our observed cumulative incidence of EoE is similar to recent reports.^{5,36} This finding, and the later peak age of diagnosis of EoE relative to other allergic conditions, are of particular clinical relevance because EoE is among the least recognized allergic morbidities.

Our study lays the foundation for large-scale, longitudinal study of pediatric allergic disease patterns and potential associated risk factors that are readily available in the EHR. This is especially important as risk of allergy is modified by a complex and incompletely understood interplay of genetics and environmental factors, such as early life exposures, climate, air pollutants, and exposure to indoor and outdoor aeroallergens.³⁷⁻³⁹ Although there is variability with respect to the number and sequence of allergic conditions that children develop over time at the individual level, prior population-level studies have shed light on predictable sequences of allergy, a paradigm known as the allergic march.³⁷ In general, the incidence patterns in our study support the allergic march, with peak incidence of AD occurring first, consistent with the hypothesis that allergic sensitization via the skin is one mechanism by which allergy may develop later in life.³⁷ Furthermore, more than

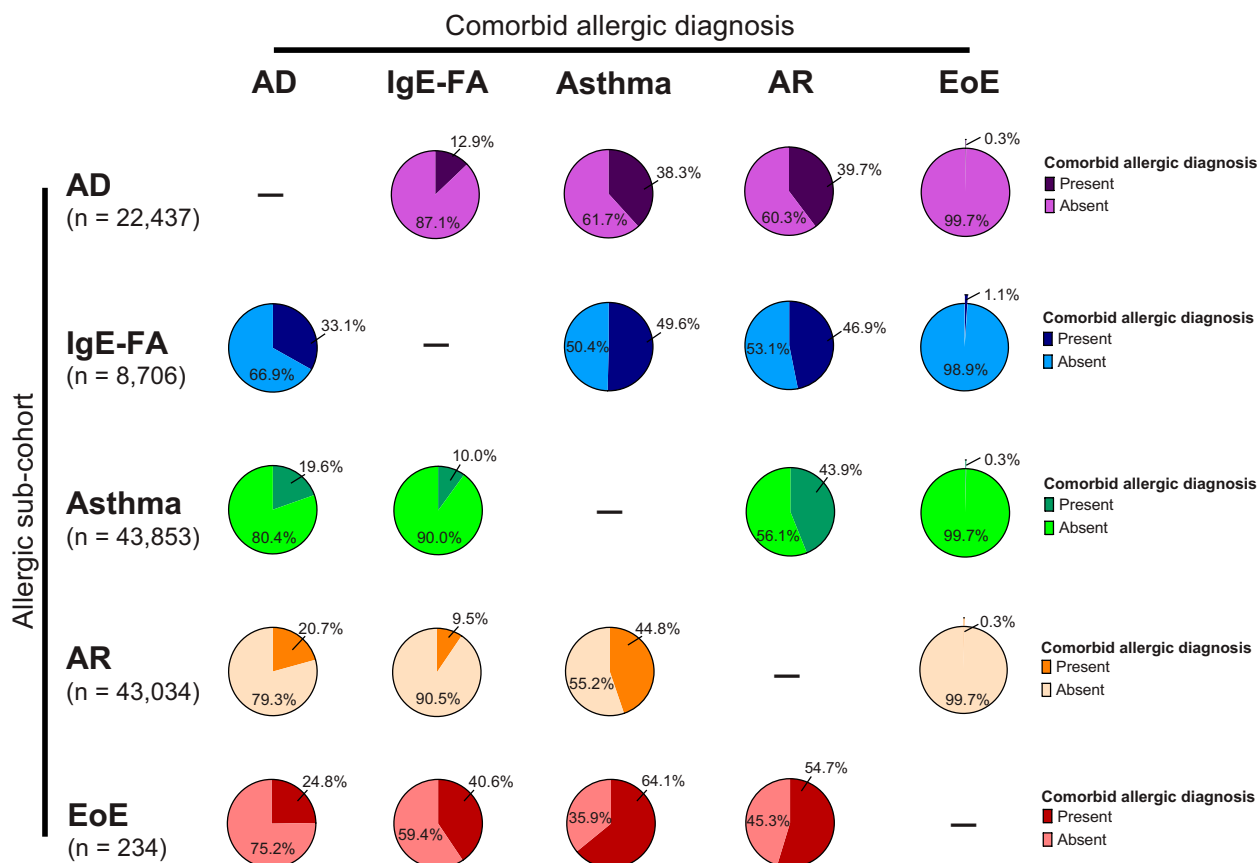


FIGURE 4 Allergic comorbidity. Percentage of subjects in allergic subcohorts who did or did not develop a comorbid allergic diagnosis. AD, atopic dermatitis; IgE-FA, immunoglobulin E-mediated food allergy; AR, allergic rhinitis; EoE, eosinophilic esophagitis.

13% of children in our cohort had at least 2 allergic manifestations, with several remarkable comorbidity patterns: (1) asthma and AR (ie, respiratory allergies) were markedly comorbid with each other, as were IgE-FA and EoE (ie, food allergies); (2) respiratory allergies were markedly (>38%) comorbid with AD and with food allergies; and (3) particularly high rates of comorbidity (>24%) with all allergic conditions were seen in the EoE subcohort. These patterns are relevant to both the primary care and specialist settings, because they encourage maintenance of clinical suspicion for possible development of 1 or more allergies later in life in children who have a single allergic condition. Future studies are needed to quantify risk relationships and define high-risk allergy populations that may benefit from screening.

Because disproportionate rates of adverse health outcomes occur in children from specific racial and ethnic minority backgrounds, it is imperative that studies of disease patterns are attuned to the complex interplay of factors that underlie these differences; for example, racism embedded in housing, employment, and education can adversely impact access to and delivery of care.^{9,40,41} Although it was not possible to determine specific insurance types as a proxy for socioeconomic status, a larger limitation of our dataset is that it does not capture those children who ultimately could not access care. Although it is impossible to delineate specific causes of disparities, we recognize several notable trends among the allergic subcohorts. First, we observed higher representation of Black children within the AD and respiratory allergy (ie, asthma and AR) subcohorts, consistent with previously reported higher prevalence and severity of AD, aeroallergen sensitization, and asthma prevalence in Black compared with White children.^{10,42,43} With the exception of asthma, we also detected lower rates of food, skin, and respiratory allergy in Hispanic children compared with non-Hispanic White and non-Hispanic Black children, consistent with prior reports.¹⁰ Last, we observed a higher representation of White male children in the EoE subcohort though with notably higher rates of EoE in non-White subjects than previously reported.^{5,44} In light of evolving knowledge about differences in clinical symptoms and endoscopic features of EoE in White versus non-White racial groups,⁴⁵ this could indicate that prior studies of EoE racial predominance were impacted by diagnostic and/or other biases. We note that, compared with the general US population, our cohort contains a higher representation of self-identified Black children (31.9% vs. 14%) and a lower representation of self-identified Hispanic children (10.2% vs. 26%), underscoring the caveat that this cohort is not nationally representative.⁴⁶

There are additional limitations of our study that should be considered. First, diagnosis codes do not necessarily indicate the presence of disease but may rather reflect clinical suspicion. To minimize the effects of these limitations, we

required at least 2 consecutive visits with a respective diagnosis code as well as prescriptions for relevant medications. We also note that in prior regional EHR-based studies, chart review of longitudinal medical records demonstrated good correlation between provider documentation and diagnosis code utilization.⁶ In addition, by requiring an observation period of at least 5 years, some children may be lost to follow-up. However, a sensitivity analysis of a 2-year observation period yielded comparable age-at-diagnosis and cumulative incidence findings, suggesting that subject loss is not a significant confounder. We further note that our requirement of a minimum 5-year observation period precludes rigorous analysis of annual incidence patterns, in particular during the final 5 years of the observation period (ie, 2016–2020). Although most allergic diagnoses considered (ie, AD, IgE-FA, asthma, and AR) are made based on clinical criteria that have been largely unchanged during our observation period,^{47–51} future studies should elucidate annual disease patterns, for example IgE-FA patterns following early food introduction guidelines.⁵²

In conclusion, EHR-based clinical cohorts are a valuable tool for the study of allergy disease rates and clinical patterns. Our study builds on prior, region-limited EHR analyses to describe features of provider-diagnosed allergy in a multistate cohort of pediatric practices and health systems. Our results support the population-level allergic march progression, and reveal high rates of allergic comorbidity among children, including those with food and respiratory allergies. Although direct comparisons with nationally representative surveys cannot be performed, we note that allergic disease prevalence rates in our cohort were within previously reported ranges, with notably lower rates of IgE-FA and higher rates of asthma and AR. Relevant future directions for the field include developing nationally representative EHR-based cohorts and identifying potentially modifiable disparities in disease outcomes.

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ABBREVIATIONS

AD: atopic dermatitis
AR: allergic rhinitis
CER²: Comparative Effectiveness Research through Collaborative Electronic Reporting
EHR: electronic health record
EoE: eosinophilic esophagitis
IgE-FA: immunoglobulin E-mediated food allergy

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