

Original Article

Characterizing Biphasic Food-Related Allergic Reactions Through a US Food Allergy Patient Registry

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What is already known about this topic? The incidence of biphasic food-related allergic reactions ranges from 1% to 20% of anaphylactic reactions. Most of these estimates come from individuals undergoing oral food challenges or physician-confirmed biphasic anaphylaxis.

What does this article add to our knowledge? This study provides valuable data on respondent-reported biphasic food-related allergic reactions that will inform patients and families about the probable severity of a biphasic response, depending on the reported initial reaction severity.

How does this study impact current management guidelines? Patient education on biphasic food-related allergic reactions should consider the individual's initial reaction severity.

BACKGROUND: Understanding about patient-reported biphasic food-related allergic reactions is currently sparse. **OBJECTIVE:** To characterize patient-reported biphasic food-related allergic reactions among a national food allergy registry. **METHODS:** We used two patient registry surveys established by Food Allergy Research and Education. Variables were described with proportions and 95% confidence intervals (CIs); unadjusted results were stratified by respondent type. Multivariable logistic regression evaluated the adjusted odds of reporting a biphasic reaction. **RESULTS:** The incidence of reported biphasic reactions was 16.4% (95% CI, 15.3-17.7). A total of 12.8% of parent or guardian respondents (95% CI, 12.5-14.3) and 21.8% of self-respondents (95% CI, 19.7-23.8) indicated a biphasic reaction during their most recent food-allergic reaction. Among respondents with a mild initial reaction, 7.4% reported a biphasic

reaction, compared with 30% with a very severe initial reaction. When the initial reaction was mild, 69.6% of parent or guardian respondents (95% CI, 47.2-85.4) and 52.0% of self-respondents (95% CI, 38.0-65.7) with a biphasic reaction reported a mild secondary reaction. When the initial reaction was very severe, 36.3% of parent or guardian respondents (95% CI, 26.4-47.5) and 42.9% of self-respondents (95% CI, 31.1-55.5) with a biphasic reaction reported a very severe secondary reaction. Female sex, Black race, reaction age 5-12 and 26-66 years, initial moderate, severe, or very severe reaction, and one or more annual reactions were associated with increased odds of a biphasic reaction. **CONCLUSIONS:** This study characterizes the incidence of patient-reported biphasic reactions and provides valuable information on the probable severity of a biphasic food-related allergic reaction. Further research is necessary to understand the

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This work was supported by funds from Food Allergy Research and Education.

Conflicts of Interest: R. Gupta receives research grant support from the National Institutes of Health, Food Allergy Research and Education (FARE), Stanford Sean N. Parker Center for Allergy Research, UnitedHealth Group, Thermo Fisher Scientific, Genentech, and the National Confectioners Association; and has served as a medical consultant/advisor for Aimmune Therapeutics, Genentech, Before Brands, Kaléo, DBV Technologies, ICER, DOTS Technology, and FARE. L. A. Bilaver receives research grant support from the National Institutes of Health,

Thermo Fisher Scientific, FARE, Genentech, National Confectioners Association, and Before Brands Inc. A. H. Nowak-Wegrzyn reports research support from National Institute of Allergy and Infectious Diseases, Danone, and Nestlé, and consultancy fees from Regeneron, Novartis, and Gerber Institute; she serves as the deputy editor for the *Annals of Allergy, Asthma, and Immunology* and the chair of the Medical Advisory Board of the International FPIES Association. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 19, 2020; revised May 3, 2021; accepted for publication May 4, 2021.

Available online ■■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2021.05.009>

Abbreviations used

CI- Confidence interval

ED- Emergency department

FA- Food allergy

FARE- Food Allergy Research and Education

epidemiology of food-related biphasic reactions. © 2021
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Allergy Clin Immunol Pract 2021;■:■-■)

Key words: Food allergy; Food allergic reactions; Biphasic reaction

INTRODUCTION

Food allergy (FA) is a public health concern of increasing significance, affecting approximately 8% of children¹ and 10% of adults² in the United States. Studies indicate that approximately half of children and adults with FA experience severe symptoms. Approximately one in five children¹ and one in 10 adults² visit the emergency department (ED) for symptoms of food-related allergic reactions every year. The number of fatal food reactions ranged from five to 10 per year³ over the past decade in the United States.

Existing literature characterized dual food-related allergic reactions as biphasic, defined as the development of symptoms after resolution of the initial reaction without re-exposure to the trigger.⁴ Current guidelines recommend observing patients for 4 to 6 hours,⁵ 1 hour for patients with low risk for biphasic reactions,⁶ for the reappearance of symptoms, yet reactions have occurred up to 72 hours after the initial reaction.⁷ The incidence of biphasic reactions ranges from 1% to 20%⁸⁻¹³ of anaphylactic reactions, and there are several risk factors. For example, delayed epinephrine^{8,14-16} is a major risk factor. In addition, studies show that patients experiencing biphasic reactions may require multiple epinephrine doses to alleviate the initial symptoms.¹⁷ Hypotension¹⁸ is another risk factor; European guidelines¹⁹ recommend a prolonged observation period for hypotensive pediatric patients.

Although the severity of non-biphasic food-related allergic reactions is becoming better understood, literature gaps remain regarding biphasic reactions. Most incidence estimates are based on data from oral food challenges or reactions evaluated by ED physicians. However, little is known about the incidence of biphasic reactions that occur in individuals with mild initial reaction symptoms, managed by the patient or family. Therefore, this study used a national FA registry to characterize the experiences of individuals who reported biphasic food-related allergic reactions during the most recent reaction.

METHODS

Data source

The study data source was the Food Allergy Research and Education (FARE) Patient Registry, a national online database of FA-related information. Potential respondents were informed about the Registry through FARE's e-mail list, social media, and 33 clinical research centers of excellence across the United States. Eligibility for participation in the registry is based on respondent report of at least one physician-diagnosed FA and/or a well-documented medical

history of FA. The research protocol was approved by the institutional review board at Northwestern University.

In March 2020, deidentified data were shared with Northwestern University analysts, including the Registry's FA History (n = 5973) and FA Reaction surveys (n = 3953). The analytic sample included parent or guardian respondents (reporting on behalf of food-allergic children and young adults age 26 years or less) and self-respondents (adults with FA age 18 years, who responded for themselves). We hypothesized that some young adults might not have been able to recall the food-allergic event accurately, were away at college, or worked far from home, which interfered with their ability to complete the surveys. For the purpose of these analyses, we excluded respondents with missing data on the survey item related to the respondent's relationship to the food-allergic patient (ie, "Who is completing this survey?") as well as parent or guardian respondents who reported the food-allergic patient's age as greater than 26 years. Respondents with implausible age data were also excluded (ie, >90 years), as were those with missing data on the primary outcome of interest. A total of 182 participants were excluded from the FA History dataset and 164 from the FA Reactions dataset. After we applied exclusion criteria, the final sample consisted of 3789 participants. All variables were based on respondent self-report of the most recent allergic reaction to date; only one reaction was reported per respondent.

Outcomes

The primary outcome of interest was the report of a biphasic food-related allergic reaction, based on respondent response (yes, no, or unsure) to the survey item "Did the respondent experience a biphasic reaction? (A second wave of symptoms 1 to 4 hours after initial symptoms subsided without repeated exposure to the allergen)." However, time ranges outside the 4-hour period were included as response choices for the same survey item. Thus, we discuss biphasic reactions outside this range. Other variables were characteristics of the initial reaction, including route of exposure and severity of both initial and secondary symptom waves. Severity was determined by survey items on the severity of initial and secondary reactions, with answer choices of mild, moderate, severe, very severe, and unsure. However, not all survey items specifically referenced the initial or secondary reaction. We also examined the circumstances regarding the initial reaction, such as the type and amount of food culprit consumed. In addition, we evaluated epinephrine treatment, physiologic symptoms, and type of help received.

Demographic measures

Demographic data included respondent enrollment age (years) as well as age at the time of food-related allergic reaction, sex, race, and ethnicity. Ethnicity was categorized as Hispanic, non-Hispanic, and unknown/missing. Respondents could select all applicable racial categories from the following: White, Black, Asian, American Indian/Alaskan Native, Pacific Islander, and unknown. A multiracial category was created from these responses.

Statistical analysis

The current analyses included respondents who completed the FA History and FA Reaction survey and met all inclusion criteria. We restricted the analyses of reaction-related survey items to those who reported yes to having experienced a biphasic reaction. To account for potential discrepancies in respondent experiences by age and respondent type, we stratified the sample according to respondent type (ie, parent or guardian vs self-respondent).

Univariable statistics described frequencies, percentages, and 95% confidence intervals (CIs) for survey items. For each categorical variable, missing data were assigned to their own analytic category so that

TABLE I. Characteristics of Food Allergy Research and Education Registry respondents as of March 2020

Variable	All respondents (n = 3789)					
	Parent/guardian respondents (n = 2258)			Self-respondents (n = 1531)		
	n	%*	95% confidence interval	n	%	95% confidence interval
Age at enrollment, y						
<5	475	21.0	19.4-22.8	0	0	—
5-12	1085	48.1	46.0-50.1	0	0	—
13-17	522	23.1	21.4-24.9	0	0	—
18-25	176	7.8	6.8-9.0	284	18.6	16.7-20.6
26-66	0	0	—	1117	72.9	70.7-75.2
>66	0	0	—	128	8.4	7.1-9.9
Unsure/missing	0	0	—	2	0.1	0.03-0.5
Sex						
Female	876	38.8	36.8-40.8	1317	86.0	84.2-87.7
Male	1380	61.1	59.1-63.1	214	14.0	12.3-15.8
Unsure/missing	2	0.09	0.02-0.3	0	0	—
Race						
White	1855	82.2	80.5-83.7	1312	85.7	83.8 — 87.4
Black	41	1.8	1.3-2.5	59	3.9	3.0-4.9
Asian	73	3.2	2.6-4.0	40	2.6	1.9-3.5
Native American/Alaskan Native	6	0.3	0.1-0.6	8	0.5	0.3-1.0
Pacific Islander	4	0.2	0.06-0.5	1	0.06	0.009-0.05
Multiracial	224	9.9	8.6-11.2	63	4.1	3.2-5.2
Unknown/missing	55	2.4	1.9-3.2	48	3.1	2.4-4.1
Ethnicity						
Hispanic	176	7.8	6.8-9.0	88	5.7	4.7-7.0
Non-Hispanic	1460	64.7	62.7-66.6	992	64.8	62.4-67.1
Missing/unknown	622	27.5	25.7-29.4	451	29.5	27.2-31.8
Multiple top nine food allergies						
Yes (>1)	1561	69.2	67.2-71.0	874	57.1	54.6-59.5
Reaction frequency						
<1/y	1146	50.8	48.7-52.8	503	32.9	30.5-35.2
≥1/y	649	28.7	26.9-30.6	708	46.2	43.8-48.8
Never/unsure/missing	463	20.5	18.9-22.2	320	20.9	18.9-23.0
Comorbid asthma	811	35.9	34.0-37.9	717	46.8	44.3-49.3

*Percentages may not sum to 100% owing to rounding.

the denominator for calculation of each survey item response reflected the entire pertinent subsample. Multivariable logistic regression evaluated the association between predictors (ie, sex, age, race, ethnicity, reaction frequency, multiple FAs, severity of initial reaction, comorbid asthma) and the likelihood of reporting a biphasic food-related allergic reaction. We performed a sensitivity analysis to evaluate whether the inclusion of respondents who reported the onset of secondary symptoms within 1 hour significantly affected the results. Because there were no significant differences, this subgroup was included in all analyses. Statistical significance was determined with an α level of less than .05 (two-sided). All statistical analyses were performed with Stata SE (version 15.1, College Station, TX).

RESULTS

Respondent characteristics

Among respondents who completed the FA Reaction survey and met the inclusion criteria as of March 2020 (n = 3789), there were 2258 parents or guardians and 1531 self-respondents (Table I). Among self-respondents, most were female (86.0%; 95% CI, 84.2-87.7), whereas among parent or guardian

respondents, most children and young adults were male (61.1%; 95% CI, 59.1-63.1). Overall, most were White (parent or guardian respondents: 82.2%; 95% CI, 80.5-83.7; self-respondents: 85.7%; 95% CI, 83.8-87.4) and non-Hispanic (parent or guardian respondents: 64.7%; 95% CI, 62.7-66.6; self-respondents: 64.8%; 95% CI, 62.4-67.1), and reported multiple top nine (ie, milk, egg, wheat, shellfish, fish, peanut, tree nut, soy, sesame) common food allergens (parent or guardian respondents: 69.2%; 95% CI, 67.2-71.0; self-respondents: 57.1%; 95% CI, 54.6-59.5). Over one-third of parent or guardian respondents (35.9%; 95% CI, 34.0-37.9) reported comorbid asthma, whereas nearly half of self-respondents reported comorbid asthma (46.8%; 95% CI, 44.3-49.3). Among parent or guardian respondents, median time lapse between the most recent reaction and the date of the survey was 0.76 years (interquartile range, 0.13-2.9 years). Among self-respondents, median time lapse was 0.30 years (interquartile range, 0.04-2.2 years) (results not shown).

Biphasic reactions

Overall, the incidence of biphasic reactions among most recent reactions was 16.4% (95% CI, 15.3-17.7) (Figure 1).

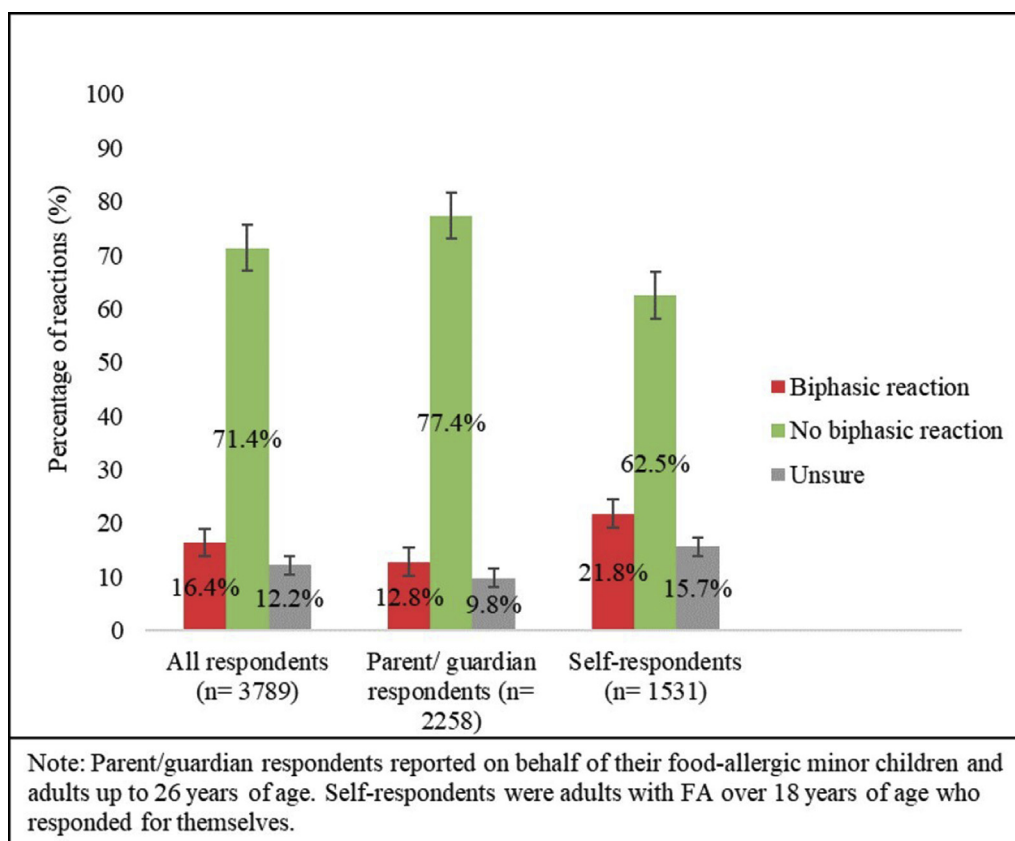


FIGURE 1. Incidence of biphasic reaction during most recent reaction. FA, food allergy.

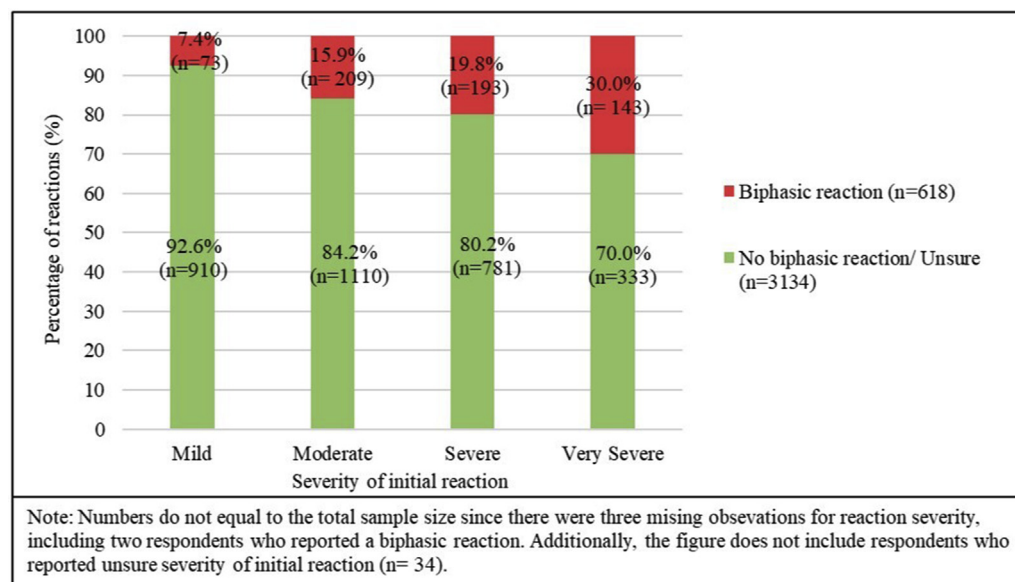


FIGURE 2. Incidence of biphasic reaction during most recent reaction, by severity of initial reaction.

Among parent or guardian respondents, 12.8% (95% CI, 11.5-14.3) of recent reactions were biphasic, compared with 21.8% (95% CI, 19.7-23.8) of self-respondents.

Among respondents with a mild initial reaction, 7.4% reported a biphasic reaction, compared with 30% who had a very severe initial reaction (Figure 2). Among parent or guardian respondents

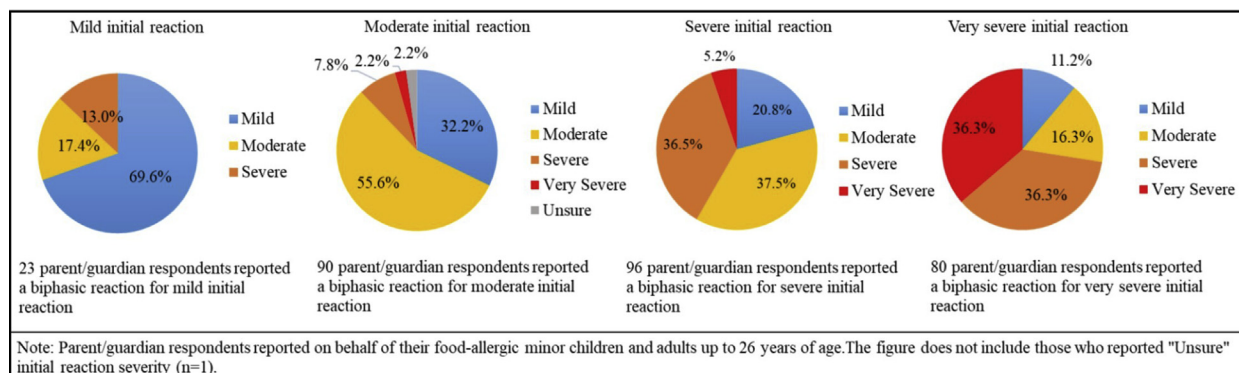


FIGURE 3. Initial and secondary reaction severity among parent or guardian respondents who indicated a biphasic reaction.

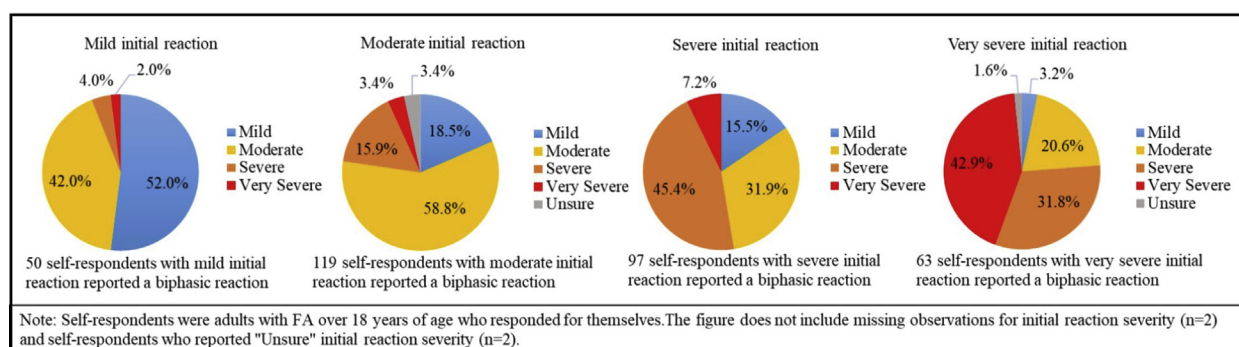


FIGURE 4. Initial and secondary reaction severity among self-respondents who indicated a biphasic reaction. FA, food allergy.

who indicated an initial mild reaction (Figure 3), nearly three-fourths (69.6%; 95% CI, 47.2-85.4) reported a secondary mild reaction. In the case of a moderate initial reaction, 55.6% (95% CI, 45.1-65.6) reported a moderate secondary reaction. When the initial reaction was severe, 36.5% (95% CI, 27.4-47.6) indicated a severe reaction, 37.5% (95% CI, 28.3-47.7) a moderate one, 20.8% (95% CI, 13.8-30.2) a mild one, and 5.2% (95% CI, 2.2-12.0) a very severe secondary reaction. When the initial reaction was very severe, 36.3% (95% CI, 26.4-47.5) reported a very severe secondary reaction, 36.3% (95% CI, 26.4-47.5) a severe one, 16.3% (95% CI, 9.6-26.2) a moderate one, and 11.2% (95% CI, 5.9-20.4) a mild secondary reaction.

Among self-respondents with biphasic reactions (Figure 4), 52.0% (95% CI, 38.0-65.7) reported a mild secondary reaction given a mild initial reaction. When the initial reaction was moderate, over half (58.8%; 95% CI, 49.7-67.4) reported a moderate secondary reaction. When the initial reaction was severe, 45.4% (95% CI, 35.6-55.4) indicated a severe one, 31.9% (95% CI, 23.4-42.0) a moderate one, 15.5% (95% CI, 9.5-24.2) a mild one, and 7.2% (95% CI, 3.4-14.5) a very severe secondary reaction. In the case of a very severe initial reaction, 42.9% (95% CI, 31.1-55.5) indicated a very severe secondary reaction, 31.8% (95% CI, 21.3-44.4) reported a severe one, 20.6% (95% CI, 12.2-32.6) a moderate one, and 3.2% (95% CI, 0.8-12.1) a mild secondary reaction.

The most common food culprits among parent or guardian respondents reporting biphasic reactions (Table II) were peanut (23.8%; 95% CI, 19.2-29.1) and milk (14.1%; 95% CI,

10.6-18.7). Among self-respondents, common culprits were tree nut (12.6%; 95% CI, 9.4-16.6) and wheat (12.0%; 95% CI, 8.9-16.0). Approximately 25% of self-respondents reported experiencing stress (26.1%; 95% CI, 21.7-31.1) or using medication (25.8%; 95% CI, 21.4-30.8) around the time of the food-related allergic reaction. Among parent or guardian respondents, 4.8% (95% CI, 2.9-8.0) reported an infection or virus, whereas 4.1% (95% CI, 2.4-7.2) reported lack of sleep or stress around the time of the initial food-related allergic reaction.

Nearly half of parent or guardian respondents reported that children and young adults who experienced a biphasic reaction (49.3%, 95% CI, 43.6-55.1) went to the ED in response to the food-related allergic reaction, 17.2% (95% CI, 13.3-22.1) were hospitalized, and 4.8% (95% CI, 2.9-8.0) were admitted to the intensive care unit. Among self-respondents, 23.4% (95% CI, 19.2-28.3) went to the ED in response to the food-related allergic reaction, 9.6% (95% CI, 6.9-13.3) were hospitalized, and 4.5% (95% CI, 2.7-7.3) were admitted to the intensive care unit. Over 60% of parents or guardian respondents (62.4%; 95% CI, 56.7-67.8) and over half of self-respondents (51.4%; 95% CI, 46.0-56.7) reported onset of the secondary reaction within 1 to 5 hours after the initial reaction. Others reported onset less than 1 hour (parent or guardian response: 16.9%, 95% CI, 13.0-21.7; self-respondents: 16.8%, 95% CI, 13.2-21.2), 6 to 10 hours (parent or guardian response: 9.7%, 95% CI, 6.7-13.6; self-respondents: 12.9%, 95% CI, 9.7-17.0), 11 to 24 hours (parent or guardian response: 5.9%, 95% CI, 3.8-9.2; self-respondents: 10.2%, 95% CI, 7.4-14.0), and more than 24

TABLE II. Characteristics of most recent food-related allergic reaction among Food Allergy Research and Education Registry respondents with reported biphasic reaction

Variable	Parent/guardian respondents (n = 290)			Self-respondents (n = 333)		
	n	%	95% confidence interval	n	%	95% confidence interval
Age at time of initial reaction, y						
<5	92	31.7	26.6-37.3	15	4.5	2.8-7.4
5-12	151	52.1	46.3-57.8	4	1.2	0.5-3.2
13-17	39	13.4	10-17.9	4	1.2	0.5-3.2
18-25	8	2.8	1.4-5.4	44	13.2	10.1-17.5
26-66	0	0	—	247	74.2	69.9-79.3
>66	0	0	—	16	4.8	3.0-7.8
Unknown/missing	0	0	—	3	0.9	0.3-2.8
Route of exposure for initial reaction						
Injection (shot)	1	0.3	0.04-2.4	0	0	—
Ingestion (eating, licking)	257	88.6	84.4-91.8	293	88	84.1-91.1
Inhalation (breathing)	6	2.1	0.9-4.5	21	6.3	4.1-9.5
Skin contact (touching)	18	6.2	3.9-9.7	14	4.2	2.5-7.0
Unsure/missing	8	2.8	1.4-5.4	5	1.5	0.6-3.6
Food culprit of initial reaction						
Peanut	69	23.8	19.2-29.1	34	10.2	7.4-14.0
Tree nut	61	21	16.7-26.1	42	12.6	9.4-16.6
Milk	41	14.1	10.6-18.7	39	11.7	8.9-15.6
Egg	37	12.8	9.4-17.1	14	4.2	2.5-7.0
Other*	37	12.8	9.4-17.1	66	19.8	15.9-24.5
Wheat	12	4.1	2.4-7.2	40	12	8.9-16.0
Sesame	9	3.1	1.6-5.9	5	1.5	0.6-3.6
Seeds (other than mustard, sesame)	6	2.1	0.9-4.5	1	0.3	0.04-2.1
Shellfish	5	1.7	0.7-4.1	18	5.4	3.4-8.4
Fruits	5	1.7	0.7-4.1	13	3.9	2.3-6.6
Vegetables	3	1	0.3-3.2	5	1.5	0.6-3.6
Nonfood items	2	0.7	0.2-2.7	3	0.9	0.3-2.8
Fin fish	1	0.3	0.04-2.4	3	0.9	0.3-2.8
Soy	1	0.3	0.04-2.4	13	3.9	2.3-6.6
Herbs or spices	1	0.3	0.04-2.4	10	3	1.6-5.5
Mustard	0	0	—	2	0.6	0.1-2.4
Beans, legumes or, pulses (other than soy)	0	0	—	5	1.5	0.6-3.6
Cereals and grains (other than wheat)	0	0	—	6	1.8	0.8-4.0
Meats	0	0	—	14	4.2	2.5-7.0
Amount of food culprit consumed						
Respondent did not consume allergen	22	7.6	5.0-11.3	27	8.1	5.6-11.6
Contact with lip or mouth without swallowing	14	4.8	2.9-8.0	19	5.7	3.7-8.7
One mouthful	135	46.6	40.9-52.3	98	28.5	23.9-33.6
Half of meal	52	17.9	13.9-22.8	73	21.9	17.8-26.7
Entire meal	32	11	7.9-15.2	85	25.6	21.1-30.5
Unsure/missing	35	12.1	8.8-16.4	34	10.2	7.4-14.0
Cofactors around time of initial reaction						
Blood transfusion	1	0.3	0.04-2.1	1	0.3	0.04-2.1
Bone marrow/organ transplantation	1	0.3	0.04-2.1	0	0	—
Alcohol consumption	0	0	—	37	11.1	8.1-15.0
Exercise before eating	6	2.1	0.9-4.5	10	3	1.6-5.5
Exercise after eating	8	2.8	1.4-5.4	10	3	1.6-5.5
Medication use	29	10	7.0-14.0	86	25.8	21.4-30.8
Infection or viruses	14	4.8	2.9-8.0	18	5.4	3.4-8.4
Stress	12	4.1	2.4-7.2	87	26.1	21.7-31.1
Tick bite	0	0	—	4	1.2	0.4-3.2
Lack of sleep	12	4.1	2.4-7.2	63	18.9	15.1-23.5

(continued)

TABLE II. (Continued)

Variable	Parent/guardian respondents (n = 290)			Self-respondents (n = 333)		
	n	%	95% confidence interval	n	%	95% confidence interval
Travel abroad	4	1.4	0.5-3.6	9	2.7	1.4-5.1
Menstrual period	3	1	0.3-3.2	22	6.6	4.4-9.8
Vaccination	7	2.4	1.1-5.0	8	2.4	1.2-4.7
Unsure	13	4.5	2.6-7.6	19	5.7	3.7-8.8
Type of help received during most recent reaction						
Ambulance/911	72	24.8	20.2-30.1	35	10.5	7.6-14.3
Admitted to hospital	50	17.2	13.3-22.1	32	9.6	6.9-13.3
Admitted to intensive care unit	14	4.8	2.9-8.0	15	4.5	2.7-7.3
Family/friends	130	44.8	39.2-50.6	111	33.3	28.5-38.6
General practitioner	36	12.4	9.1-16.8	16	4.8	3.0-7.7
Allergist	32	11	7.9-15.2	17	5.1	3.2-8.1
Pharmacy	2	0.7	0.2-2.7	9	2.7	1.4-5.1
Visited emergency room	143	49.3	43.6-55.1	78	23.4	19.2-28.3
Visited urgent care	17	5.9	3.7-9.2	14	4.2	2.5-7.0
Time to onset of secondary reaction, h						
<1	49	16.9	13.0-21.7	56	16.8	13.2-21.2
1-5	181	62.4	56.7-67.8	171	51.4	46.0-56.7
6-10	28	9.7	6.7-13.6	43	12.9	9.7-17.0
11-24	17	5.9	3.8-9.2	34	10.2	7.4-14.0
>24	14	4.8	2.9-8.0	27	8.1	5.6-11.6
Unknown/missing	1	0.3	0.04-2.4	2	0.6	0.1-2.4
Time elapsed before epinephrine was administered after initial reaction						
Not treated with epinephrine	174	60.0	54.2-65.5	258	77.5	72.7-81.7
Immediately	31	10.7	7.6-14.8	21	6.3	4.1-9.5
<30 min	56	19.3	15.2-24.3	32	9.6	6.9-13.3
30-60 min	14	4.8	2.9-8.0	10	3.0	1.6-5.5
1-2 h	8	2.8	1.4-5.4	5	1.5	0.6-3.6
>2 h	7	2.4	1.2-5.0	6	1.8	0.8-4.0
Unsure/missing	0	0	—	1	0.3	0.04-2.1
Epinephrine doses to treat initial reaction						
Not treated with epinephrine	174	60.0	54.2-65.5	258	77.5	72.7-81.7
1	89	30.7	25.6-36.3	44	13.2	10.0-17.3
2	22	7.6	5.0-11.3	20	6.0	3.9-9.1
≥3	4	1.4	0.5-3.6	7	2.1	1.0-4.3
Unsure/missing	1	0.3	0.05-2.4	4	1.2	0.4-3.2

*Other refers to foods other than those featured in the table.

hours (parent or guardian response: 4.8%, 95% CI, 2.9-8.0; self-respondents: 8.1%, 95% CI, 5.6-11.6) after the initial reaction.

Among respondents who reported a biphasic reaction, 40% of parent or guardian respondents and 22.5% of self-respondents used epinephrine. Among parent or guardian respondents, 19.3% indicated epinephrine administration less than 30 minutes of the initial reaction whereas 9.6% of self-respondents received epinephrine less than 30 minutes of the initial reaction. Among those who reported biphasic reactions, 30.7% of parent or guardian respondents (95% CI, 25.6-36.3) and 13.2% of self-respondents (95% CI, 10.0-17.3) reported treatment with one epinephrine dose, compared with 7.6% of parent or guardian respondents (95% CI, 5.0-11.3) and 6.0% of self-respondents (95% CI, 3.9-9.1) who reported treatment with two epinephrine doses. Among respondents with a resurgence of symptoms less than 1 hour after the initial reaction, 57.1% (95% CI, 42.7-70.4) of parents or guardians reported the child received

epinephrine, whereas 33.9% (95% CI, 22.6-47.5) of self-respondents received epinephrine.

Food-related allergic symptoms among respondents with biphasic reactions

Respondents with biphasic reactions experienced skin symptoms (parent or guardian respondents: 96.9%; 95% CI, 94.1-98.4; self-respondents: 91.6%; 95% CI, 88.1-94.1) and gastrointestinal symptoms (parent or guardian respondents: 82.8%; 95% CI, 77.9-86.7; self-respondents: 89.2%; 95% CI, 85.4-92.1) (Table III) during the most recently reported food-related allergic reaction. Hives (72.4%; 95% CI, 67.0-77.3) were the most common symptom among parent or guardian respondents, followed by itching of the skin (59.3%; 95% CI, 53.5-64.8) and rash (53.1%; 95% CI, 47.3-58.8). The most prevalent gastrointestinal symptoms were vomiting (44.0%; 95% CI, 38.5-49.9) and nausea (35.5%; 95% CI, 30.2-41.2). Oral

TABLE III. Food-related allergic symptoms among respondents with reported biphasic reactions

Type of symptom	Parent/guardian respondents (n = 290)			Self-respondents (n = 333)		
	n	%	95% confidence interval	n	%	95% confidence interval
Any skin	281	96.9	94.1-98.4	305	91.6	88.1-94.1
Hives (welts, urticaria)	210	72.4	67.0-77.3	124	37.2	32.2-42.6
Itching	172	59.3	53.5-64.8	178	53.5	48.1-58.8
Rash (redness of skin)	154	53.1	47.3-58.8	142	42.6	37.4-48.0
Swelling (angioedema)	130	44.8	39.2-50.6	113	33.9	29.0-39.2
Flushing	126	43.5	37.8-49.2	148	44.4	39.2-49.8
Red, itchy, or watery eyes	100	34.5	29.2-40.2	88	26.4	22.0-31.4
Eczema/atopic dermatitis	63	21.7	17.3-26.8	32	9.6	6.9-13.3
Sweating	39	13.5	10.0-17.9	72	21.6	17.5-26.4
Dry skin	26	9	6.2-12.9	46	13.8	10.5-18.0
Unsure	3	1	0.3-3.2	4	1.2	0.4-3.2
Any gastrointestinal	240	82.8	77.9-86.7	297	89.2	85.4-92.1
Bloating	19	6.6	4.2-10.0	117	35.1	30.2-40.4
Bloody stools	3	1	0.3-3.2	8	2.4	1.2-4.7
Constipation	5	1.7	0.7-4.1	36	10.8	7.9-14.6
Diarrhea	57	19.7	15.5-24.7	130	39	33.9-44.4
Difficulty swallowing	57	19.7	15.5-24.7	100	30	25.3-35.2
Itchy or tingling mouth, tongue, throat, or ear canal	104	35.9	30.5-41.6	169	50.8	45.4-56.1
Nausea	103	35.5	30.2-41.2	130	39	33.9-44.4
Odd taste in mouth or metallic taste	23	7.9	5.3-11.8	45	13.5	10.2-17.6
Reflux	15	5.2	3.1-8.4	56	16.8	13.2-21.2
Stomach pain or cramps	99	34.1	28.9-39.8	165	49.6	44.2-54.9
Swelling of mouth or tongue	64	22.1	17.6-27.2	104	31.2	26.5-36.4
Throat tightness	77	26.5	21.8-32.0	131	39.3	34.2-44.7
Vomiting	128	44.1	38.5-49.9	55	16.5	12.9-20.9
Unsure	15	5.2	3.1-8.4	1	0.3	0.04-2.1
Any cardiovascular	84	29.0	24.0-34.5	161	48.4	43.0-53.7
Cardiac arrest	2	0.7	0.1-2.7	2	0.6	0.1-2.3
Chest pain	8	2.8	1.4-5.4	43	12.9	9.7-17.0
Irregular heart rate	15	5.2	3.1-8.4	36	10.8	7.9-14.6
Lightheadedness or dizziness	36	12.4	9.1-16.8	109	32.7	27.9-38.0
Loss of consciousness or passed out	14	4.8	2.9-8.0	13	3.9	2.3-6.6
Low blood pressure	22	7.6	5.0-11.3	30	9	6.3-12.6
Rapid heartbeat (tachycardia)	30	10.3	7.3-14.4	80	24	19.7-28.9
Slow heartbeat (bradycardia)	7	2.4	1.2-5.0	6	1.8	0.8-4.0
Turning blue	16	5.5	3.4-8.8	9	2.7	1.4-5.1
Weak pulse	12	4.1	2.4-7.2	10	3	1.6-5.5
Unsure	80	27.6	22.7-33.0	38	11.4	8.4-15.3
Any behavior/neurologic	200	69.0	63.4-74.0	278	83.5	79.1-87.1
Anxiety	112	38.6	33.2-44.4	173	52	46.6-57.3
Blurred vision	2	0.7	0.2-2.7	33	9.9	7.1-13.6
Confusion	37	12.8	9.4-17.1	51	15.3	11.8-19.6
Depression	6	2.1	0.9-4.5	30	9	6.3-12.6
Fatigue	56	19.3	15.2-24.3	109	32.7	27.9-38.0
Headache	31	10.7	7.6-14.8	109	32.7	27.9-38.0
Irritability	69	23.8	19.2-29.1	79	23.7	19.4-28.6
Feeling of impending doom	39	13.5	10.0-17.9	82	24.6	20.3-29.6
Panic	69	23.8	19.2-29.1	84	25.2	20.8-30.2
Sleep disturbances	16	5.5	3.4-8.8	66	19.8	15.7-24.5
Seizures	0	0	—	1	0.3	0.04-2.1
Withdrawal from social and recreational activities	26	9	6.2-12.9	47	14.1	10.8-18.3
Unsure	33	11.4	8.2-15.6	4	1.2	0.4-3.2

TABLE IV. Adjusted odds of biphasic food-related allergic reactions*

Variable	Adjusted odds ratio	95% confidence interval	P
Sex			
Male (reference)	1.0	—	—
Female	1.6	1.3-2.0	<.001
Race			
White (reference)	1.0	—	—
Black or African-American	1.7	1.0-2.8	.04
Asian	0.7	0.4-1.3	.2
American Indian/Alaska Native	1.6	0.5-5.2	.5
Pacific Islander	0.8	0.08-8.7	.8
Multiracial	1.0	0.7-1.5	.6
Unknown	0.8	0.5-1.5	.6
Ethnicity			
Non-Hispanic or Latinx (reference)	1.0	—	—
Hispanic or Latinx	1.4	1.0-2.0	.05
Unknown	1.0	0.8-1.2	.9
Age at time of initial reaction, y			
<5 (reference)	1.0	—	—
5-12	1.4	1.1-1.9	.01
13-17	1.1	0.7-1.6	.7
18-25	1.1	0.8-1.7	.5
26-66	2.1	1.6-2.8	<.001
>66	1.5	0.9-3.3	.1
Unknown	0.9	0.2-3.2	.9
Multiple top nine food allergies			
No (reference)	1.0	—	—
Yes (>1)	1.1	0.9-1.4	.5
Reaction frequency			
<1/y (reference)	1.0	—	—
≥1/y	2.3	1.8-2.9	<.001
Unknown	1.7	1.3-2.3	<.001
Severity of initial reaction			
Mild (reference)	1.0	—	—
Moderate	2.5	1.9-3.3	<.001
Severe	3.7	2.8-5.0	<.001
Very severe	7.1	5.1-9.9	<.001
Unknown	2.9	1.0-8.3	.05
Comorbid asthma			
No (reference)	1.0	—	—
Yes	1.1	0.9-1.3	.4

*Logistic regressions evaluate which respondent or reaction characteristics are associated with the adjusted odds of reporting a biphasic reaction. Model includes 3326 children and adults. Respondents who were uncertain whether they had a biphasic reaction were excluded (n = 462), as were respondents who had missing data on sex (n = 1).

symptoms included an itchy mouth, tongue, ear, throat, or ear canal (35.9%; 95% CI, 30.5-41.6). Neurologic symptoms included anxiety (38.6%; 95% CI, 33.2-44.4), irritability (23.8%; 95% CI, 19.2-29.1), and panic (23.8%; 95% CI, 19.2-29.1).

Among self-respondents, itching of the skin (53.5%; 95% CI, 48.1-58.8) was the most common symptom, followed by anxiety (52.0%; 95% CI, 46.6-57.3), and an itchy mouth, tongue, ear, throat, or ear canal (50.8%; 95% CI, 45.4-56.1). Self-respondents reported fatigue (32.7%; 95% CI, 27.9-38.0),

headaches (32.7%; 95% CI, 27.9-38.0), and panic (25.2%; 95% CI, 20.8-30.2).

Associations with reported biphasic reaction

Compared with male respondents, females were 1.6 (95% CI, 1.3-2.0) times more likely to report a recent biphasic reaction (Table IV). Black respondents were nearly twice (odds ratio [OR] = 1.7; 95% CI, 1.0-2.8) as likely to report a biphasic reaction compared with White respondents. Compared with respondents who were less than age 5 years at the time of the reaction, respondents aged 5 to 12 years were 1.4 times as likely to report a biphasic reaction (95% CI, 1.1-1.9), and those aged 26 to 66 years were over twice as likely (OR = 2.1; 95% CI, 1.6-2.8). Compared with respondents with a mild initial reaction, respondents with a moderate, severe, or very severe reaction were more likely to report a biphasic reaction (moderate OR = 2.5, 95% CI, 1.9-3.3; severe OR = 3.7, 95% CI, 2.8-5.0; very severe OR = 7.1, 95% CI, 5.1-9.9). Respondents with one or more annual reactions were over twice as likely (OR = 2.3, 95% CI, 1.8-2.9) to report a biphasic reaction compared with respondents with less than one annual reaction. There were no other significant predictors.

DISCUSSION

In a national FA registry, we demonstrated that one in eight parent or guardian respondents and one in five self-respondents reported a biphasic reaction during the most recent food-related allergic reaction. Our data showed that 9.6% of parent or guardian respondents and 15.7% of self-respondents were unsure whether they had experienced a biphasic reaction. We found that respondents' perceived secondary reaction severity was associated with perceived initial reaction severity. Among respondents who reported a biphasic food-related reaction, only 40% of parent or guardian respondents and 22.5% of self-respondents used epinephrine to treat the initial food-related allergic reaction.

The overall incidence of biphasic reactions in this study was 16.4%, which is consistent with existing literature reporting an incidence of 1% to 20%.^{4,8-10,12} Among respondents who reported biphasic food-related allergic reactions in this study, approximately two-thirds of parent of guardians and half of self-respondents reported the second wave of symptoms between 1 and 5 hours after the initial reaction. Interestingly, 17% of respondents reported a second wave less than 1 hour after the initial reaction. We recognize that experiencing secondary symptoms less than 1 hour after the initial reaction might represent a continuation of the initial reaction.

Prior research focused solely on biphasic reactions after anaphylaxis, and many studies vary in their cohort composition (children vs adults vs mixed).^{10,11,20} Our study comprehensively characterizes respondent-reported severity of biphasic food-related allergic reactions from mild to very severe in parent or guardians as well as self-respondents. Although the occurrence of a biphasic food-related allergic reaction was highly variable, we noticed some trends. For example, a small proportion of respondents with a mild initial reaction reported a biphasic reaction. Among those with very severe initial reactions, approximately one in three individuals reported a biphasic reaction. Respondents who indicated a moderate, severe, or very severe initial reaction were more likely to report a biphasic reaction than were those with a mild initial reaction. Our results agree with previous data¹⁶ and highlight the importance of informing

patients and families about the increased risk for a biphasic food-related allergic reaction after a severe initial reaction. This is consistent with previous study results indicating that most biphasic reactions are similar to the original reaction in severity and can range in symptoms from mild to fatal.^{9,11,13} Moreover, this study provides incidence estimates because less severe secondary reactions may go unreported since they are often managed at home by self-administered treatment and do not result in a visit to the ED or physician's office. A 1-hour asymptomatic observation period may be appropriate for patients with a less severe initial reaction and a history of less than one annual reaction. However, our data suggest that high-risk patients, including those with a severe initial reaction and a history of one or more annual reactions, should be observed for longer for a potential biphasic reaction. It is imperative to observe all patients until symptoms have resolved.

Other significant findings in our study include epinephrine use reported by only 40% of parent or guardian respondents and 22.5% of self-respondents to treat the initial reaction. There are several possible reasons, including the lack of epinephrine auto-injector availability during the reaction among children at school,²¹ inaccurately perceived initial reaction severity, and/or physician's recommendation to administer medications other than epinephrine. In a previous study, while 50% of anaphylactic reactions in ED were classified as severe, only 16% received epinephrine.²² Antihistamines and corticosteroids are often the first drugs prescribed by physicians to patients presenting with anaphylaxis.²¹ Previous studies suggested that epinephrine dosage and time from symptom onset to epinephrine administration are predictors of a biphasic reaction.¹⁷ A delay in epinephrine administration to treat initial symptoms has been associated with a biphasic reaction.¹⁶

Our finding that self-respondents were almost twice as likely as parents or guardians to report a biphasic reaction contrasts with a recent study¹³ that found that the biphasic reaction rate did not vary among children and adults or across specific age groups. However, our study was restricted to food-induced allergic reactions, which might account for this difference. The higher occurrence might be affected by accurate recognition of the food-related biphasic reaction by the adult population. Although there are few existing data to confirm whether adults experience biphasic reactions more often than do children, one prospective study²³ that examined biphasic reactions after allergen-specific immunotherapy found that older individuals were more likely to experience a biphasic reaction. Of the children in that study who had an allergic reaction, none had reactions that were biphasic.²³ In the current study, more than half of children with a reported biphasic reaction were aged 5 to 12 years at the time of the initial reaction. A prior study¹⁶ assessing clinical predictors of biphasic reactions in children found that children aged 6 to 9 years were 3.6 times more likely to experience a biphasic reaction. There were also differences regarding the food culprit responsible for the allergic reaction among respondents within the current cohort. Among parents or guardians who reported biphasic reactions, peanut and milk were the most prevalent culprits, whereas tree nut and wheat were the most common food culprits among self-respondents.

In addition, 86% of self-respondents in our study were female and 61% of parent or guardian respondents reported that the subject was male. Previous studies on asthma and FA suggest a higher prevalence in boys before puberty, although this is

reportedly reversed after puberty.²⁴ Another study found that severe food-allergic reactions show a 60:40 female over male dominance in adolescence and adulthood.²⁵

Previous studies showed that cutaneous manifestations are commonly reported during the initial phase of a biphasic reaction.^{10,26} This is consistent with the current study, because both respondents frequently reported skin symptoms. Similar to previous research on biphasic reactions after allergy immunotherapy,^{23,27} there were no specific symptoms in the current study that implicated biphasic reactions. Although hypotension¹¹ was a commonly reported symptom among patients with biphasic reactions after allergen immunotherapy, it affected less than one in 10 of both respondent groups in the current study.

Limitations

Although this study provides important data on biphasic food-related allergic reactions, there are limitations. First, not all survey questions specified whether the question was regarding the initial or secondary reaction. Second, the data are based on respondent self-report and parent proxy, which is subject to reporter and recall biases, particularly for reactions that have occurred in the distant past. However, for most respondents, the time lapse between the most recent reaction and the survey was short. Furthermore, self-report and assessment of severity are not confirmed by a physician, which may lead to misclassification, and they lack the specifics given by ED-based studies. Selection bias may also be an issue, because participation in the Registry is voluntary and has attracted motivated respondents. Therefore, the results of the current study may not be generalizable to the overall food allergic population. In addition, the study is cross-sectional, which does not allow for the temporal analyses of biphasic symptom development, or for the longitudinal assessment of relationships.

CONCLUSION

This study provides comprehensive incidence estimates of biphasic food-related allergic reactions, because self-report reflects reactions that may have been resolved with or without medical attention. Furthermore, the study demonstrates that the severity of the initial food-related allergic reaction is associated with the severity of the secondary reaction. These data are helpful to understand the risk for and potential severity of biphasic reactions.

Acknowledgments

The authors thank Dana Ward for her overall planning efforts and contribution to the manuscript.

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