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ORIGINAL ARTICLE **Epidemiology of Allergic Disease**

Anaphylaxis to foods in a population of adolescents: incidence, characteristics and associated risks

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Summary

Background Information about severe reactions to foods in adolescence is limited.

Objective To describe reactions to foods, including anaphylaxis, with regard to incidence, characteristics and associated risks, among 16-year-olds (adolescents) in a large, population-based birth cohort.

Methods Parent-reported questionnaire data from ages 2–3 months, and 1, 2 and 16 years were used ($N = 3153$). Anaphylaxis at age 16 years was defined per NIAID/FAAN criteria. Immunoglobulin E (IgE) antibodies to 14 common food and inhalant allergens were analysed at ages 4 ($n = 2283$) and 16 years ($n = 2510$). Among adolescents with food-related symptoms (FRS) and for whom blood was available ($n = 221$), 25 additional food allergen extracts or allergen components were analysed. Associations between reactions to foods, and sensitization and allergic multimorbidity were investigated.

Results In the 12 months prior to the 16-year assessment, 8.5% of adolescents had FRS. This included 0.8% ($n = 24$) adolescents who were classified as having anaphylaxis, yielding an incidence rate of 761/100 000 person-years. One-third of adolescents accessed health care during anaphylaxis. Allergic multimorbidity in infancy, as well as sensitization to foods and airborne allergens at age 4 years, was associated with an increased risk for FRS in adolescence. Peanuts and tree nuts were the most common culprit foods for anaphylaxis, and fruits and vegetables for non-anaphylactic reactions. Adolescents with anaphylaxis were significantly more likely to be sensitized to storage proteins (Ara h 2, Cor a 9, Cor a 14) and to be polysensitized to foods ($P < 0.001$ vs. non-anaphylactic reactions).

Conclusions and Clinical Relevance The incidence of food-induced anaphylaxis during adolescence in our population-based birth cohort is higher than previously reported. Adolescents with anaphylaxis differ from adolescents with non-anaphylactic FRS with regard to culprit foods and sensitization. Adolescents with previous anaphylaxis are likely to be polysensitized to foods, particularly tree nut and peanut storage proteins, and which warrants consideration at follow-up.

Keywords allergen-specific immunoglobulin E, anaphylaxis, children, epidemiology, food allergy, food-related symptoms

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Introduction

Food allergy is a major paediatric public health concern, affecting up to 8% of children and adolescents [1, 2]. Hospitalizations for allergic reactions, including food allergy, are increasing, and foods are the most common cause of anaphylaxis in young people [3–6]. Adolescents are at increased risk for food-induced anaphylaxis, because of risk-taking behaviours [7, 8]. Until recently, studies of the epidemiology of anaphylaxis

have been hindered by a lack of agreement on the definition of anaphylaxis. However, criteria for anaphylaxis were proposed in 2006 [9] and are now widely accepted [8].

Population-based incident estimates of anaphylaxis among adolescents and young adults are scarce [10–13]. Those available vary from 6.6–8.7 [12] to 124.5 [13] episodes per 100 000 person-years. In previous studies, anaphylaxis cases were identified from public healthcare settings [11–14] and health maintenance organizations [10]. As such, these rates may underestimate the true incidence as not all individuals who experience anaphylaxis seek health care [15].

To date, few prospective birth cohort studies of allergic disease and sensitization extend to adolescence [16–19]. Furthermore, to our knowledge, no studies have investigated immunoglobulin E (IgE) antibody responses to food allergens and food allergen components among adolescents with food reactions in a population-based setting.

The objective of this study was to describe reactions to foods, including anaphylaxis, with regard to incidence, characteristics and associated risks, among 16-year-olds (adolescents) in a large, population-based birth cohort.

Material and methods

Study population

Participants were enrolled in BAMSE, a population-based, unselected birth cohort of children born in 1994–1996 in Stockholm, Sweden. In total, 4089 children were included in the baseline cohort at ages 2–3 months [20]. Information on background characteristics was obtained by questionnaires at baseline. Information on food-related symptoms (FRS) and environmental and lifestyle exposures was obtained though follow-up questionnaires at ages 1, 2, 4, 8, 12 and 16 years. The follow-up response rate at age 16 years (adolescence) was 78%. At ages 4 and 16 years, 2605 (64%) and 2547 (62%), respectively, of the children participated in a clinical examination including venipunctures.

Participants with available questionnaire data at baseline and ages 1, 2 and 16 years were included in the present study ($n = 3153$, 77% of the baseline cohort). Information on sensitization to food allergens and airborne allergens was available in 2283 (72%) children at age 4 years and 2510 (80%) children at age 16 years.

Ethical permission was obtained by the Regional Ethics Review Board, Karolinska Institutet, Stockholm, Sweden. Parents provided informed consent.

Definitions of food-related symptoms including anaphylaxis at age 16 years

Food-related symptoms. Parent-reported symptom(s) to at least one specified food and at least one specified symptom within the past 12 months prior to the 16-year assessment. The specified foods were cow's milk, hen's egg, codfish, shellfish, wheat or other cereals, soya, sesame seed, apple/pear, peach/nectarine/plum/cherry, kiwi, banana, raw carrot, cashew/pistachio, peanut, hazelnut, walnut/pecan, Brazil nut and almond. The specified symptoms involved the dermatological, respiratory, gastrointestinal and/or cardiovascular systems and/or the oral cavity. As the aim was not to study coeliac disease or lactose intolerance, reports of only gastrointestinal symptoms (vomiting, stomach ache) after exposure to cow's milk and/or wheat were excluded.

Food-induced anaphylaxis ('anaphylaxis'). Anaphylaxis was classified according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria for anaphylaxis [9] and defined as a reaction involving two or more of the following organ systems with any of the symptoms listed below:

Dermatological: generalized urticaria, facial swelling.
Lower respiratory: breathing difficulties, asthma, dyspnoea, cough, hoarseness, indistinct speech.
Gastrointestinal: vomiting, stomach ache.
Cardiovascular: unconsciousness.

As symptoms were based on questionnaire data, information on blood pressure, heart rate or oxygen saturation was not available.

Adolescents with FRS within the past 12 months were classified into one of two mutually exclusive groups: anaphylaxis or non-anaphylaxis.

Foods implicated in anaphylactic and non-anaphylactic reactions are referred to as culprit foods. Culprit foods were not mutually exclusive groups.

Definitions of diagnosis and healthcare contacts

The variable 'doctor-diagnosed food allergy' was based on the parental response to the question 'Has your child ever been diagnosed by a doctor with a food allergy?' at the 16-year assessment. Adolescents were classified as having sought medical care during food-related reactions if parents responded 'yes' to the question, 'Has your child – in the past 12 months – needed acute medical care because of an allergic reaction to a food?' at the 16-year assessment.

Dispensing of epinephrine autoinjectors

Information on dispensed epinephrine autoinjectors (EAI) prescriptions was obtained via linkage to the

Swedish Prescribed Drug Register [21] using each adolescent's unique personal identity number. This register is maintained by Sweden's National Board of Health and Welfare and contains information on all dispensed prescriptions in ambulatory care for the entire Swedish population. For this study, we extracted information on dispensing of EAI (ATC code C01CA24) during the 24 months prior to the 16-year assessment.

Definitions of background characteristics and allergic multimorbidity

Definitions of background characteristics, allergic multimorbidity in infancy and at the 16-year assessment are presented in Table 1.

IgE reactivity

Sera were analysed with fx5®, a mix of food allergens consisting of cow's milk, hen's egg, codfish, wheat, soya and peanut, and with Phadiatop®, a mix of airborne allergens consisting of pollens of timothy, birch and mugwort, danders of cat, dog and horse, as well as house dust mite (*Dermatophagoides pteronyssinus*) and mould (*Cladosporium herbarum*) (ImmunoCAP System; Thermo Fisher Scientific/Phadia AB, Uppsala, Sweden). If either fx5® or Phadiatop® was scored positive (IgE $\geq$ 0.35 kU_A/L), IgE antibodies to the individual food allergens and airborne allergens listed above were analysed.

In addition, for adolescents with FRS within 12 months prior to the 16-year assessment, and for whom sera were available (n = 221), IgE antibodies were further analysed to allergen extracts of hazelnut, walnut, cashew, Brazil nut, almond, sesame and the peach lipid transfer protein (Pru p 3). Pru p 3 was used as a proxy for Lipid transfer proteins (LTPs) from fruits and vegetables [22]. If IgE to any allergen extracts was $\geq$ 0.35 kU_A/L, IgE to allergen components of the associated extract was analysed (Hazelnut: Cor a 1, Cor a 8, Cor a 9, Cor a 14; Walnut: Jug r 1, Jug r 3; Cashew: Ana o 3; Brazil nut: Ber e 1; Peanut: Ara h 1, Ara h 2, Ara h 3, Ara h 8 and Ara h 9). For adolescents with anaphylaxis to soya, the soya allergen components Gly m 4, Gly m 5 and Gly m 6 were analysed. As for food allergens and airborne allergens, an IgE level $\geq$ 0.35 kU_A/L was considered positive. In the heat map (Fig. 1), IgE levels are presented as continuous colour gradients, ranging from the lowest positive level (0.35 kU_A/L) in yellow to the highest levels ($\geq$ 101 kU_A/L) in bright red. Polysensitization was defined as sensitization to $\geq$ 4 foods. All samples were analysed per the manufacturer's instructions at the Department of Clinical Immunology and Allergy, Karolinska University Hospital Solna, Stockholm, Sweden.

Table 1. Definitions of background characteristics and allergic multimorbidity in infancy and at the 16-year assessment (adolescence) among participants in the BAMSE study

Variables	Definition
Background characteristics	
Parental allergy	Doctor-diagnosed asthma and/or hayfever in combination with allergy to furred pets and/or pollen at enrolment for any or both parents
Tobacco smoking	Mother smoked at least 1 cigarette per day during pregnancy and/or any of the parents smoked at least 1 cigarette per day at the time of enrolment
Socio-economic status	Socio-economic status for the household (two categories: white collar worker and blue collar worker)
Allergic multimorbidity in infancy	
Food reactions	Food hypersensitivity between age 3 months and 2 years
Asthma	At least three episodes of wheeze during the two first years of life in combination with treatment with inhaled glucocorticoids and/or sign of suspected hyperactivity without concurrent upper respiratory infection
Rhinitis	Symptoms from eyes/nose (suspected or evident) after exposure to furred pets and/or pollen and/or doctor-diagnosed allergic rhinitis between the ages of 3 months and 2 years
Eczema	Dry skin and itchy rashes for 2 weeks or more with specific localization of rash and/or doctor-diagnosed eczema between the ages of 3 months and 2 years
Allergic multimorbidity at the 16-year assessment (adolescence)	
Asthma	At least four episodes of wheeze in the last 12 months prior to the date of questionnaire 16 or at least one episode of wheeze in the last 12 months in combination with prescribed inhaled steroids occasionally or regularly
Rhinitis	Symptoms of sneezing, a runny or blocked nose, or itchy, red and watery eyes after exposure to furred pets or pollen in the latest 12 months and/or doctor-diagnosed allergic rhinitis between the 12- and 16-year assessments
Eczema	Dry skin in combination with itchy rash and typical localization (arms/legs flexures or wrists/ankles or neck) in the last 12 months prior to the 16-year assessment, and/or doctor's diagnosis of eczema between the 12- and 16-year assessments

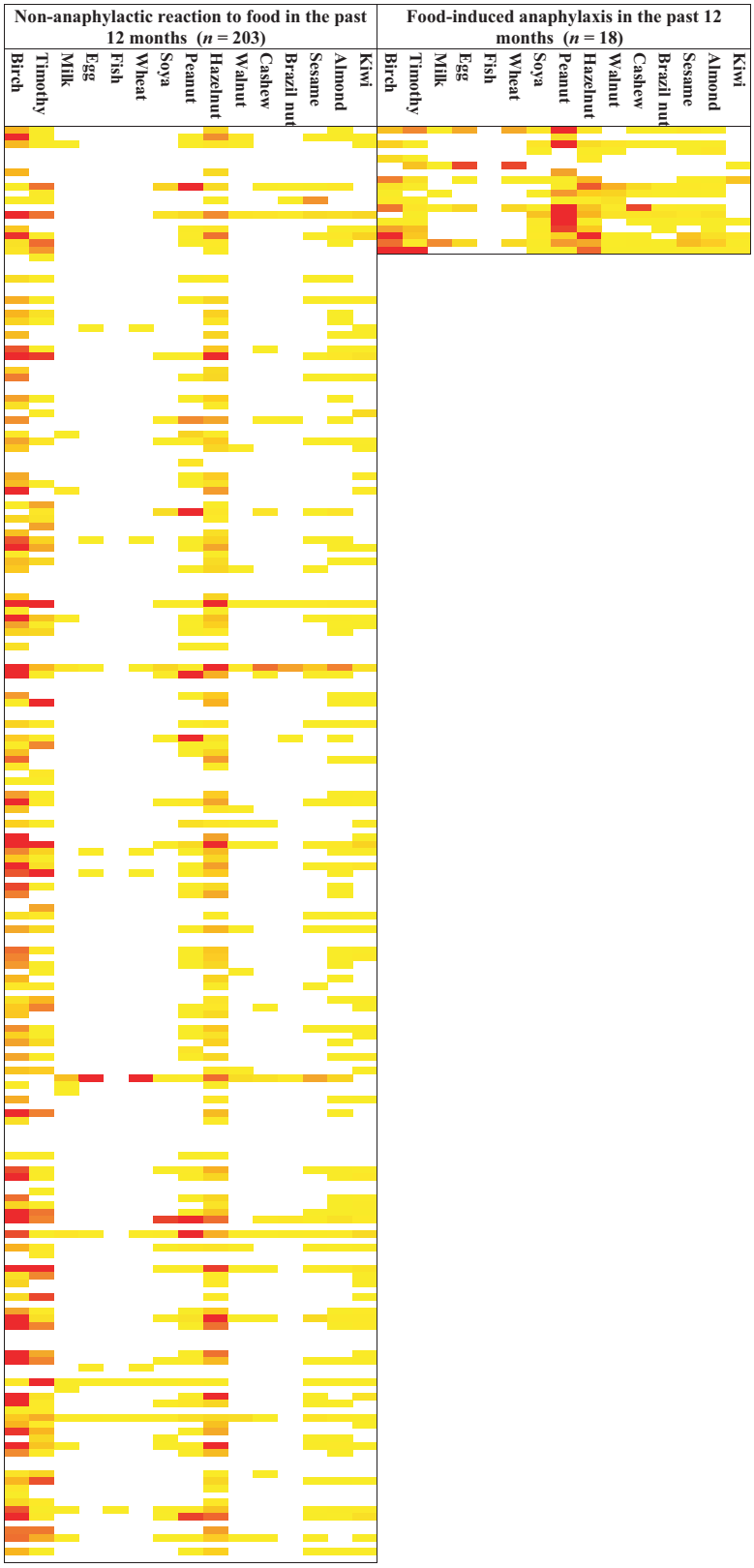


Fig. 1. Heat map depicting positive immunoglobulin E (≥ 0.35 kU_A/L) to selected foods and to timothy and birch pollens among BAMSE participants with food-related symptoms the previous 12 months and for whom sera were analysed at the 16-year assessment, stratified by anaphylaxis. IgE levels are presented as continuous colour gradients, ranging from the lowest positive level (0.35 kU_A/L) in yellow to the highest levels (≥ 101 kU_A/L) in bright red.

Statistics

Descriptive statistics included median, percentages and 95th percent confidence intervals (95% CI). Differences in proportions between groups were analysed using chi-square or Fisher's exact tests, as appropriate. The incidence rate of anaphylaxis per 100 000 person-years was calculated from the number of anaphylaxis cases divided by the number of adolescents in the study population. The incidence rate of anaphylaxis per 100 000 person-years was calculated from the number of anaphylaxis cases divided by the sum of person-time at risk during the 12 months prior to the questionnaire. Any adolescent with anaphylaxis could only contribute with one event. Associations between the outcomes (no food reaction; non-anaphylactic reactions; anaphylactic reactions) and allergic multimorbidity in infancy and at age 16, as well as sensitization at ages 4 and 16 years, were estimated using multivariable logistic regression and expressed as odds ratio (OR) and 95% CI. Potential confounders included sex, parental allergy, socio-economic status and parental smoking. The first three covariates were included in the final model as they changed the crude OR point estimate by > 10%. Parental smoking was not included in analyses restricted to any food reactions vs. anaphylaxis as no parents in the latter group reported smoking. As early life reactions to foods, allergic multimorbidity and sensitization to food and airborne allergens are intercorrelated [23], they were not included in the final model. Analysis was performed with STATA Statistical Software (release 12.1; StataCorp, College Station, TX, USA).

Results

Our study population ($N = 3153$) corresponded well with the original cohort (Table 2). Allergic multimorbidity in infancy (food reactions, asthma, eczema and rhinitis) and sensitization to food allergens and airborne allergens (measured with fx5® and Phadiatop®) at age 4 years did not differ between our study population and the original cohort (data not shown).

Incidence of food-related symptoms and anaphylaxis among adolescents

In total, 269 adolescents (8.5%) had FRS within the 12 months prior to the 16-year assessment. Twenty-four of these adolescents (0.8% of the study population) fulfilled the criteria for anaphylaxis, yielding an incidence rate of 761/100 000 person-years (95% CI 488–1133). Of these 24 adolescents, the parents of eight participants (33%) reported that medical care was sought during a food-related reaction in the 12 months prior to the 16-year assessment. If only these eight adolescents had been taken into account, the incidence of anaphylaxis would have been 254/100 000 person-years (95% CI 110–500).

Table 2. Descriptive information of the original cohort and the final study population among participants in the BAMSE birth cohort

	Percent (95% CI)	
	Original cohort ($n = 4089$)	Study population ($n = 3153$)
Sex (male)	50.5 (49.0–52.0)	49.7 (48.0–51.5)
Parental allergy*	29.7 (28.3–31.1)	30.7 (29.1–32.4)
Maternal age < 26 years	7.8 (7.0–8.7)	7.2 (6.4–8.2)
White collar workers	82.7 (81.5–83.9)	84.3 (82.9–85.5)
Tobacco smoking†	24.9 (23.5–26.2)	24.3 (22.8–25.8)
Exclusive breastfeeding ≥ 4 months	79.5 (78.2–80.8)	80.3 (78.9–81.7)

*Doctor's diagnosis of asthma and/or hayfever in combination with allergy to furred pets and/or pollen at enrolment for either or both parents.

†Mother smoked at least one cigarette per day during pregnancy and/or either or both parents smoked ≥ 1 cigarette per day at the time of enrolment.

Doctor-diagnosed food allergy and epinephrine autoinjectors dispensing among adolescents

In the study population ($n = 3153$), parent-reported doctor-diagnosed food allergy was 12% and 2.6% had been dispensed an EAI in 24 months prior to the 16-year assessment. The corresponding proportions among the 245 adolescents with non-anaphylactic reactions were 42% and 7.8%, respectively.

Among the 24 adolescents with anaphylaxis, 91% had parent-reported doctor-diagnosed food allergy ever and 67% had been dispensed an EAI in 24 months prior to the 16-year assessment.

Allergic multimorbidity in adolescence and early childhood

Allergic multimorbidity was common among adolescents with FRS within 12 months prior to the 16-year assessment irrespective of severity of the reaction (Table 3). A total of 71% of all adolescents with FRS had asthma, rhinitis and/or eczema at the 16-year assessment. The corresponding proportions were 76% among adolescents with anaphylaxis and 71% among adolescents with non-anaphylactic reactions. Asthma, rhinitis, eczema and sensitization to food and airborne allergens at age 16 years were significantly associated with FRS with a stronger association among adolescents with anaphylaxis than among adolescents with non-anaphylactic reactions (Table 3).

Table 3. Background characteristics, allergic multimorbidity and sensitization at 16 years in relation to food-related symptoms (FRS) among participants in the BAMSE birth cohort with complete information on FRS at 1, 2 and 16 years (n = 3153)

	FRS* in the 12 months prior to the 16-year assessment			Adjusted† OR	
	Yes		No		
	Anaphylaxis A	Not anaphylaxis B	C		
	N = 24	N = 245	N = 2884		
	n (%)	n (%)	n (%)	A vs. C	B vs. C
N = 3153					
Background characteristics					
Sex – boys	11 (45.8)	100 (40.8)	1456 (50.5)	0.81 (0.36–1.82)	0.66 (0.50–0.86)
Parental allergy	12 (50.0)	106 (43.8)	842 (29.5)	2.40 (1.07–5.37)	1.89 (1.44–2.47)
Socio-economic status-parents white collar workers	19 (79.2)	198 (82.5)	2400 (84.5)	0.68 (0.25–1.83)	0.84 (0.59–1.19)
Allergic multimorbidity at 16 years of age					
Asthma	11 (45.8)	32 (13.4)	153 (5.4)	13.1 (5.67–30.2)	2.36 (1.55–3.59)
Rhinitis	18 (75.0)	151 (63.2)	609 (21.6)	10.4 (4.03–26.7)	6.33 (4.74–8.45)
Eczema	8 (33.3)	56 (23.1)	242 (8.4)	5.06 (2.12–12.0)	3.08 (2.21–4.30)
	N = 18	N = 205	N = 2287		
	n (%)	n (%)	n (%)		
N = 2510					
Sensitization at 16 years					
Food allergens‡	17 (94.4)	52 (25.4)	258 (11.3)	129 (17.1–980)	2.41 (1.69–3.44)
Airborne allergens§	16 (88.9)	151 (73.7)	920 (40.2)	11.4 (2.59–50.6)	4.05 (2.90–5.64)

*Reactions to specified foods. Adolescents with only gastrointestinal symptoms after exposure to milk, and/or wheat and other cereals are excluded.

†Adjusted for sex, parental allergy and socio-economic status.

‡Sera with ≥ 0.35 kU_A/L to food mix (fx5®).

§Sera with ≥ 0.35 kU_A/L to Phadiatop®.

We also examined the association between allergic multimorbidity in infancy and sensitization at age 4 years in relation to FRS in adolescence (Table 4). Early life food reactions and allergic multimorbidity were associated risks for FRS in adolescence, as were sensitization to foods and airborne allergens at age 4 years. All observed associations were stronger for adolescents with anaphylaxis than for adolescents with non-anaphylactic reactions.

In total, 74% of adolescents with anaphylaxis had food-related reactions in infancy. The corresponding number for adolescents with non-anaphylactic reactions was 31% ($P < 0.001$ vs. anaphylaxis).

Culprit foods, symptoms and allergen-specific IgE levels

Culprit foods and associated symptoms for the 24 adolescents with anaphylaxis are presented in Table 5. Common culprit foods included peanut (n = 7), tree nuts (n = 5), egg (n = 3) and soya (n = 3). Six individuals (ID 9, 12, 14, 21, 22, 23) had FRS fulfilling the criteria for anaphylaxis to more than one specified food (Table 5). Dermatological symptoms were most prevalent (92%), followed by symptoms involving the lower respiratory tract and oral cavity (each 83%). Unconsciousness was reported for one adolescent. One adolescent (ID nr 6, culprit food apple/pear, peach) would not have been classified as having had anaphylaxis if the symptoms hoarseness and indistinct speech had not been considered as respiratory symptoms indicative of anaphylaxis. None of the three adolescents with reported fruit/vegetable-induced anaphylaxis (ID 6, 14, 22) had been dispensed an EAI in 24 months prior to the 16-year assessment, nor had they sought medical care during the reaction.

Sera from the 16-year assessment were available for 18/24 adolescents with anaphylaxis for whom specific IgE to the culprit foods was analysed in 17/18 (94%). In total, 16/17 (94%) adolescents had positive IgE to the culprit food (Table 5). All adolescents with anaphylaxis to peanut, tree nuts and soya and for whom sera were available (n = 9) were sensitized to tree nut/peanut storage proteins (Table 5). The three adolescents with anaphylaxis to soya (ID nr 4, 18 and 20) had IgE levels to soya extract (2.0, 6.7, and 25.0 kU_A/L, respectively). But these adolescents had IgE levels to peanut which were higher (> 100, > 100 and 93 kU_A/L, respectively) than their levels to soya. Further, all three had IgE reactivity to both soya and peanut storage proteins. Both adolescents with reported fruit/vegetable-induced

Table 4. Allergic multimorbidity and sensitization in early life in relation to food-related symptoms (FRS) in adolescence among participants in the BAMSE birth cohort with complete information on FRS at 1, 2 and 16 years (n = 3153)

	FRS* in the 12 months prior to the 16-year assessment			Adjusted† OR	
	Yes*		No		
	Anaphylaxis A	Not anaphylaxis B	C		
	N = 24	N = 245	N = 2884		
	n (%)	n (%)	n (%)	A vs. C	B vs. C
N = 3153					
Allergic multimorbidity in infancy					
Reactions to foods	17 (73.9)	70 (30.8)	367 (13.5)	17.7 (6.91–45.2)	2.87 (2.11–3.91)
Asthma	9 (37.5)	30 (12.7)	228 (8.2)	6.42 (2.72–15.1)	1.60 (1.05–2.43)
Rhinitis	6 (25.0)	28 (12.1)	181 (6.6)	4.18 (1.59–10.9)	1.89 (1.22–2.92)
Eczema	19 (79.2)	109 (46.4)	653 (23.5)	11.7 (4.34–31.6)	2.63 (1.99–3.46)
	N = 18	N = 168	N = 2097		
	n (%)	n (%)	n (%)		
N = 2283					
Sensitization at age 4 years					
Food allergens‡	14 (77.8)	57 (33.9)	292 (13.9)	20.9 (6.80–64.1)	3.13 (2.21–4.43)
Airborne allergens§	11 (61.1)	76 (45.2)	264 (12.6)	11.0 (4.15–29.1)	5.66 (4.02–7.95)

*Reactions to specified foods. Adolescents with only gastrointestinal symptoms after exposure to milk, and/or wheat and other cereals are excluded.

†Adjusted for sex, parental allergy and socio-economic status.

‡Sera with ≥ 0.35 kU_A/L to food mix (fx5®).

§Sera with ≥ 0.35 kU_A/L to Phadiatop®.

anaphylaxis for whom sera were available (ID nr 6 and 22) were sensitized to birch pollen (12 and > 100 kU_A/L, respectively). One of these two was also sensitized to Pru p 3 (ID nr 22).

Among the 245 adolescents with non-anaphylactic reactions, fruits and vegetables were the dominating culprit foods (75%) followed by hazelnut (16%). Apple/pear were the most common triggers, followed by kiwi and peach/nectarine/plum/cherry. Irrespective of culprit food, the most common symptom was oral itch (73%). Sera were available from 203/245 (83%) adolescents with non-anaphylactic reactions. Specific IgE to the culprit foods was analysed in 146/204 (71.9%) adolescents, of whom 44% had positive IgE to the culprit food. Among adolescents with non-anaphylactic reactions to fruits and vegetables, 73% were sensitized to birch and/or timothy pollens and 9 (5.8%) were sensitized to Pru p 3.

Patterns of sensitization

The heat map in Fig. 1 illustrates the patterns of IgE reactivity to selected foods and pollens among 227/269 (84%) of adolescents with FRS in the 12 months prior to the 16-year assessment and for whom sera were available at the 16-year assessment, stratified by anaphylaxis. Polysensitization, primarily to peanut and multiple tree nuts, was significantly more common among adolescents with anaphylaxis compared to adolescents with non-anaphylactic reactions (77% and 31%, respectively, P-value < 0.001). By far, hazelnut was the most common sensitizing food among adolescents with non-anaphylactic reactions (60%). Cosensitization to birch and/or timothy pollen was common among adolescents with anaphylaxis and adolescents with non-anaphylactic reactions (83% vs. 66%; P-value = 0.13).

Figure 2 shows the prevalence of sensitization and median IgE levels to various allergen components from individual plant foods at age 16 years among adolescents with FRS, stratified by anaphylaxis. The majority (67%) of adolescents with anaphylaxis were sensitized to at least one storage protein (Ara h 2 from peanut, Cor a 9 or Cor a 14 from hazelnut), vs. 13% of the adolescents with non-anaphylactic reactions (P-value < 0.001). Sensitization to the birch pollen homologues Ara h 8 from peanut or Cor a 1 from hazelnut was common in both groups (62% and 59%, respectively, P-value = 0.45).

Discussion

To our knowledge, this is the first study on the incidence and characteristics of FRS including anaphylaxis among adolescents in a population-based birth cohort with a prospective design and data collection beginning

Table 5. Culprit foods, symptoms and allergen-specific IgE levels among 24 adolescents with anaphylaxis to foods in the 12 months prior to the 16-year assessment ('adolescence') in the BAMSE study

		Symptoms								Allergen-specific IgE levels kUA/l in adolescence	
ID nr	Culprit foods	D	UR	LR	L	GI	OC	CV	N	Food	Components
1	Milk			X		X	X			Milk 1.8	
3	Peanut	X		X			X			Peanut 11	Ara h 1 0.53, Ara h 2 9.8, Ara h 3 < 0.35, Ara h 8 < 0.35, Ara h 9 < 0.35
4	Soya	X	X	X			X			Soya 6.7	Gly m 4 < 0.35, Gly m 5 2.4, Gly m 6 7.4
										Peanut > 100	Ara h 1 22, Ara h 2 80, Ara h 3 27, Ara h 8 2.4, Ara h 9 < 0.35
5	Hazelnut	X		X			X			Hazelnut 2.2	Cor a 1 < 0.35, Cor a 8 < 0.35, Cor a 9 2.7, Cor a 14 2.5
6	Apple/pear, peach etc.*	X			X		X			Fruits n.a.	Pru p 3 < 0.35
9	Egg	X				X	X			Egg 87	
	Banana	X				X				Banana n.a.	
10	Peanut	X		X			X		X	Peanut 42	Ara h 1 12, Ara h 2 38, Ara h 3 0.26, Ara h 8 < 0.35, Ara h 9 < 0.35
11	Egg	X	X			X				Egg 0.67	
12	Hazelnut	X		X		X	X		X	Hazelnut 80	Cor a 1 3.6, Cor a 8 < 0.35, Cor a 9 63, Cor a 14 70
	Cashew/pistachio	X		X		X	X		X	Cashew 12 Pistachio 7.3	Ana o 3 10
15	Milk	X				X	X			Milk 0.59	
16	Walnut/pecan	X	X	X		X	X			Walnut 9 Pecan 2.8	Jug r 1 2.1, Jug r 3 < 0.10
17	Egg	X				X	X			Egg 13	
18	Soya	X		X						Soya 25	Gly m 4 < 0.35, Gly m 5 7.2, Gly m 6 21
										Peanut > 100	Ara h 1 > 101, Ara h 2 > 101, Ara h 3 > 101, Ara h 8 < 0.35, Ara h 9 0.67
19	Peanut	X		X		X	X			Peanut > 100	Ara h 1 90, Ara h 2 40, Ara h 3 24, Ara h 8 0.15, Ara h 9 < 0.35
20	Soya	X	X	X			X			Soya 2	Gly m 4 1.4, Gly m 5 < 0.35, Gly m 6 1.4
										Peanut 89	Ara h 1 28, Ara h 2 46, Ara h 3 15, Ara h 8 3.1, Ara h 9 < 0.35
22	Apple/pear, peach etc.*	X		X			X			Fruits n.a.	Pru p 3 0.50
	Raw carrot	X		X			X			Carrot n.a.	
23	Milk	X	X	X	X	X	X		X	Milk 56	
	Egg	X	X	X	X	X	X		X	Egg 12	
24	Fish	X		X			X			Fish < 0.35	
	Missing allergen-specific IgE levels in adolescence										
2	Egg				X	X	X	X	X	Missing	
7	Peanut	X		X	X	X	X			Missing	
8	Peanut	X		X	X	X	X			Missing	
13	Peanut	X	X	X						Missing	
14	Apple/pear	X	X	X	X		X			Missing	
	Kiwi	X		X	X		X				
	Hazelnut	X		X	X		X				
21	Peanut	X		X						Missing	
	Walnut/Pecan, Hazelnut, Brazil nut	X		X							

D, dermatological (generalized urticaria, facial swelling); UR, upper respiratory tract (itchy eyes or nose, nasal congestion or rhinorrhea); LR, lower respiratory tract (breathing difficulties, asthma, dyspnoea, cough); L, laryngeal (hoarseness, indistinct speech); GI, gastrointestinal (vomiting, stomach ache); OC, oral cavity (Swollen feeling in mouth, throat, itch in mouth, throat, ears), CV, cardiovascular (unconsciousness); N, neurological (pronounced tiredness, decreased consciousness); n.a., not analysed.

*Peach/plum/nectarine/cherry.

in early life. To date, cases of anaphylaxis have been retrieved primarily from public healthcare settings, thereby hampering extrapolation of the findings to the general population. Previous studies indicate that only half of patients with anaphylaxis are treated at the emergency department [10, 13, 24]. As we identified

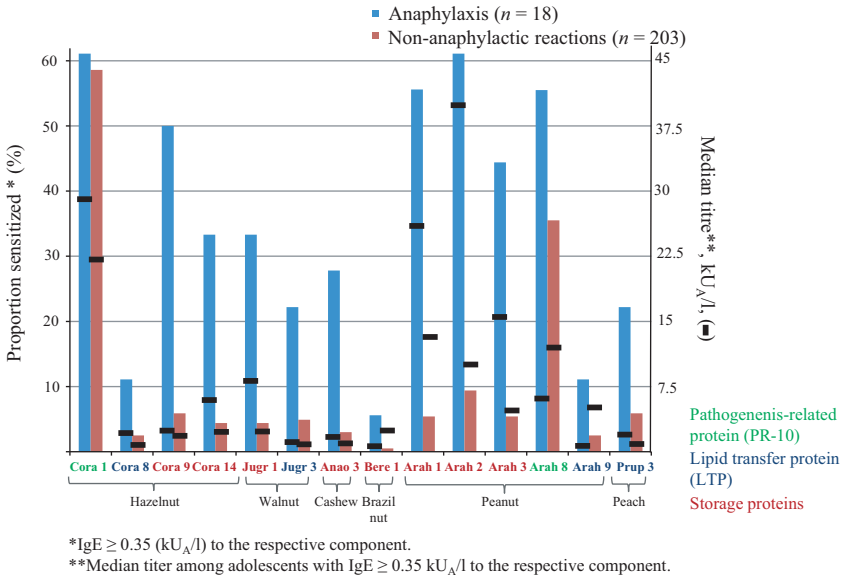


Fig. 2. Sensitization to plant food allergen components at 16 years among 221 adolescents in the BAMSE cohort with food-related symptoms in the past 12 months and for whom sera were available, stratified by anaphylaxis.

anaphylaxis in a population-based cohort, we were able to capture episodes of anaphylaxis irrespective of contact with health care.

In the present study, 8.5% (n = 269) of adolescents had parent-reported FRS in the 12 months prior to the 16-year assessment and 0.8% (n = 24) fulfilled the NIAID/FAAN criteria for anaphylaxis. At most, only one-third of the adolescents who fulfilled the criteria for anaphylaxis contacted health care during anaphylaxis. Similarly, other authors have reported comparable estimates in relation to severe reactions to peanuts [15]. As anaphylaxis may resolve either spontaneously or upon administration of an EAI, individuals may not be prompted to seek acute medical care. However, our data need to be interpreted with caution as numbers are low.

The incidence rate of reported food-induced anaphylaxis in this adolescent population was 761/100 000 person-years (95% CI 488–1133), or 254/100 000 person-years (95% CI 110–500) if restricted to adolescents who had contacted health care. Yet, these rates are higher than previously reported incidence rates of anaphylaxis among adolescents [10–13]. This is not surprising given that earlier studies on the epidemiology of anaphylaxis in adolescence captured anaphylaxis episodes only if an individual sought health care [10–14, 25]. For example, in a population-based survey among American adults, it was estimated that at least one in 50 adults, but perhaps as frequently as one in 20 adults, had a prior episode of anaphylaxis [26]. In addition to differences in study design, diverse classifications of anaphylaxis may also contribute to the divergent estimates [10–13]. In the context of our study, the incidence rate of healthcare provider diagnosed anaphylaxis of 125 per 100 000 person-years (95% CI 73.8–197) among adolescents aged 15–19 years reported by Tejedor Alonso et al. [13] is particularly interesting, as their criteria for anaphylaxis paralleled those which we used.

The incidence of anaphylaxis in our study population is high also when compared to earlier estimates of the incidence in the general population [27, 28]. This may be partly explained by age, given that risk-taking behaviours are common among food-allergic adolescents [29–33]. In fact, Turner et al. [25] recently reported that when investigating fatalities and admissions due to food-induced anaphylaxis in the general population in England and Wales over a 20-year period, fatalities peaked in the age group 15–19. In addition, the incidence of admissions due to food-induced anaphylaxis was the second highest in this particular age group.

In our study population, FRS in adolescence were significantly associated with allergic multimorbidity and sensitization both in infancy and in adolescence. Although the relationship between food allergy, allergic multimorbidity and sensitization in childhood is well established [16, 17, 34–37], there are few studies on associated risks for anaphylaxis in adolescence.

Our finding that peanuts and tree nuts were the dominating culprit foods among the adolescents with anaphylaxis aligns with others' findings [4, 5, 24, 38–40]. In contrast, among adolescents with non-anaphylactic reactions, oral itch was the most frequently reported symptom and fruits and vegetables were the most common culprit foods, findings which are consistent with a

previous report [41]. Adolescents with anaphylaxis were more likely to be sensitized to multiple foods and to hazelnut and peanut storage proteins, which are associated with severe reactions (Ara h 2 from peanut, Cor a 9 and Cor a 14 from hazelnut) [42, 43]. This differed from adolescents with non-anaphylactic reactions, who were more commonly sensitized to the birch pollen homologues Ara h 8 from peanut or Cor a 1 from hazelnut, and infrequently sensitized to the storage proteins. As such, these findings indicate that many non-anaphylactic reactions were caused by pollen-associated oral allergy syndrome. Although this syndrome usually is associated with mild and local symptoms, some individuals may, under certain conditions, experience systemic symptoms [44–46]. In our study population, three of the 187 adolescents with FRS to fruits/vegetables fulfilled the criteria for anaphylaxis. Hypopharyngeal symptoms, which are a manifestation of oral allergy syndrome, may be misinterpreted by adolescents as lower respiratory symptoms and thus may have resulted in misclassification of anaphylaxis herein. However, such individuals may also by misclassified by healthcare providers.

The severity of an allergic reaction to foods depends on multiple factors, related to both the host and the event, with the dose of the allergen being of great importance [47]. In the present study, we did not have information about cofactors such as exercise, nor did we have information about the ingested dose of the culprit foods. It is most likely that some of the 245 adolescents with non-anaphylactic reactions would have been at risk for anaphylaxis had the ingested dose been sufficiently large.

The strength of this study is its prospective design, with data collection beginning in early life. Almost yearly follow-ups in early life minimize recall bias for both symptoms and exposures. As well, the population-based design with a large sample size and small losses to follow-up permits high generalizability of the results. Furthermore, a large number of the participants were tested for IgE at both ages 4 and 16 years. At the latter age, we expanded the number of food allergen tested from 6 to 25 food allergens or food allergen components.

Some limitations should be considered when interpreting our results. Due to our study design, we cannot dismiss the possibility of misclassification of anaphylaxis. First, in the absence of validated questionnaires designed to capture anaphylaxis as clinical outcome, we used the currently accepted NIAID/FAAN criteria. However, as these criteria are intended to be used for reactions observed by physicians; adapting these criteria to parental questionnaire data could cause misclassification of anaphylaxis. For example, according to the NIAID/FAAN criteria, gastrointestinal symptoms should be persistent to be considered indicative of anaphylaxis. However, in our study, we could not discriminate between short lasting and persistent symptoms. In addition, some queried symptoms, such as abdominal pain and facial swelling, could not be graded by severity. One could speculate that some adolescents may have had only mild abdominal pain or mild lip swelling, which should not be considered as indicative of anaphylaxis [9]. However, we regarded abdominal pain and facial swelling as subcriteria for anaphylaxis which may have overestimated the incidence of anaphylaxis. Second, the limitation of using parent-reported information to assess the incidence of anaphylaxis must be acknowledged, as self-reported and/or parent-reported rates may overestimate the true rate of anaphylaxis [48, 49]. We did not have the opportunity to perform oral food challenges to confirm anaphylaxis cases in this epidemiologic study. Albeit not fully compensating for this limitation, we believe that our data on sensitization and EAI dispensing add important information about the severe phenotype of the anaphylaxis cases in our study. For example, among adolescents with anaphylaxis to peanut, tree nuts or soya and for whom sera were available ($n = 9$), all were sensitized to storage proteins within the culprit food. In addition, the majority (67%) of the anaphylaxis cases had been dispensed an EAI in 24 months prior to the 16-year assessment. Although dispensing practices for EAIs vary between countries and regions [50], most physicians would agree that a previous episode of anaphylaxis is an indication for prescription.

Concerns about selection bias might be raised given that our study population compromised those 77% of the baseline cohort for whom we had sufficient data. However, the study population and the original cohort were comparable regarding allergic multimorbidity and related risk factors, as well as allergen sensitization at 4 years of age. Moreover, heredity for allergic disease did not differ between the non-responders and actively excluded families compared with the original cohort as described in detail elsewhere [51]. Thus, selection bias should be modest. Finally, due to the geographical variability of pollen cross-reactivity [52], the generalizability of our results relating to sensitization patterns to pollens, plant foods and their components is limited to Scandinavia.

To summarize, in a Swedish population-based birth cohort followed to 16 years, food-induced anaphylaxis is rare, yet more common than previously reported. Adolescents experiencing food-related anaphylaxis infrequently seek acute medical care, which may lead to an underreporting of the incidence of anaphylaxis. We confirm a strong association between allergic multimorbidity in early life and FRS in adolescence. Differences between adolescents with anaphylaxis vs.

non-anaphylactic reactions were identified: peanut and tree nuts were the most common culprit food in the former group, whereas fruits and vegetables were the dominating triggers in the latter group. Furthermore, adolescents with anaphylaxis were significantly more commonly sensitized to the culprit food, to multiple foods and to tree nut/peanut storage proteins as compared to adolescents with non-anaphylactic reactions.

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Author contributions

MV contributed to the design of this study, performed the data analysis and drafted and revised the manuscript. She is the guarantor. JP aided in the data analysis and the drafting of the manuscript, and also revised the manuscript for important intellectual content. GL has contributed to interpretation of data and critically revised the manuscript for important intellectual content. IK aided in the data collection at the various assessments and critically revised the manuscript for important intellectual content. GH has substantially contributed to interpretation of data and has critically revised the manuscript for important intellectual content. MvH performed the IgE analyses (fx5®, Phadiatop® and allergen components) and critically revised the manuscript for important intellectual content. EÖ and AB contributed to the design of this study, interpretation of data and revised the manuscript for important intellectual content. MW contributed to the design of this study, revised the manuscript for important intellectual content and is the founder of BAMSE. All authors have given their final approval of the version to be published.

Conflict of interest

The authors declare no conflict of interest.

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