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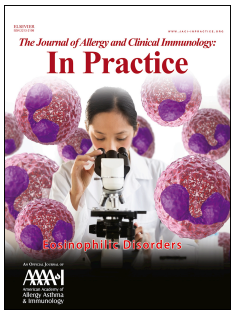

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Prevalence and Characteristics of Shellfish Allergy in the Pediatric Population of the United States

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Abstract

Background: Shellfish allergy (SA) is one of the most common food allergies causing anaphylaxis in adults and children. There is limited data showing the prevalence of SA in US children.

Objective: To determine the prevalence and reaction characteristics of SA in the US pediatric population.

Methods: A cross-sectional food allergy prevalence survey was administered via phone and web by the National Opinion Research Center at the University of Chicago from 2015-2016. Point prevalence SA estimates, complex survey weighted proportions and 95% confidence intervals were determined. Relative proportions of demographic characteristics were compared using weighted Pearson chi-square statistics.

Results: The prevalence of SA was 1.3% (95% CI 1.1–1.5) with more children allergic to crustacean (1.2%; 95% CI 1.0–1.3) than mollusk (0.5%; 95% CI 0.4–0.6). Mean ages of shellfish, crustacean, and mollusk allergy diagnosis were 5.0 (95% CI, 4.4–5.6), 5.1 (95% CI, 4.6–5.6), and 7.7 years old (95% CI, 5.7–9.7), respectively. More than half (54.9%; 95% CI 48.1-61.4) of SA pediatric patients had >1 lifetime food allergy related emergency room visit but only 45.7% (95% CI 39.2-52.4) carried an epinephrine auto-injector. Children with shellfish allergy were more likely to be Black/Hispanic/Latino, and have comorbid asthma, allergic rhinitis or a parental history of asthma, environmental or other food allergies ($p<0.001$).

Conclusion: The epidemiology of SA in the US pediatric population shows crustacean allergy is more common than mollusk allergy. A disparity in SA children and epinephrine

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auto-injector carriage exists. Results from this study will lead to increased awareness of the need for detailed histories, specific diagnostic tests, and rescue epinephrine for anaphylaxis in US children with SA.

Highlights

1. What is already known about this topic?

Shellfish allergy (SA) can cause severe reactions including anaphylaxis and is among the most common food allergies in US children.

2. What does this article add to our knowledge?

This is the first comprehensive study specifically examining and comparing the characteristics of SA and its subtypes (crustacean and mollusk allergy) among US children, using a comprehensive sampling approach and a strict diagnostic algorithm to confirm self-reported SA prevalence, which is 1.3% with the most prevalence in children 6 – 17 years old.

3. How does this study impact current management guidelines?

While SA has been traditionally considered more of an adult food allergy, with the significant prevalence in this study, shellfish allergy should be aggressively assessed and managed in the pediatric population, with consideration of the importance of emergency medication carriage. Further delineation between crustacean versus mollusk allergy should be considered as well in the pediatric population.

Keywords: Shellfish allergy, mollusk allergy, crustacean allergy, prevalence, children

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Introduction

Shellfish allergy (SA) is one of the most common food allergies in the world.[1] In the United States (US), it is the most common food allergy among adults[2] and third most common among children.[3] It is one of the top causes of severe reactions[3–5] with some studies showing it as the leading cause of anaphylaxis in food allergy.[6,7] Within the last two decades, there have been modest advancements in understanding the immunologic mechanisms that contribute to the pathophysiology of SA such as the discovery of tropomyosin, a shellfish allergen which causes cross-reactivity between the two main categories of SA, crustacean and mollusks.[8–12] However, there is a substantial gap in literature evaluating the prevalence and characteristics of shellfish allergy among children in the United States.

The two main categories of SA, crustacean (shrimp, crab, lobster, etc.) and mollusk (clam, oyster, mussel, scallop, etc.), have some immunological cross-reactivity[13,14] and there is a paucity of data evaluating the epidemiology of these two groups separately, especially in children. A recent meta-analysis examining SA globally found difficulty in comparing results due to the high level of heterogeneity among the studies and too few studies examining prevalence.[15] The present study bridges this gap in the literature and not only estimates the prevalence, characteristics, and severity of SA

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but compares the differences between crustacean allergy and mollusk allergy by leveraging a sample of over 38,000 US children, using a comprehensive sampling approach and a strict diagnostic algorithm to confirm self-reported SA prevalence.

Methods

As detailed in Gupta et al (2018)[16] a population-based survey was administered to a nationally-representative sample of US households by NORC at the University of Chicago, an objective non-partisan research institution that delivers reliable data and rigorous analysis to guide critical programmatic, business, and policy decisions, between October 2015 and September 2016, resulting in parent-proxy responses for 38,408 children. Informed consent was obtained from all participants and study activities were approved by the NORC and Northwestern University Institutional Review Boards.

Survey Development and Design

The survey utilized for this study was an updated, expanded version of a previous survey administered in 2009-2010 to determine the US population-level prevalence and severity of childhood food allergy.[3] While the core constructs from the 2009-2010 survey were retained, additional questions were added to the instrument to assess emerging research issues relating to the etiology and management of food allergy among US children, including a variety of specific SA. (See Online Repository Appendix A) The final 2015-2016 survey was administered via web or phone and incorporated skip-logic to minimize participant burden. All write-in responses were hand-coded and reviewed by an expert

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panel of pediatricians, pediatric allergists, and survey methodologists to ensure accuracy of final data.

Outcome Measures

The primary outcome measures for the present study were the prevalence and characteristics of SA in the US pediatric population. A stringent symptom list was developed by the expert panel and used for defining food allergies including SA as well as classifying allergy severity, via a food allergy categorization (Figure 1A and B) used in previous work[2]. Specifically, SA was defined as having at least one stringent symptom upon ingestion of the responsible allergen, patient report of physician diagnosed SA was used as physician-diagnosed SA and for each SA, the definition of a severe reaction required at least one stringent symptom across two or more different organ systems (i.e., skin/oral mucosa, gastrointestinal (GI), respiratory, cardiovascular). If multiple allergies were reported, each allergy was evaluated separately to determine the accuracy and severity of reaction to the reported allergen. For example, if a patient reported both shrimp and clam allergy, reported reaction symptoms to each allergen would be evaluated separately. Moreover, for the presented analyses that systematically compared characteristics of crustacean-allergic children vs mollusk-allergic children, individuals reporting both allergies were excluded.

Coastal residence was determined at the county level using the National Oceanic and Atmospheric Administration (NOAA) definitions of coastal state, coastal watershed county (counties where land use and water quality changes most directly impact coastal ecosystems), and coastal shoreline county (counties that are directly adjacent to the open

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ocean, major estuaries, and the Great Lakes)—excluding counties bordering the Great Lakes coastline.[17] SA children were also described based on their residence in the region of the U.S. defined by the U.S. Census Bureau. (See Supplemental Figure E1.)

Four regions were assessed (Northeast, Midwest, South and West) and these were further subdivided into 9 divisions (1: New England, 2: Middle Atlantic, 3: East North Central, 4: West North Central, 5: South Atlantic, 6: East South Central, 7: West South Central, 8: Mountain, 9: Pacific).

Study Participants, Survey Weighting, and Statistical Analysis

Both parents (≥18 years old) and children (< 18 years old) residing in a US household who could complete a survey in English or Spanish either online or via telephone were eligible to participate in the present study. This study relied upon a nationally-representative household panel to support population-level inference.[3] Study participants were first recruited from NORC at the University of Chicago's nationally-representative probability-based AmeriSpeak Panel, where a survey completion rate of 51.2% was observed. AmeriSpeak is a probability-based panel, with households selected from a documented randomly selected list of households in the US are sampled by address, and then contacted by U.S. mail and by NORC telephone and field interviewers. It provides at least 97 percent sample coverage of the U.S. population by supplementing the U.S. Postal Service Delivery Sequence File. To increase precision, these population-weighted AmeriSpeak responses were augmented by calibration-weighted, non-probability-based responses obtained through Survey Sampling International. The final, combined sample weight was derived by applying an optimal composition factor that minimizes mean

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square error associated with food allergy prevalence estimates.[18,19] See Gupta et al. for additional detail regarding the sampling, weighting, and analysis procedures utilized.[2]

Complex survey weighted proportions and 95% confidence intervals were calculated using the "svy": family of commands in STATA 14, while relative proportions of demographic characteristics were compared using weighted Pearson chi-square statistics, which are corrected for the complex survey design. Covariate-adjusted complex survey weighted logistic regression models compared relative prevalence and other assessed SA outcomes by participant characteristics. Two-sided hypothesis tests were utilized, with p-value <0.05 considered statistically significant.

Results

Surveys were completed for 38,408 children. Ninety-two percent (92.4%) of participants (n= 35,489) of the total 38,408 participants had no convincing history of food allergy. Seven (7.6%) had a history of convincing allergy. Of those, 599 children were found to have convincing SA, with 322 children with only crustacean allergy, 50 children with only mollusk allergy, and 227 children with both crustacean and mollusk allergy. Prevalence of shellfish allergy by allergen types and age categories is presented in **Table 1**. Overall, the prevalence of SA was 1.3% (95% CI 1.1 – 1.5) with more children allergic to crustacean than mollusk at a prevalence of 1.2% (95% CI 1.0 – 1.3) and 0.5% (95% CI 0.4 – 0.6) respectively. The greatest prevalence of crustacean allergy appeared in children 6 – 17 years old, while the prevalence of mollusk allergy did

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not increase until children were 14 – 17 years of age [0.8%; 95% CI (0.5 – 1.3)]. The prevalence of children with crustacean allergy only (no mollusk) [0.6%; 95% CI (0.5 – 0.8)] was greater than the prevalence of children with both crustacean and mollusk allergy [0.5%; CI (0.4 – 0.6)].

Estimated demographic characteristics, medical history, and family history of atopic diseases of this US population-weighted study population are presented in **Table 2**. The mean ages of shellfish, crustacean, and mollusk allergy diagnosis were 5.0 (95% CI, 4.4 – 5.6), 5.1 (95% CI, 4.6 – 5.6), and 7.7 years old (95% CI, 5.7 – 9.7) respectively. When combining the age of diagnosis with our adult cohort, the mean age for shellfish was 15.9 years with the average age for crustacean and mollusk allergy being 16.8 and 19.4 years, respectively. The age distribution of SA children showed higher prevalence rates among children greater than 6 years old. ($p=0.01$) Compared to the general US pediatric population, children with shellfish allergy were more likely to be Black or Hispanic/Latino, and more likely to have comorbid asthma, allergic rhinitis, as well as a family history of asthma, environmental allergies, or other food allergies ($p<0.001$). Age distribution between exclusively crustacean-allergic and exclusively mollusk-allergic children in the US where half of exclusively mollusk-allergic were 14-17 years of age, compared to only 25% of exclusively crustacean-allergic trended towards significance ($p=0.05$). Conversely, more than one-third of exclusively crustacean-allergic children were age 6-10 years compared to only 18.4% of exclusively mollusk-allergic. No significant differences in crustacean or mollusk allergy prevalence were observed between male and female respondents.

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Children exclusively allergic to crustaceans (i.e. not mollusk-allergic) were more likely to reside in the New England, Mid-Atlantic, South Atlantic, and Pacific divisions, relative to their non-shellfish-allergic peers and children who were exclusively mollusk-allergic were more likely to reside in East North Central, East South Central, and Mountain divisions compared to their non-shellfish- allergic peers ($p<0.01$). Those with both mollusk and crustacean allergy were more likely to reside in the Mid-Atlantic, South Atlantic, and West South Central divisions. Overall, children with SA were more likely to reside in a shoreline county.

The distribution of symptom characteristics, allergy severity and outcomes among children with shellfish allergy is shown on **Table 3.** In order of frequency reported, the most common systems involved in shellfish-allergic reactions were skin/oral/mucosal, respiratory, gastrointestinal, and cardiovascular. Reported symptom prevalence was similar between children with mollusk allergy and crustacean allergy in all systems except for skin/oral/mucosal tissue and cardiovascular system. Among children with crustacean allergy, 70.2% (95% CI 62.4-77.0) experienced itching compared to 32.4% (95% CI 14.6 – 57.3) in those with mollusk allergy. Children with crustacean allergy also were more likely to report chest pain than those who were mollusk-allergic [7.9%; 95% CI (4.4 – 13.9) vs. 1.5% 95% CI (0.3 – 6.7); P = 0.02]. The frequency of reported gastrointestinal and respiratory symptoms were not different between the two groups.

Over half of shellfish allergic pediatric patients had more than one lifetime food allergy-related emergency room (ED) visit and almost one fourth visited the ED in the previous year for any type of food-allergy related reaction. This is shown in Table 3 as the percentage of survey respondents who answered yes to visiting to the ED due to their

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shellfish allergy (54.9%) and having ED visits within the last year (22.7%). Fewer than half of shellfish-allergic patients carried a current epinephrine auto-injector but more than one-third had been treated with an epinephrine auto-injector for a shellfish allergic reaction in their lifetime. There were no significant differences seen in the frequency of reactions characterized as severe, nor were there significant differences in health care utilization between crustacean and mollusk allergic children.

Table 4 shows the adjusted associations between a variety of demographic/comorbid atopic disease characteristics and key shellfish allergy outcomes. Children living in a shoreline county residence were significantly associated with having only crustacean allergy (OR: 1.4, 95% CI 1.1 – 1.9). Children reporting Black, Non-Hispanic race/ethnicity were more likely to have shellfish allergy (OR: 2.3, 95% CI 1.6 – 3.4) and crustacean allergy (OR: 2.6, 95% CI 1.8 – 3.8) compared to their White counterparts. Additionally, the odds of having only mollusk allergy were increased among Black (OR: 2.6, 95% CI 1.5 – 4.6) and Hispanic (OR: 1.9, 95% CI 1.1 – 3.1) children, relative to White children. Children 6 – 10 years and 14 – 17 years of age had increased odds of having crustacean allergy (OR: 2.1, 95% CI 1.2 – 3.6;OR: 1.8, 95% CI 1.1 – 3.1, respectively). Children with comorbid insect sting or latex allergies had greater odds of crustacean allergy, which may be a potential indicator of atopic predisposition.

Figure 2 reports rates of comorbidity among and between shellfish allergies and the co-existence of other common food allergies. The highest rates were observed among shrimp, crab and lobster allergies and between crustacean and mollusk allergy. This co-existence of clinical allergic disease may be caused by cross reactivity of pan-allergens like tropomyosin or other unique allergens. Prior studies have reported only 14% of

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patients with crustacean allergy reporting a mollusk allergy.[13] In our study, of the children who were crustacean-allergic, 45% were also allergic to mollusks, however, of the mollusk allergic children, 81% were also allergic to crustaceans. Among children with mollusk allergy, the most common accompanying allergy was shrimp (70%) followed by lobster (65%), crab (63%) and fin fish (36%). Children with mollusk allergy had higher rates of co-existing fin fish (36%) and peanut allergy (33%) than those with crustacean allergy (26% and 24% respectively). A greater percentage of children with fin fish allergy also had comorbid crustacean allergy (54%) compared to mollusk allergy (42%). The percentage of children with peanut allergy who also have crustacean allergy was 13% while those with concurrent mollusk allergy was 10%.

Discussion

This study bridges a large gap in SA literature by defining the prevalence and comparing the characteristics of crustacean and mollusk allergy in a large, representative group of children living in the United States. This is the largest study to date of shellfish allergy and no previous cross-sectional studies of this caliber exist in this population. Our strict criteria for defining shellfish allergy give a more complete prevalence of SA in the US and we also had the unique opportunity to examine demographic information of both the pediatric and adult population. The pediatric prevalence of shellfish allergy in our study was 1.3%, which is substantial and within range of previously reported studies.[1]

Our findings indicate that the average age of the first reaction to shellfish in SA is younger than previously acknowledged and suggests that SA affects the pediatric population to a significant degree. When examining both children and adults together, the

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average age of shellfish diagnosis across the US population was 15.9 years with the average age for crustacean and mollusk allergy being 16.8 and 19.4 years, respectively. Previous studies report the average age of diagnosis is in adulthood[13] while others analyzed age of onset in children and adults separately.[20,21] Another possible explanation for this low age of diagnosis is that shellfish has become gradually more ubiquitous in the US diet[22] and more children may be exposed at an earlier age.

It is also important to note the geographic differences between mollusk and crustacean allergic children in the United States. Previous studies of coastal Asian populations have reported high prevalence rates of SA compared to populations living away from the coast, suggesting a possible relationship between increased exposure to shellfish and SA risk.[23–25] Based on these studies, the determination of SA risk in the US population could include "proximity to the coast" which may increase the likelihood of shellfish exposure, thus increasing the risk of SA development. There have been no previous studies evaluating this hypothesis.

While our data shows consistency with the "proximity to the coast" hypothesis in children with shellfish allergy and crustacean allergy, this was not the case with mollusk allergy. Children with mollusk only allergy were more likely to reside in inland states or non-costal watershed counties. A possible explanation for this finding may be preparation of mollusks inland (cooked) compared to near the coast (raw). Inland states have less ingestion of raw shellfish, as evidenced by the increased number of seafood associated infections inland.[26] Inland seafood ingestion is more likely to be cooked, given the risks of infection. Changes in food allergenicity with cooking have been shown to occur in other foods, such as peanuts, milk, and eggs.[27–30] The effect on allergenicity through

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heating shellfish has been shown to influence IgE binding in squid and scallops.[31,32] Additionally, different species of mollusk may result in an increased risk of developing an allergy in specific regions. While in Thailand, SA patients with anaphylaxis to fresh water shrimp may not have the same reaction to saltwater shrimp or vice versa[31], this has not been explored for mollusks and our current study did not examine the specific species of shellfish consumed. Further studies are needed to explore the effects of cooking modalities in shellfish allergenicity and species-specific immune responses on SA prevalence.

There is a paucity of data evaluating the epidemiology and prevalence of mollusk allergy among children in the US. Our study is the first study of this size to directly compare presentation of crustacean allergy with mollusk allergy and to define the characteristics of mollusk allergy. We specifically explored the prevalence of crustacean allergy and mollusk allergy, which was 1.2% and 0.6% respectively. This is consistent with a recent meta-analysis that found crustacean allergy to be more prevalent than mollusk allergy globally.[15] More than 80% of consumption of seafood in the US in 2017 was comprised of ten fish and shellfish products, with shrimp as the top consumed seafood at 4.4 pounds per person and clam as the tenth at 0.31 pounds per person. (https://www.seafoodhealthfacts.org/seafood-choices/overview-us-seafood-supply, Accessed 9/2/2019)[33]. The relative difference in exposure by consumption may contribute to the higher prevalence of crustacean vs mollusk allergy in US children.

Previously reported prevalence in 2004 by Sicherer et. al was 0.5%[13] and the NHANES survey from 2007-2010 reported a prevalence of 0.87%.[32] This trend suggests

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that pediatric SA may have been increasing since the early 2000s. For comparison, the estimated prevalence of peanut allergy among US children has ranged from 1.2% - 2.2%[1,33] suggesting that shellfish allergy should be a public health concern in the pediatric population. In a study using information from the National Electronic Injury Surveillance System, a database that captures a nationally represented sample of food allergic and anaphylactic events at the emergency department (ED), the most common food for ED visits was shellfish in children 6-18 years old and shellfish was one of the top foods to result in hospitalizations.[7] Another analysis of a private insurance claims database from 2007-2016 shows increasing rates of all food allergies, but also demonstrated an increase in claims for SA from ages 6 – 10 years old.[34] A more recent study analyzing information from a national administrative claims database found that while there was an increase in ED visits over the last decade for shellfish, there were also increases for all the other top food allergies with peanuts being most common for ED visits.[35] It is important to note though that both studies were limited to patients with insurance or Medicare Advantage and excluded data from families who were uninsured or had Medicaid.

A concerning finding in our study is that a significant proportion of SA pediatric patients have had more than one lifetime food allergy related ED visit and more than one-third have been treated with an epinephrine auto-injector in their life time. Despite these results, less than half of these patients carried a current epinephrine auto-injector indicating a large number of children at risk of life threatening allergic reactions without immediate access to treatment. This disparity in the carriage of epinephrine auto-injectors implies that greater education and awareness remains needed in the field of food allergy.

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359 It is assumed by most physicians that there is a high rate of cross-reactivity for
360 shellfish and if a patient is allergic to crustacean, they are likely allergic to mollusks as
361 well. Perhaps the greatest attestation to this assumption is the fact that ICD-9 and ICD-10
362 do not have separate diagnosis codes for mollusk allergy or crustacean allergy.[34] This
363 study shows that the proportion of children with crustacean allergy who are also allergic
364 to mollusk is less than 50%. Sicherer et. al. previously suggested that those who are
365 crustacean allergic may be able to tolerate mollusks.[13] These findings demonstrate the
366 importance for clinicians to ascertain whether a patient is allergic to crustaceans or
367 mollusk before recommending blanket avoidance of all shellfish. This will not only
368 provide the patient more options in their diet but also help better understand the nature of
369 shellfish allergy in the future.

370 There were increased odds of having shellfish, crustacean, or mollusk allergy
371 among Black children versus White children which has been demonstrated in previous
372 studies.[3,36] Of note, there were no significant differences in odds of shellfish, crustacean,
373 or mollusk allergy among different household incomes. This suggests race is a stronger
374 predictor of the development of food allergy than socioeconomic status and that there
375 may be a genetic predisposition for the development of SA. As shown in Figure E2, this
376 appears to be true for each assessed race/ethnicity except for Asians. The difference in
377 predicted probabilities of shellfish allergy between Asians from households earning >50K
378 and Asians from households earning <50K is indeed statistically significant ($p=0.015$)
379 Possible explanations for higher probability of shellfish allergy in higher income Asian
380 households may be due increased chances of exposure or a higher likelihood of adopting

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a western diet and differences in self-reporting. The potential gene-environment interaction has previously been demonstrated in the case of peanut allergy[37] but has not been carefully studied among SA patients.

The major limitation of our study is potential recall bias with a self-report survey and selection bias, as those with food allergy may be more likely to respond to surveys. The use of the AmeriSpeak panel, a sociodemographically and graphically representative sample of US households with children, was used to minimize some selection bias. This study could not assess shellfish specific SPT or sIgE levels to support diagnosis along with an adverse reaction history. This limitation was ameliorated as much as possible by implementing strict confirmatory diagnostic criteria, including stringent symptoms, to eliminate children with histories that are inconsistent with IgE-mediated allergy (i.e. intolerance or oral allergy syndrome). Lack of proper physician diagnosis may also have influenced epinephrine carriage rates. Another limitation to this study was the significantly lower number of subjects with mollusk allergy. While this is consistent with other studies both in the United States and around the world,[13,22,38–41] this leads to correspondingly greater variability in estimates pertaining to mollusk allergy outcomes relative to crustacean allergy. Ingestion habits of children were not recorded, so it is possible that some children who had never ingested foods like mollusks were not considered allergic to that food.

Conclusion

SA affects 1.3% of children in the United States, with the most prevalence in children 6 – 17 years old. The present study closes a gap in the literature by examining the prevalence,

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distribution, and characteristics of shellfish allergic US children via a large, population-based survey, with a particular emphasis on comparing and contrasting the two main subgroups of shellfish allergy —crustacean and mollusk allergy. In summary, the average age of diagnosis of shellfish allergy was in adolescence at 16 years, crustacean allergy was more common than mollusk allergy in all age categories, more than half of pediatric patients visit an emergency room in their lifetime due to shellfish allergy, but less than half carry an epinephrine auto-injector. This study has improved our understanding of the epidemiology and presentation of shellfish allergy in the US pediatric population and highlighted areas of need for future study.

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Table 1. Prevalence Estimates of Shellfish, Crustacean and Mollusk Allergy Among US Children.

Age Groups	% (95%CI) of US Children with Convincing Shellfish Allergy	% (95%CI) of US Children with both Crustacean and Mollusk Allergy	% (95%CI) of US Children with Any Convincing Crustacean Allergy	% (95%CI) of US Children with Any Convincing Mollusk Allergy	% (95%CI) of US Children with Convincing Crustacean Allergy Only (no mollusk allergy)	% (95%CI) of US Children with Convincing Mollusk Allergy Only (no crustacean allergy)
Convincing shellfish allergy prevalence among all children						
All ages	1.3 (1.1-1.5)	.5 (.4-.6)	1.2 (1.0-1.3)	.6 (.5-.8)	.6 (.5-.8)	.12 (.06-.23)
0-2 Years	.6 (.4-1.0)	.2 (.1-.6)	.5 (.3-.8)	.3 (.2-.6)	.2 (.1-.4)	.07 (.03-.18)
3-5 Years	1.1 (.7-1.7)	.6 (.3-1.1)	1.1 (.7-1.7)	.6 (.3-1.2)	.5 (.3-.9)	.02 (.004-.09)
6-10 Years	1.5 (1.1-1.9)	.6 (.4-.9)	1.4 (1.1-1.8)	.7 (.5-1.0)	.8 (.6-1.1)	.08 (.04-.15)
11-13 Years	1.5 (1.2-1.9)	.5 (.3-.8)	1.4 (1.1-1.8)	.6 (.5-.9)	.9 (.7-1.2)	.13(.07-.26)
14-17 Years	1.5 (1.1-2.0)	.6 (.4-.8)	1.2 (1.0-1.5)	.8 (.5-1.3)	.7 (.5-.9)	.27 (.09-.87)
Physician-diagnosed convincing shellfish allergy prevalence among all children						
All ages	.8 (.6-.9)	.2 (.2-.3)	.7 (.6-.8)	.3 (.2-.4)	.4 (.4-.5)	.11 (.05-.23)
0-2 Years	.3 (.1-.6)	.05 (.02-.12)	.2 (.1-.3)	.2 (.1-.5)	.1 (.1-.2)	.14 (.03-.57)
3-5 Years	.5 (.4-.7)	.2 (.1-.4)	.5 (.4-.7)	.2 (.1-.4)	.3 (.2-.5)	.01 (.002-.10)
6-10 Years	.8 (.6-1.1)	.2 (.1-.3)	.7 (.5-1.0)	.2 (.2-.4)	.5 (.3-.8)	.05 (.02-.11)
11-13 Years	1.1 (.8-1.4)	.4 (.2-.6)	1.0 (.7-1.3)	.5 (.3-.7)	.6 (.4-.9)	.10 (.05-.22)
14-17 Years	1.0 (.7-1.5)	.2 (.2-.4)	.8 (.6-1.0)	.5 (.2-1.0)	.5 (.4-.7)	.22 (.05-.91)

Table 2. Demographic Characteristics of the Study Population % (95% CI)

Variable	All Children	Children with Convincing Shellfish Allergy	p-value	Children with Convincing Crustacean Allergy Only (no mollusk allergy)	Children with Convincing Mollusk Allergy Only (no crustacean allergy)	p- value comparing mollusk vs crustacean allergic
Age (y)						
0-2 Years	16.1 (15.2-16.9)	7.6 (4.9-11.7)	0.01	6.0 (3.7-9.5)	9.1 (3.0-24.3)	0.05
3-5 Years	16.2 (15.5-17.0)	13.6 (8.9-20.3)		12.6 (7.3-20.9)	2.6 (.5-12.2)	
6-10 Years	27.9 (26.9-28.8)	31.7 (25.7-38.4)		34.2 (26.5-42.8)	18.4 (7.8-37.7)	
11-13 Years	16.6 (15.9-17.4)	19.7 (15.7-24.4)		22.9 (17.4-29.6)	17.9 (7.2-38.0)	
14-17 Years	23.4 (22.4-24.4)	27.3 (21.5-34.0)		24.3 (18.7-31.0)	52.1 (24.0-78.9)	
Gender						
Female	48.9 (47.8-50.0)	46.5 (39.9-53.2)	0.48	48.2 (40.2-56.2)	39.4 (17.7-66.4)	0.54
Male	51.1 (50.0-52.2)	53.5 (46.8-60.1)		51.8 (43.8-59.8)	60.6 (33.6-82.3)	
Race/ethnicity						
Asian, Non-Hispanic	3.2 (2.8-3.7)	4.3 (2.8-6.7)	<.001	5.0 (3.0-8.3)	4.2 (.9-17.3)	0.11
Black, Non-Hispanic	13.2 (12.3-14.2)	22.9 (17.6-29.1)		23.1 (16.5-31.4)	9.5 (3.2-25.0)	
White, Non-Hispanic	52.8 (51.2-54.4)	39.9 (33.5-46.7)		45.0 (37.0-53.1)	69.4 (44.8-86.4)	
Hispanic/Latino	24.1 (22.5-25.7)	27.3 (21.2-34.4)		21.3 (15.2-28.9)	15.8 (6.2-34.8)	
Multiple/Other	6.6 (6.1-7.3)	5.7 (4.0-8.0)		5.6 (3.6-8.7)	1.1 (.1-7.8)	
Country of Birth						
Born in US	97.8 (97.4-98.1)	97.5 (93.2-99.1)	0.81	98.2 (94.7-99.4)	100	0.47
Born outside US	2.2 (1.9-2.6)	2.5 (.9-6.8)		1.8 (.6-5.3)	0	
Household income						
<25K	16.1 (14.9-17.3)	16.2 (10.9-23.3)	0.56	12.8 (8.3-19.1)	6.1 (1.6-20.6)	0.16
25K-49K	22.2 (20.9-23.5)	19.6 (14.9-25.2)		21.8 (15.1-30.3)	23.7 (9.9-46.8)	
50K-99K	31.1 (29.8-32.5)	34.2 (28.7-40.2)		33.1 (26.6-40.3)	31.6 (14.4-56.0)	
100K-149K	19.2 (18.0-20.5)	16.3 (12.5-20.9)		18.1 (13.0-24.5)	2.9 (.7-10.3)	
150K+	11.4 (10.3-12.6)	13.8 (8.6-21.5)		14.3 (8.4-23.3)	35.8 (9.2-75.3)	
Census Region						
West	24.5 (23.0-26.0)	22.4 (17.0-28.9)	0.04	24.5 (19.0-30.9)	45.0 (16.9-76.7)	0.14
Midwest	20.7 (19.6-21.9)	16.0 (12.1-20.8)		12.5 (8.6-17.9)	18.9 (7.7-39.5)	
South	38.6 (37.1-40.2)	38.8 (32.6-45.5)		37.8 (30.1-46.1)	28.1 (12.4-51.9)	
Northeast	16.2 (15.1-17.3)	22.8 (17.1-29.7)		25.3 (18.1-34.2)	8.0 (2.9-20.0)	
Census Division						
New England	3.9 (3.4-4.5)	4.3 (2.0-8.9)	0.17	5.1 (1.7-14.0)	1.6 (.3-7.8)	0.005
Mid-Atlantic	12.4 (11.4-13.5)	18.6 (13.4-25.3)		20.5 (14.2-28.7)	6.4 (2.1-17.7)	
East North Central	12.5 (11.6-13.5)	9.9 (7.2-13.4)		8.2 (5.0-13.0)	13.1 (4.6-31.9)	
West North Central	8.9 (8.2-9.7)	6.3 (3.8-10.4)		4.5 (2.4-8.1)	5.9 (1.8-17.3)	
South Atlantic	19.6 (18.4-20.8)	22.4 (17.3-28.4)		23.2 (16.6-31.4)	14.8 (5.9-32.4)	
East South Central	5.7 (5.0-6.5)	3.8 (2.3-6.2)		4.2 (2.2-7.9)	7.9 (2.1-25.0)	
West South Central	13.7 (12.5-14.9)	12.9 (9.1-18.1)		10.9 (6.8-16.9)	5.4 (1.5-17.3)	
Mountain	7.7 (7.0-8.6)	8.4 (4.2-16.0)		6.8 (4.2-10.9)	36.4 (9.7-75.4)	
Pacific	15.6 (14.3-17.0)	13.4 (10.4-17.1)		16.7 (12.3-22.4)	8.6 (2.9-22.8)	
Residential Proximity to the coast						
Coastal States	60.0 (58.5-61.4)	65.0 (58.0-71.4)	0.15	66.7 (58.4-74.0)	33.0 (15.0-57.9)	0.008
Inland States	40.0 (38.6-41.5)	35.0 (28.6-42.0)		33.3 (26.0-41.6)	67.0 (42.1-85.0)	
Coastal Watershed Counties	50.3 (48.7-51.9)	54.0 (47.1-60.8)	0.29	56.9 (48.7-64.6)	30.3 (13.6-54.7)	0.04
Non-Coastal Watershed Counties	49.7 (48.1-51.3)	46.0 (39.2-52.9)		43.1 (35.4-51.3)	69.7 (45.3-86.5)	
Shoreline Counties	36.9 (35.3-38.4)	44.1 (37.6-50.9)	0.03	48.1 (40.0-56.3)	25.6 (11.2-48.3)	0.06
Non-Shoreline Counties	63.2 (61.6-64.7)	55.9 (49.1-62.4)		51.9 (43.7-60.0)	74.4 (51.7-88.8)	
Age of SA diagnosis (Mean, 95%CI)		5.0 (4.4-5.6)		5.1 (4.6-5.6)	7.7 (5.7-9.7)	
Physician diagnosed comorbidities						
Asthma	12.2 (11.4-13.0)	41.7 (34.7-48.9)	<.001	37.4 (29.8-45.6)	44.2 (16.2-76.5)	0.7
Eczema	5.9 (5.3-6.5)	14.7 (10.2-20.6)	<.001	11.9 (6.6-20.4)	11.2 (3.5-30.6)	0.92
Allergic Rhinitis	12.8 (12.0-13.6)	33.0 (27.5-39.2)	<.001	29.3 (23.1-36.3)	25.3 (11.0-48.2)	0.71
Insect sting allergy	2.2 (1.9-2.6)	12.3 (8.3-17.9)	<.001	12.1 (6.9-20.5)	13.7 (5.1-32.2)	0.82
Latex allergy	1.0 (.8-1.3)	7.4 (5.3-10.2)	<.001	9.1 (5.9-13.7)	3.4 (.9-12.1)	0.14
Medication allergy	4.2 (3.7-4.7)	11.7 (8.4-16.0)	<.001	12.3 (8.1-18.3)	16.4 (6.2-36.9)	0.58
Eosinophilic esophagitis	.16 (.12-.22)	.57 (.23-1.40)	0.005	.85 (.31-2.34)	0	0.45
Family history of allergic diseases						
Parental asthma	18.3 (17.2-19.5)	43.4 (36.6-50.4)	<.001	43.1 (35.0-51.6)	22.4 (9.9-43.0)	0.06
Parental eczema	15.6 (14.5-16.7)	29.3 (23.2-36.3)	<.001	23.8 (18.3-30.3)	17.4 (6.6-38.3)	0.49
Parental environmental allergies	40.1 (38.6-41.6)	62.6 (55.6-69.2)	<.001	60.3 (52.1-67.9)	38.2 (17.2-64.9)	0.12
Parental FA	19.4 (18.3-20.5)	59.8 (52.8-66.5)	<.001	64.8 (56.5-72.4)	35.4 (16.1-61.1)	0.03

Table 3. Symptom Characteristics and Outcomes of Children with Shellfish Allergy, % (95% CI) with stringent symptoms in italics

Symptoms	All Shellfish	Children with Convincing Crustacean Allergy Only	Children with Convincing Mollusk Allergy Only	P value comparing symptoms between Crustacean vs Mollusk allergic
Skin/Oral/Mucosal Tissue				
Any Skin/Oral/Mucosal Tissue Symptom(s) to Shellfish	96.4 (93.8-97.9)	96.9 (93.6-98.6)	97.6 (91.1-99.4)	0.76
Any ***Stringent*** Skin/Oral/Mucosal Symptom(s) to Shellfish	85.3 (80.8-88.9)	88.0 (81.1-92.7)	93.5 (80.7-98.0)	0.26
Hives	75.3 (68.9-80.8)	71.6 (64.1-78.1)	83.6 (66.0-93.0)	0.17
Itching	70.9 (64.1-77.0)	70.2 (62.4-77.0)	32.4 (14.6-57.3)	0.002
Rash	64.7 (58.8-70.2)	58.5 (50.6-65.9)	66.1 (40.6-84.8)	0.56
Swelling	35.7 (29.3-42.7)	29.1 (22.3-37.1)	14.7 (6.0-31.6)	0.1
Lip/tongue swelling	34.4 (28.2-41.2)	29.3 (22.5-54.4)	19.4 (8.2-39.2)	0.31
Difficulty swallowing	31.2 (25.3-37.8)	25.2 (19.5-31.9)	23.1 (9.9-45.2)	0.83
Hoarse voice	12.6 (9.6-16.5)	11.8 (8.4-16.2)	12.1 (4.4-29.4)	0.96
Itchy mouth	34.1 (27.8-40.9)	31.3 (24.4-39.2)	23.3 (10.0-45.4)	0.45
Throat tightening	30.2 (23.5-37.9)	19.9 (14.9-26.0)	48.7 (20.6-77.7)	0.04
Mouth or throat tingling	17.8 (13.8-22.6)	14.3 (10.3-19.6)	3.7 (1.1-11.6)	0.02
Respiratory				
Any Respiratory Symptom(s) to Shellfish	52.4 (45.6-59.0)	48.0 (40.0-56.1)	55.0 (27.3-79.9)	0.37
Any ***Stringent*** Respiratory Symptom(s) to Shellfish	44.1 (37.3-51.2)	37.0 (29.9-44.8)	46.8 (18.7-77.2)	0.57
Chest tightening	19.3 (13.6-26.6)	15.4 (10.9-21.3)	32.8 (7.2-75.5)	0.29
Nasal congestion	14.6 (10.7-19.5)	12.1 (7.8-18.2)	6.0 (1.9-17.9)	0.25
Repetitive cough	15.9 (11.2-22.2)	10.5 (7.2-15.0)	12.8 (4.7-30.4)	0.71
Trouble breathing	27.0 (20.5-34.7)	17.1 (12.9-22.4)	37.5 (10.5-75.4)	0.2
Wheezing	22.8 (16.9-30.0)	16.4 (11.2-23.3)	40.6 (13.0-75.8)	0.11
Gastrointestinal				
Any Gastrointestinal Symptom(s) to Shellfish	42.0 (35.4-48.8)	34.2 (27.3-41.8)	23.7 (10.6-44.9)	0.46
Any ***Stringent*** Gastrointestinal Symptom(s) to Shellfish	17.9 (13.4-23.5)	10.9 (7.5-15.7)	7.5 (2.7-18.9)	0.47
Belly pain	19.1 (14.0-25.5)	10.1 (6.6-15.1)	13.0 (5.3-28.8)	0.6
Cramps	13.9 (9.3-20.2)	6.1 (3.8-9.7)	11.3 (4.3-26.7)	0.26
Diarrhea	19.0 (13.5-26.0)	12.8 (8.5-19.0)	10.7 (3.9-26.1)	0.73
Nausea	19.0 (14.8-24.1)	14.3 (10.2-19.8)	7.5 (2.6-19.7)	0.22
Vomiting	17.9 (13.4-23.5)	10.9 (7.5-15.7)	7.5 (2.7-18.9)	0.47
Cardiovascular				
Any Cardiovascular Symptom(s) to Shellfish	27.9 (21.9-34.7)	23.9 (18.0-31.0)	8.4 (3.3-19.8)	0.02
Any ***Stringent*** Cardiovascular Symptom(s) to Shellfish	26.9 (21.1-33.7)	22.4 (16.8-29.2)	8.4 (3.3-19.8)	0.03
Chest pain	10.1 (6.9-16.8)	7.9 (4.4-13.9)	1.5 (.3-6.7)	0.02
Rapid heart rate	15.5 (10.7-22.0)	8.0 (5.1-12.3)	3.0 (.7-11.7)	0.17
Fainting, dizziness, or feeling light headed	12.1 (8.4-17.1)	8.3 (5.5-12.3)	3.5 (1.2-10.1)	0.13
Low blood pressure	4.2 (2.5-7.0)	4.1 (2.1-8.1)	1.4 (.2-10.3)	0.31
Shellfish Allergy Outcomes				
Multiple Food Allergies (including individual shellfish allergies)	74.0 (68.0-79.2)	55.7 (47.3-63.7)	58.1 (30.8-81.2)	0.9
Multiple Food Allergies (besides shellfish allergies)	37.6 (31.1-44.4)	26.3 (20.6-32.8)	13.6 (5.3-30.8)	0.13
Only Mild to moderate reactions to Shellfish	51.3 (44.5-58.1)	56.0 (48.1-63.6)	52.4 (22.6-80.5)	0.83
1+ Severe reactions to Shellfish	48.7 (41.9-55.5)	44.0 (36.4-51.9)	47.6 (19.5-77.4)	
1+ Lifetime FA-related ED Visit	54.9 (48.1-61.4)	46.9 (39.0-54.9)	61.6 (35.0-82.7)	0.3
1+ Last Year FA-related ED Visits	22.7 (17.1-29.4)	18.7 (14.0-24.6)	9.0 (2.8-25.0)	0.18
Has Current Epinephrine Auto-Injector Prescription	45.7 (39.2-52.4)	50.7 (42.7-58.8)	34.7 (15.5-60.6)	0.24
Has been treated with EAI for shellfish-allergic reaction	37.8 (31.1-45.0)	35.5 (28.1-43.7)	55.2 (27.6-80.0)	0.19
Has been treated with Albuterol for shellfish-allergic reaction	24.7 (18.2-32.7)	19.1 (13.7-26.0)	36.4 (9.7-75.3)	0.3

Table 4. Adjusted Associations for Demographics, Comorbid Diseases, and Severity of the Diagnosis Among Children with Shellfish Allergy and Shellfish Allergy Subgroups.

Variable	Odds of Convincing Shellfish Allergy Among All Children (95% CI)	Odds of Convincing Crustacean Allergy (with or without mollusk) Among All Children (95% CI)	Odds of Convincing Mollusk Allergy (with or without Crustacean Allergy) Among All Children (95% CI)	Odds of Severe Shellfish Reactions Among Children with Convincing Shellfish Allergy (95% CI)
Shoreline County				
Yes vs. No	1.3 (1.0-1.8)	1.4 (1.1-1.9)	1.1 (.7-1.8)	1.1 (.6-1.8)
Race/ethnicity (vs. White, non-Hispanic)				
Asian, non-Hispanic	1.7 (.9-3.1)	1.8 (1.0-3.3)	1.5 (.5-4.3)	.6 (.2-1.8)
Black, non-Hispanic	2.3 (1.6-3.4)	2.6 (1.8-3.8)	2.6 (1.5-4.6)	1.4 (.7-2.8)
Hispanic	1.4 (.9-2.0)	1.5 (1.0-2.2)	1.9 (1.1-3.1)	.6 (.3-1.1)
Multiple/other	.9 (.6-1.5)	1.1 (.7-1.8)	1.1 (.6-2.1)	1.5 (.6-3.6)
Sex				
Female vs. Male	.9 (.7-1.2)	1.0 (.7-1.3)	.9 (.6-1.4)	1.0 (.6-1.6)
Country of Birth				
Born in US	.9 (.3-2.5)	.8 (.3-2.3)	.7 (.2-2.7)	.4 (.1-3.1)
Age (vs. <3 years)				
3-5 Years	1.5 (.8-2.9)	1.9 (1.0-3.9)	1.6 (.6-4.3)	1.9 (.6-6.1)
6-10 Years	1.7 (1.0-2.8)	2.1 (1.2-3.6)	1.5 (.7-3.2)	.8 (.3-2.1)
11-13 Years	1.5 (.9-2.6)	1.8 (1.0-3.2)	1.2 (.6-2.6)	1.3 (.5-3.8)
14-17 Years	1.7 (1.0-2.9)	1.8 (1.1-3.1)	1.9 (.9-4.0)	1.3 (.5-3.6)
Household income, $ (v <$25,000)				
25,000-49,999	.9 (.5-1.6)	.9 (.5-1.6)	.7 (.3-1.7)	.2 (.1-.6)
50,000-99,999	1.3 (.8-2.1)	1.3 (.8-2.1)	1.2 (.6-2.6)	.6 (.2-1.3)
100,000-149,000	.9 (.5-1.6)	1.0 (.6-1.8)	.8 (.3-1.8)	.3 (.1-.7)
>150,000	1.4 (.7-2.9)	1.2 (.6-2.3)	1.3 (.4-4.0)	.4 (.1-1.4)
Comorbid Conditions (vs. not)				
Asthma	3.5 (2.4-5.2)	3.5 (2.5-5.0)	4.3 (2.3-8.0)	2.2 (1.3-3.7)
Atopic dermatitis	1.5 (.9-2.5)	1.4 (.8-2.5)	1.7 (.9-3.1)	.7 (.3-1.6)
Allergic Rhinitis	2.0 (1.4-2.9)	2.1 (1.5-2.9)	2.3 (1.3-4.0)	1.3 (.8-2.2)
Insect Sting Allergy	4.7 (2.8-7.8)	4.2 (2.3-7.4)	3.6 (1.8-7.2)	.9 (.4-1.9)
Latex Allergy	4.2 (2.3-7.8)	4.6 (2.5-8.5)	2.9 (1.3-6.6)	2.2 (1.0-4.7)
Medication Allergy	1.6 (1.0-2.7)	1.4 (.8-2.4)	1.2 (.6-2.4)	1.0 (.5-1.9)
Eosinophilic Esophagitis	.9 (.2-3.9)	.9 (.2-4.3)	.3 (.0-3.0)	.6 (.1-3.3)

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Figure 1A. Food Allergy Categorization Flow Diagram
Figure 1B. List of allergic reaction symptoms highlighting stringent symptoms indicative of convincing shellfish allergy.

Figure 2. Comorbidities Among Shellfish Allergies and Other Co-existing Food Allergies. Each cell has the percentage of children with each column allergy who also are allergic to the row allergen

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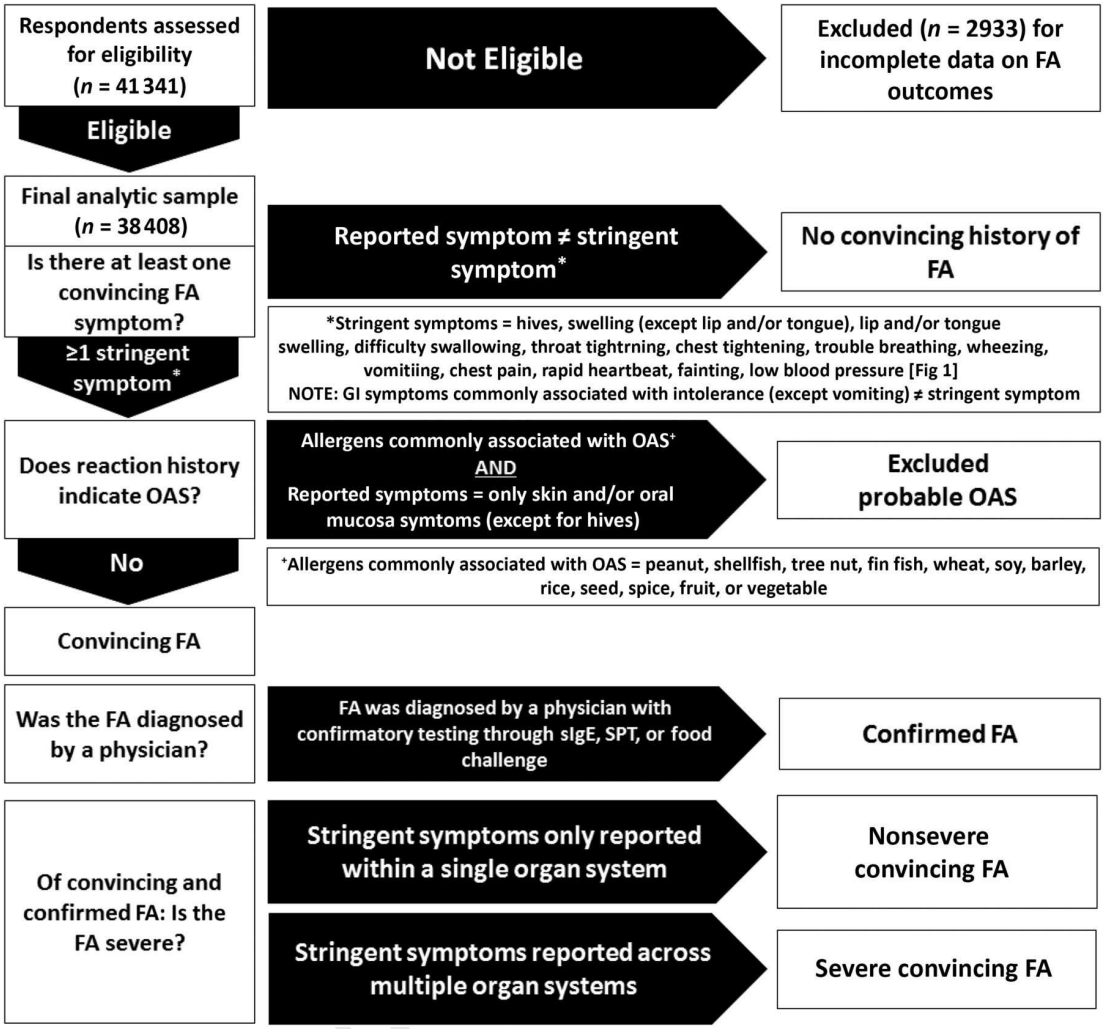
1A


Respondents assessed for eligibility (n = 41 341)
Not Eligible
Excluded (n = 2933) for incomplete data on FA outcomes
Eligible
Final analytic sample (n = 38 408)
Is there at least one convincing FA symptom?
Reported symptom ≠ stringent symptom*
No convincing history of FA
≥1 stringent symptom*
*Stringent symptoms = hives, swelling (except lip and/or tongue), lip and/or tongue swelling, difficulty swallowing, throat tightrning, chest tightening, trouble breathing, wheezing, vomitiing, chest pain, rapid heartbeat, fainting, low blood pressure [Fig 1]
NOTE: GI symptoms commonly associated with intolerance (except vomiting) ≠ stringent symptom
Does reaction history indicate OAS?
Allergens commonly associated with OAS+
AND
Reported symptoms = only skin and/or oral mucosa symtoms (except for hives)
Excluded probable OAS
No
+Allergens commonly associated with OAS = peanut, shellfish, tree nut, fin fish, wheat, soy, barley, rice, seed, spice, fruit, or vegetable
Convincing FA
Was the FA diagnosed by a physician?
FA was diagnosed by a physician with confirmatory testing through sIgE, SPT, or food challenge
Confirmed FA
Of convincing and confirmed FA: Is the FA severe?
Stringent symptoms only reported within a single organ system
Nonsevere convincing FA
Stringent symptoms reported across multiple organ systems
Severe convincing FA

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1B

- □ Skin and/or Oral Mucosa Symptoms
  - □ ***Hives***
  - □ Itching
  - □ Rash
  - □ ***Swelling*** (except lip and/or tongue swelling)
  - □ ***Lip and/or tongue swelling***
  - □ ***Difficulty swallowing***
  - □ Hoarse voice
  - □ Itchy mouth
  - □ ***Throat tightening***
  - □ Mouth or throat tingling
  - □ Other: _____
- □ Respiratory Symptoms
  - □ ***Chest tightening***
  - □ Nasal congestion
  - □ Repetitive cough
  - □ ***Trouble breathing***
  - □ ***Wheezing***
  - □ Other: _____
- □ Gastrointestinal Symptoms
  - □ Belly pain
  - □ Cramps
  - □ Diarrhea
  - □ Nausea
  - □ ***Vomiting***
  - □ Other: _____
- □ Cardiovascular and/or Heart Symptoms
  - □ ***Chest pain***
  - □ ***Rapid heart rate***
  - □ ***Fainting, dizziness, or feeling light headed***
  - □ ***Low blood pressure***
  - □ Other: _____
- □ Other Symptoms
  - □ Anxiety
  - □ Feeling of impending doom
  - □ Headache
  - □ Other: _____

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Figure 2. Comorbidities Among Shellfish Allergies and Other Co-existing Food Allergies

	Percentage of children with each column allergy who also are allergic to the row allergen.							
	Shellfish	**Mollusk**	**Crustacean**	**Shrimp**	**Lobster**	**Crab**	**Fin Fish**	**Peanut**
Shellfish	100	100	100	100	100	100	56	15
Mollusk	49	100	45	46	74	64	42	10
Crustacean	90	81	100	100	100	100	54	13
Shrimp	75	70	83	100	82	75	48	11
Lobster	44	65	49	48	100	74	42	8
Crab	49	63	54	49	83	100	40	9
Fin Fish	24	36	26	27	40	35	100	9
Peanut	25	33	24	24	32	30	38	100
Milk	11	12	12	12	15	11	15	13
Tree Nut	14	19	15	14	23	19	24	33
Egg	11	15	11	12	15	11	20	12
Wheat	8	10	8	8	9	6	11	5
Soy	7	10	8	9	12	8	12	7
Sesame	5	6	4	4	7	5	9	5