Prevalence of food allergy among schoolchildren in Kuwait and its association with the coexistence and severity of asthma, rhinitis, and eczema: A cross-sectional study

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ABSTRACT

Background: Food allergy (FA) is a common public health problem that affects both children and adults. Empirical knowledge of the burden of FA in Kuwait is limited. This study sought to estimate the prevalence of FA among schoolchildren in Kuwait and assess associations between FA and the coexistence and severity of asthma, rhinitis, and eczema.

Methods: Schoolchildren aged 11–14 years (n = 3,864) were enrolled in a cross-sectional study. Parents completed questionnaires regarding their children’s early life exposures and clinical history of FA and allergic diseases. Study-defined FA was ascertained by a convincing clinical history. Associations were assessed using Poisson regression with robust variance estimation, and adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) were estimated.

Results: The 12-month prevalence of study-defined FA was estimated to be 4.1% (154/3,738), with more girls being affected than boys (aPR = 1.44, 95% CI: 1.04–1.99). Egg (2.7%), fish (1.6%), shellfish (1.3%), peanut (1.3%), and tree nut (1.2%) were the most reported offending food allergens. Underweight and adiposity, cesarean section delivery, exposure to household dogs during infancy, and parental history of doctor-diagnosed FA were associated with an increased prevalence of study-defined FA. However, later birth order was associated with a reduced prevalence of study-defined FA. The prevalence of eczema only was higher in children with study-defined FA than in those without study-defined FA (aPR = 3.49, 95% CI: 2.37–5.14). In contrast, this association was not pronounced for children who had asthma only (aPR = 1.56, 95% CI: 0.94–2.57) or rhinitis only (aPR = 1.40, 95% CI: 0.86–2.28). Study-defined FA was associated with a 9.20-fold (95% CI: 4.50–18.78) higher prevalence of coexisting asthma, rhinitis, and eczema. Moreover, study-defined FA was associated with increased severity of symptoms of asthma, rhinitis, and eczema.

Conclusions: FA affects a considerable proportion of schoolchildren in Kuwait, and the most reported offending food allergens are similar to those reported in Western countries. Study-defined FA was associated with the coexistence and increased severity of asthma, rhinitis, and eczema, indicating that FA may link the manifestations of allergic diseases and contribute to their chronicity and severity.
avoidance of the offending food allergen(s), which, in some instances, is not feasible and may lead to accidental adverse reactions.\textsuperscript{15}

Epidemiologic investigations indicate that the prevalence of FA has increased in recent decades,\textsuperscript{14,16} an emergence that has been regarded as the “second wave” of the allergy epidemic,\textsuperscript{17} following the “first wave” of asthma, rhinitis,\textsuperscript{18} and eczema.\textsuperscript{19} Determining accurate prevalence estimates of FA is hampered by the varying manifestations and severity of the disease and the various definitions used and lack of standardization in the current scientific literature.\textsuperscript{20} Prevalence estimates based on self-/parent-reported FA are generally higher than estimates confirmed by the gold standard of oral food challenges (OFC). A European systematic review and meta-analysis of FA epidemiology reported overall pooled lifetime and point prevalence estimates of self-reported FA to be 17.3\% and 5.9\%, respectively.\textsuperscript{21} The same study reported an overall pooled point prevalence of FA, as defined by clinical history or OFC, to be 2.6\%.\textsuperscript{22} Another meta-analysis, with no geographical boundaries, showed that the prevalence of self-reported FA varied from 3\% to 35\%,\textsuperscript{23} marking significant heterogeneity in FA prevalence that could be attributed to differences in study design and methodology, study populations, and geographic regions.

The interrelationships between allergic diseases have been explained by two concepts, namely, “allergic march” and “allergic multimorbidity”. The allergic march concept suggests a temporal progression from early-onset eczema to asthma and rhinitis;\textsuperscript{24} however, the data supporting the sequential development of allergic diseases are contradictory.\textsuperscript{14,17} In contrast, the allergic multimorbidity concept supports the coexistence (co-occurrence) of allergic diseases.\textsuperscript{17–19} Since FA is considered to be second wave of the allergic epidemic, understanding the role of FA in the development of allergic diseases is essential. Emerging investigations show associations between FA and the development of asthma, rhinitis, and eczema.\textsuperscript{20–22}

A global survey by the World Allergy Organization on FA burden among children showed that more than one-half of the surveyed countries (52/89) had no estimates of FA prevalence.\textsuperscript{23} This finding highlights the paucity of data on FA in most countries worldwide and indicates a need to obtain information on the disease burden and its impact in different settings. Moreover, although emerging studies have indicated that rates of food-induced anaphylaxis are rapidly increasing among schoolchildren and adolescents,\textsuperscript{24,25} few studies have described the burden of FA in this age group compared to preschool-aged children.\textsuperscript{20}

To this end, due to the lack of epidemiologic data on FA in Kuwait, this large cross-sectional study sought to estimate the prevalence of FA, as defined by a convincing clinical history, among schoolchildren in Kuwait and to assess associations between FA and the coexistence (multimorbidity) and severity of asthma, rhinitis, and eczema.

**Methods**

**Study setting, design, and participants**

Kuwait is a small country overlooking the Persian (Arabian) Gulf with a total approximate area of 18,000 km\(^2\). In December 31, 2017, the total population of Kuwait was estimated to be approximately 4.5 million people, and approximately 24.6\% of the population is ≤19 years of age. Geographically, Kuwait is divided into six governorates, and the school districts follow a similar geographic division. Education in Kuwait is mainly provided by free public schools funded by the state and, to a lesser extent, by private schools. The education system can be divided into four stages, namely, kindergarten, elementary school (1\textsuperscript{st}-5\textsuperscript{th} grade), middle school (6\textsuperscript{th}-9\textsuperscript{th} grade), and high school (10\textsuperscript{th}-12\textsuperscript{th} grade), and the latter three stages are segregated by gender. Schooling is compulsory for all children aged 6–14 years.

This cross-sectional study enrolled schoolchildren (n = 3,864) attending public middle schools throughout the State of Kuwait that mostly included subjects aged between 11 and 14 years. The schoolchildren were enrolled in the study during the 2016/2017 school year (September 2016 to May 2017) and the first semester of the 2017/2018 school year (September to December 2017). A stratified two-stage cluster sampling method was used to select a representative study sample of schoolchildren from a random sample of schools. At the inception of the study, there were 207 public middle schools in Kuwait enrolling approximately 106,320 students (50,655 boys and 55,665 girls). From a list obtained from the Ministry of Education, Kuwait, of all public middle schools stratified by school district and gender, schools were randomly selected using randomly generated numbers. Since the total number of students differs across the six school districts, proportional allocation was used to determine the number of participants needed from each school district by estimating gender-stratified weights relative to the student body size in each given school district. Hence, the number of schools selected in each school district was based on the number of students needed from the respective district. On average, each school enrolled around 500 students (i.e., provided a list with around 500 student names), and we have a priori decided to enroll 50\% of students from each selected school. Hence, some schools might have enrolled more/less than 500 students. Once we have obtained the list of student names (sampling frame) from each school, we used simple random sampling methods to enroll 50\% of students in each selected school. Hence, in total, 21 schools served as recruitment venues for enrolling the required sample size of 4,000 students. To account for 30\% refusals and absentees, we planned to invite 5,200 schoolchildren to participate in the study. Ethical approval for the current study was obtained from the Standing Committee for Coordination of Health and Medical Research, Ministry of Health, Kuwait (no. 2016/451).

The children were asked to take home the study-specific questionnaire and a standardized questionnaire (i.e., the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire\textsuperscript{27}) for parent/guardian completion and return them to school. The questionnaires gathered information on the demographic data, lifestyle factors, environmental exposures, and clinical history and symptoms of FA, asthma, rhinitis, and eczema (without following the complete ISAAC methodology), whereas we constructed a FA-related module using previously published literature\textsuperscript{28,29} to gather information on FA. Written informed consent for each enrolled child was obtained from the parents or legal guardians.

**Definitions**

**Food allergy**

We used previously published robust clinical diagnostic criteria\textsuperscript{30–32} to determine FA status among study participants in the past 12 months (i.e., current FA status). The applied a priori definition of FA was based on convincing clinical history that encompassed the following criteria:

1. reporting at least one adverse reaction to a common food allergen, including cow’s milk, egg, peanut, tree nut, fish, shellfish, soy, wheat, and sesame;
2. reporting at least one recognized allergic symptom, including the following:
   a. localized symptoms: itching, sting/burning of the lips/mouth or throat, urticaria/hives, angioedema;
   b. abdominal symptoms: nausea, vomiting, crampy/colicky abdominal pain, diarrhea;
   c. respiratory symptoms: wheeze, stridor, watery rhinitis, redness of eyes/nose;
   d. skin symptoms: urticaria, itching, flushed skin, worsening eczema;
   e. systemic reactions: anaphylaxis, syncope; and
3. reporting a temporal relationship of a reaction, with symptoms occurring within 2 h of food ingestion.

Children were classified as having FA if they fulfilled criteria 1, 2, and 3. This approach allowed us to estimate the 12-month (current)
prevalence of FA. In the remainder of the paper, we refer to this variable as “study-defined FA”.

In addition, we estimated the lifetime prevalence of parent-reported perceived food allergy, which was defined by a positive answer to the question “Has this child ever had food allergy?”. Additionally, an affirmative response to the question “Has this child ever been diagnosed with food allergy by a doctor?” was used to estimate the lifetime prevalence of parent-reported doctor-diagnosed food allergy.

**Asthma**

Current asthma (i.e., asthma in the past 12 months) was defined by an affirmative response to the items “history of physician-diagnosed asthma” and “wheezing in the past 12 months” and/or “asthma treatment in the past 12 months”. The severity of asthma symptoms in the past 12 months was assessed by inquiring about the following symptoms: frequency of wheezing attacks; wheezing severe enough to limit speech to only one or two words at a time between breaths; and wheezing leading to disturbed sleep.

**Rhinitis**

Current rhinitis was defined as “ever doctor-diagnosed rhinitis” and “having problems with a sneezing, runny, or blocked nose in the absence of a cold or flu in the past 12 months”. The severity of rhinitis symptoms was assessed by asking about the extent to which rhinitis in the past 12 months had interfered with daily activities.

**Eczema**

Following the Hanifin and Rajka criteria, current eczema was defined as “ever doctor-diagnosed eczema” and/or “having ever had a recurrent itchy rash for at least six months” plus “having an itchy rash at any time in the past 12 months that affected the folds of the elbows or the areas behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes.” The severity of eczema symptoms was assessed by asking if the itchy rash has ever cleared in the past 12 months and whether the itchy rash has caused night waking in the past 12 months.

**Coexistence of allergic diseases**

Combinations of current asthma, current rhinitis, and current eczema resulted in eight nonoverlapping groups of single and coexisting allergic diseases: a group with “no allergic disease”, “asthma only”, “rhinitis only”, “eczema only”, “asthma + rhinitis”, “asthma + eczema”, “rhinitis + eczema”, and “asthma + rhinitis + eczema”.

**Ascertainment of exposure and covariate variables**

Information regarding exposures and covariates was obtained from questionnaires completed by the parents/guardians. Since body mass index (BMI), which is a measure of general adiposity, markedly changes in children with growth, we estimated the BMI-for-age z-scores (standard deviation [SD] scores) using the WHO growth reference for those aged between 5 and 19 years. The BMI-for-age score was categorized as follows: underweight (thinness): <-2 SD, normal: -2 to 1 SD, overweight: >1 to 2 SD, and obese: >2 SD. Exposure to environmental tobacco smoke (ETS) was assessed by inquiring whether any member of the household smokes cigarettes or tobacco-related products inside the home. To ascertain exposure to household cats and dogs during infancy, the following two separate questions were asked: “Did you have a cat/dog in your home during the first year of this child’s life?” Breastfeeding status was determined by asking whether the child was ever directly fed at the breast during infancy. The questionnaire also asked about the child’s birth order, which was categorized as follows: first-born, second-born, third-born and higher. Moreover, information on parental history of FA was obtained by asking the following question: “Has the child’s mother/father ever been diagnosed with FA by a doctor?”

**Statistical analysis**

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina, USA). The statistical significance level was set to α = 0.05 for all association analyses. Descriptive analyses were conducted to determine the frequencies and proportions of the categorical variables and the medians and 5th and 95th percentiles of the quantitative variables. To assess whether the analytical study sample (n = 3,738) and participants with complete information regarding study-defined FA, asthma, rhinitis, and eczema status was representative of the total study sample (n = 3,864), we compared proportions of categorical variables (using χ² tests) and means of continuous variables (using t-tests) across these two samples. The 12-month prevalence of study-defined FA, lifetime prevalence of parent-reported doctor-diagnosed FA, lifetime prevalence of parent-reported perceived FA, and the 12-month prevalence of single morbidity and the coexistence of asthma, rhinitis, and eczema were estimated, along with their binomial 95% confidence intervals (CIs).

The crude and adjusted associations were assessed by applying a modified Poisson regression with robust variance estimation using the GENMOD procedure in SAS 9.4 to estimate and infer the prevalence ratios (PRs) and their 95% CIs. Variables that demonstrated possible association with study-defined FA (outcome variable) in the crude models (i.e., p-value ≤ 0.2, as suggested by Maldonado and Greenland) were simultaneously entered into the multivariable regression models. Regardless of statistical significance, sex and age were included as potential confounders in all multivariable regression models. In further analysis, we considered study-defined FA as the exposure variable and assessed its association with allergic diseases occurring as a single entity or coexisting with other conditions. Moreover, we determined whether study-defined FA (the exposure variable) was associated with symptoms of the severity of asthma, eczema, and rhinitis.

**Results**

**Description of the study sample**

In total, 5,228 schoolchildren (2,483 boys and 2,745 girls) were invited to participate, and 3,864 schoolchildren (1,695 boys and 2,169 girls) were enrolled in the study (response proportion: 73.9%). The analytical sample (n = 3,738; restricted to participants with information regarding study-defined FA, asthma, rhinitis, and eczema status) and the total sample (n = 3,864) were similar in all characteristics investigated (Table 1). The median (5th, 95th percentile) age of the study participants was 12.0 (11.0, 14.0) years. The BMI-for-age groups indicated that 25.4% (929/3,663) and 28.8% (1,055/3,663) of the schoolchildren were overweight and obese, respectively. In total, 1,703 (45.7%) children were reported to have been exposed to ETS. A parental history of doctor-diagnosed FA was reported for 717 (19.5%) of the children enrolled in the study (Table 1). Prevalence estimates of maternal and paternal reported history of doctor-diagnosed FA were 12.8% (462/3,597) and 9.9% (349/3,536), respectively.

Additional descriptive information is shown in the Online Supplementary, Table S1. In the total analytical study sample (n = 3,738), 65.9% (n = 2,465), 27.6% (n = 1,030), and 6.5% (n = 243) of the returned questionnaires were completed by mothers, fathers, and legal guardians, respectively. Majority of children’s mothers (43.1%, 1,600/3,717) and fathers (36.1%, 1,338/3,701) reported having a bachelor’s degree or higher. The most commonly reported (28.5%, 954/3,349) total monthly household income was between 1,000 and 1,500 Kuwaiti Dinar (~$3,300 to $4,900). The majority of children were of Kuwaiti nationality (92.5%, 3,459/3,738), and a small proportion were of non-Kuwait nationality (7.5%, 279/3,738). Moreover, none of the previously described attributes were associated with study-defined FA (see Online Supplementary, Table S1).
Reactions to foods and 50.1% (78/154) reported symptoms from two or more symptoms due to adverse reactions.

59.1% (91/154) reported two or more symptoms due to adverse reactions.

Sex, n (%)  
Male 1695 (43.9) 1652 (44.2)  
Female 2169 (56.1) 2086 (55.8)

Age (years)  
Median (5th, 95th percentile) 12.0 (11.0, 14.0) 12.0 (11.0, 14.0)

BMI-for-age groups, n (%)  
Underweight (< -2 SD) 219 (5.8) 212 (5.8)  
Normal (-2 to 1 SD) 1517 (40.1) 1467 (40.0)  
Overweight (>1 to 2 SD) 961 (25.3) 928 (25.4)  
Obese (>2 SD) 1089 (28.8) 1055 (28.8)  
Missing, n 78 75

Mode of Birth, n (%)  
Vaginal 3106 (81.8) 3019 (81.7)  
Cesarean section 692 (18.2) 678 (18.3)  
Missing, n 66 41

Birth order, n (%)  
First 1103 (28.7) 1070 (28.7)  
Second 801 (20.8) 790 (21.2)  
≥ Third 1940 (50.5) 1870 (50.1)  
Missing, n 20 8

Breastfeeding ever, n (%)  
Yes 2894 (76.3) 2812 (76.2)  
Missing, n 72 49

Environmental tobacco smoke exposure, n (%)  
Yes 1755 (45.8) 1703 (45.7)  
Missing, n 28 13

Cat exposure in infancy, n (%)  
Yes 232 (6.1) 225 (6.1)  
Missing, n 35 19

Dog exposure in infancy, n (%)  
Yes 85 (2.2) 84 (2.3)  
Missing, n 32 16

Parental history of food allergy a, n (%)  
Yes 728 (19.5) 717 (19.5)  
Missing, n 129 65

BMI: body mass index; SD: standard deviation.  
a Refers to the sample of participants with complete information regarding study-defined food allergy, asthma, rhinitis, and eczema status (i.e., excluding 126 subjects with incomplete information regarding allergic manifestations).  
b Maternal and/or paternal history of doctor-diagnosed food allergy.

Prevalence estimates of FA

The lifetime prevalence estimates of parent-reported perceived and doctor-diagnosed FA were 12.7% (469/3,692) and 8.2% (297/3,611), respectively (Table 2). The prevalence of perceived FA was higher in girls than boys (14.4% vs. 10.6%, p-value < 0.001), whereas doctor-diagnosed FA affected girls and boys equally (8.4% vs. 8.0%, p-value = 0.712). The 12-month (current) prevalence of study-defined FA was estimated to be 4.1% (154/3,738), with more girls being affected than boys (4.7% vs. 3.5%; p-value = 0.067; Table 2).

Prevalence estimates of reported allergies to common food allergens are presented in a descending manner. Reported allergies to fresh fruits and vegetables are also presented.

Reactions to foods

Table 3 presents frequencies of reported reactions to foods according to the affected organ systems. Among children with study-defined FA, 59.1% (91/154) reported two or more symptoms due to adverse reactions to foods and 50.1% (78/154) reported symptoms from two or three or more foods.

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more organ systems. Symptoms related to the ingestion of foods mainly involved the skin (72.1% for urticaria/hives, itching, or flushing), gastrointestinal tract (33.1% for itchy lips, mouth, or throat), and respiratory tract (26.6% for throat tightness).

Factors associated with study-defined FA

Associations between various factors and study-defined FA were explored (Table 4). Compared with the normal BMI-for-age group, individuals in the underweight (aPR = 2.13, 95% CI: 1.16–3.93), overweight (aPR = 1.63, 95% CI: 1.07–2.49), and obese (aPR = 1.93, 95% CI: 1.28–2.90) groups had a higher prevalence of study-defined FA (Table 4). Cesarean section delivery (aPR = 1.42, 95% CI: 1.05–2.16), exposure to household dogs in infancy (aPR = 3.33, 95% CI: 1.92–5.79), and parental history of doctor-diagnosed FA (aPR = 2.75, 95% CI: 2.01–3.76) were associated with increased prevalence of study-defined FA. However, children who were second-born (aPR = 0.64, 95% CI: 0.41–0.98) and third-born or higher (aPR = 0.72, 95% CI: 0.51–0.99) had a lower prevalence of study-defined FA compared with first-born children.

Study-defined FA and coexistence of allergic diseases

Associations between study-defined FA and the single occurrence and coexistence of asthma, rhinitis, and eczema were assessed (Table 5). The prevalence of asthma only (aPR = 1.56, 95% CI: 0.94–2.57) and rhinitis only (aPR = 1.40, 95% CI: 0.86–2.28) was increased in children with study-defined FA than in those without study-defined FA, although these associations were not statistically significant (Table 5). In contrast, study-defined FA was significantly associated with an increased prevalence of eczema only (aPR = 3.49, 95% CI: 2.37–5.14). Similarly, children with study-defined FA were more likely to have coexisting allergic diseases than those without study-defined FA. For instance, study-defined FA was associated with a 9.20-fold (95% CI: 4.50–18.78) higher prevalence of having coexisting asthma, rhinitis, and eczema.

Study-defined FA and the severity of symptoms of allergic diseases

Associations between study-defined FA and the severity of symptoms of asthma, rhinitis, and eczema were explored (Table 6). Study-defined FA was associated with an increased prevalence of severe asthma symptoms, including 4 or more wheezing attacks (aPR = 1.63, 95% CI: 1.20–2.21), wheezing that limited speech (aPR = 1.64, 95% CI: 1.10–2.46), and wheezing that disturbed sleep during one or more nights per week (aPR = 1.56, 95% CI: 1.28–1.88). Regarding the severity of rhinitis symptoms, children with study-defined FA reported more frequently than those without study-defined FA that rhinitis moderately (aPR = 1.37, 95% CI: 0.91–2.04) and severely (aPR = 1.71, 95% CI: 0.81–3.63) affected their daily activities, although these associations did not show statistical significance. Compared to children without study-defined FA, those with study-defined FA were less likely to experience complete remission of their itchy rash (aPR = 0.74, 95% CI: 0.53–1.03), whereas they were more likely to experience one or more night wakeings per week caused by their itchy rash (aPR = 2.63, 95% CI: 1.68–4.14; Table 6).

Discussion

This is the first study to estimate the prevalence of FA, defined by a convincing clinical history, among schoolchildren in Kuwait. Moreover, this study assessed associations between study-defined FA with various

Table 4

Crude and adjusted associations between personal attributes and risk factors and study-defined food allergy.

| Personal attribute | Study-defined food allergy, % (n/total) | Crude PR (95% CI) | Adjusted PR (95% CI) |
|--------------------|----------------------------------------|-------------------|---------------------|
| **Sex**            |                                        |                   |                     |
| Male               | 3.5 (57/1652)                          | 1.00 (Ref.)       | 1.00 (Ref.)         |
| Female             | 4.7 (97/2086)                          | 1.35 (0.98–1.86)  | 1.44 (1.04–1.99)    |
| **Age (years)**    |                                        |                   |                     |
| Per additional year of age | –                                | 1.08 (0.96–1.22)  | 1.06 (0.93–1.20)    |
| **Dog exposure in infancy** |                   |                   |                     |
| No                 | 3.9 (140/3638)                        | 1.00 (Ref.)       | 1.00 (Ref.)         |
| Yes                | 14.3 (12/84)                           | 3.71 (2.15–6.42)  | 3.33 (1.92–5.79)    |
| **Parental history of food allergy** |                   |                   |                     |
| No                 | 3.0 (90/2956)                         | 1.00 (Ref.)       | 1.00 (Ref.)         |
| Yes                | 8.7 (62/717)                          | 2.84 (2.08–3.88)  | 2.75 (2.01–3.76)    |
| **BMI-for-age groups** |                                      |                   |                     |
| Underweight (< -2 SD) | 6.1 (13/212)                        | 2.14 (1.17–3.92)  | 2.13 (1.16–3.93)    |
| Normal (-2 to 1 SD)  | 2.9 (42/1467)                        | 1.00 (Ref.)       | 1.00 (Ref.)         |
| Overweight (>1 to 2 SD) | 4.6 (43/929)                      | 1.62 (1.07–2.45)  | 1.63 (1.07–2.49)    |
| Obese (>2 SD)       | 5.2 (55/1055)                         | 1.82 (1.23–2.70)  | 1.93 (1.28–2.90)    |
| **Cat exposure in infancy** |                                      |                   |                     |
| No                 | 4.0 (139/3494)                        | 1.00 (Ref.)       | 1.00 (Ref.)         |
| Yes                | 5.8 (13/225)                          | 1.45 (0.84–2.52)  | 1.02 (0.56–1.88)    |
| **Mode of Birth**   |                                        |                   |                     |
| Vaginal            | 3.8 (114/3019)                        | 1.00 (Ref.)       | 1.00 (Ref.)         |
| Cesarean section   | 5.3 (36/678)                          | 1.41 (0.98–2.03)  | 1.42 (1.05–2.16)    |
| **Environmental tobacco smoke exposure** |                     |                   |                     |
| No                 | 3.6 (73/2022)                         | 1.00 (Ref.)       | 1.00 (Ref.)         |
| Yes                | 4.7 (80/1703)                         | 1.30 (0.95–1.78)  | 1.10 (0.80–1.50)    |
| **Breastfeeding ever** |                                      |                   |                     |
| No                 | 3.8 (33/877)                          | 1.00 (Ref.)       | 1.00 (Ref.)         |
| Yes                | 4.2 (118/2812)                        | 1.12 (0.76–1.63)  |                     |
| **Birth order**    |                                        |                   |                     |
| First              | 5.4 (58/1070)                         | 1.00 (Ref.)       | 1.00 (Ref.)         |
| Second             | 3.3 (26/790)                          | 0.61 (0.39–0.96)  | 0.64 (0.41–0.98)    |
| ≥ Third            | 3.7 (66/1870)                         | 0.68 (0.48–0.96)  | 0.72 (0.51–0.99)    |

PR: prevalence ratio; CI: confidence interval; BMI: body mass index; SD: standard deviation; Ref.: reference.

a Variables that had a p-value ≤ 0.2 in the crude model were simultaneously included in the adjusted (multivariable) model, except for age and sex, which were included in all adjusted models.

b Maternal and/or paternal history of doctor-diagnosed food allergy.
The aforementioned approaches are known to overestimate the true prevalence of FA. However, a limited number of population-based studies have estimated the prevalence of FA using the gold standard of OFC, which must be performed in a controlled clinical setting, making OFC an unfeasible option in large epidemiologic studies. An alternative is OFC an unfeasible option in large epidemiologic studies. An alternative is performing skin prick test (SPT) sensitization to common food allergens. This method of determining FA should identify typical IgE-mediated allergy. To this end, caution should be practiced when interpreting and comparing FA prevalence estimates due to the different approaches used to ascertain FA, a method that has been shown to be crucial when assessing FA in clinical settings.38,39

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In the current study, we based our analysis on study-defined food allergy (exposure variable) and severity of asthma symptoms were assessed among subjects with current asthma. Associations between study-defined FA (exposure variable) and severity of rhinitis symptoms were assessed among subjects with current rhinitis. Associations between study-defined FA (exposure variable) and severity of eczema symptoms were assessed among subjects with current eczema.

The 12-month prevalence of study-defined FA was estimated to be 4.1% (95% CI: 3.5–4.8). Egg, fish, shellfish, peanut, and tree nut were more than the most reported offending food allergens, with each affecting more than 1% of the total number of study subjects. Factors associated with the increased prevalence of study-defined FA included the female sex, underweight and adiposity, cesarean section delivery, exposure to household dogs during infancy, and parental history of doctor-diagnosed FA. However, later birth order was associated with a reduced prevalence of study-defined FA. Our study showed that study-defined FA was associated with an increased prevalence of the coexistence of asthma, rhinitis, and eczema. Moreover, study-defined FA was associated with increased severity of symptoms of allergic diseases.

Prevalence estimates of FA have mainly been based on self-/parent-reported perceived or doctor-diagnosed FA or specific immunoglobulin E (IgE) or skin prick test (SPT) sensitization to common food allergens. The aforementioned approaches are known to overestimate the true prevalence of FA. However, a limited number of population-based studies have estimated the prevalence of FA using the gold standard of OFC, which must be performed in a controlled clinical setting, making OFC an unfeasible option in large epidemiologic studies. An alternative is to use “convincing clinical history” to ascertain FA, a method that has provided comparable prevalence estimates to OFC-confirmed FA and has been shown to be crucial when assessing FA in clinical settings. To this end, caution should be practiced when interpreting and comparing FA prevalence estimates due to the different approaches used to ascertain FA.

In the current study, we based our analysis on study-defined FA, which was ascertained using convincing clinical history that encompassed the characteristics of the reaction, timing from exposure to the development of symptoms, and exposure to common offending food allergens. This method of defining FA should identify typical IgE-mediated FA rather than food poisoning and intolerance. Using this approach yielded a prevalence estimate (4.1%) that is comparable to estimates...
from other reports using OFC or convincing clinical history for the
diagnosis of FA among similarly aged study populations. For instance, the
SchoolNuts cross-sectional study, conducted among adolescents aged
10–14 years residing in Melbourne, Australia, estimated the prevalence of
FA, defined based on positive OFC or clinical history with IgE sensi-
tization, to be 4.5% (95% CI: 3.9–5.1). Similarly, data from the Isle of
Wight birth cohort study based on the United Kingdom indicated that
4.1% (95% CI: 3.2–5.4) of participants aged 18 years had FA, which was
defined using convincing clinical history. In the United States, the re-
sults from the National Health and Nutrition Examination Survey
2005–2006 estimated that 3.8% (standard error: ± 0.4) of children aged
6–19 years had clinically defined FA. At the national level, a previous
report estimated the prevalence of FA, defined by convincing clinical
history, to be 5.4% among Kuwait University students (mean age ± SD:
20.7 ± 1.2 years).

In this report, parent-reported perceived FA and parent-reported
doctor-diagnosed FA presented lifetime prevalence estimates, whereas
the study-defined FA estimated the prevalence in the past 12 months. As
expected, parent-reported perceived FA yielded the highest prevalence
estimate (12.7%) followed by parent-reported doctor-diagnosed FA
(8.2%) and study-defined FA (4.1%). Our estimated parent-reported
perceived FA prevalence (12.7%) is close to a pooled estimate (~10%)
from a large meta-analysis. Similarly, our parent-reported doctor-
diagnosed FA (8.2%) is consistent with estimates among American
(8.0%) and Canadian (7.14%) children. FA is known to be a condition of early childhood (i.e., highly preva-
 lent among preschool children). For instance, the HealthNuts cohort
study in Melbourne, Australia, estimated the prevalence of challenge-
confirmed FA at age 1 and 4 years to be 11.0% (95% CI: 10.1–11.9)
and 3.8% (95% CI: 3.3–4.4), respectively; indicating that nearly two-
thirds of FA has resolved by school age. Similarly, the global survey
by the World Allergy Organization on FA burden showed that challenge-
confirmed FA is higher among infants and preschool children aged
≤5 years (range: 1%–10%) compared to schoolchildren aged > 5
years (range: 0.2%–2.5%). Such observations indicate that a large
proportion of FA cases may resolve by school age. Hence, our estimated
prevalence of study-defined FA (4.1%) among schoolchildren aged
11–14 years may not reflect the burden of FA in infancy and early
childhood.

Regarding the prevalence of common food allergens, egg, fish,
shellfish, peanut, and tree nut were the most reported food triggers in
our study. The observed prevalence estimates in our study are com-
parable to estimates reported in large meta-analyses. Surprisingly,
fish (1.6%) and shellfish (1.3%) were among the most commonly re-
ported food allergens in our study, which was not expected due to the
fact that seafood forms a major food source in Kuwait. Similarly, al-
lergy to fish/shellfish is common in coastal Asian countries where
seafood consumption is also high. Although it is suggested that the
increased global consumption of seafood may have led to more
frequent reporting of adverse reactions, food processing, dietary habits,
and cultural practices (e.g., age of introduction of seafood) could
contribute to the etiology of seafood allergy and explain the increasing
trends and differences across nations. Nevertheless, adverse reactions
to seafood may not always resemble true allergy, rather they can in fact
be secondary to food contamination, toxins, or preservatives. Moreover,
a large proportion of study participants reported allergies to fresh fruits (4.6%) and vegetables (1.6%). Such allergies are mainly
associated with a localized IgE-mediated reaction known as oral allergy
syndrome (also called pollen-food allergy syndrome), which is caused
by cross-reactivity with pollen/inhalant allergens. A systematic re-
view of the literature showed that the prevalence of self-/parent-reported perceived allergy to any fruit ranged between 0.4% and
11.5% and to any vegetable varied from 0.3% to 3.3%. Preva-

ience estimates of parent-reported fruit allergy (4.6%) and vegetable
allergy (1.6%) in our study sample are within the aforementioned
ranges.

Multiple risk factors for FA have been identified in previous in-
vestigations and have been reviewed in detail elsewhere. In our
analysis, increased prevalence of study-defined FA was seen in the
following subgroups: females (compared to males); overweight (thin),
underweight, and obese individuals (compared to those with normal
BMI-for-age); those delivered via cesarean section (compared to those
delivered vaginally); those exposed to dogs in infancy; and those with
a parental history of doctor-diagnosed FA. It has been suggested that
the male sex in children and the female sex in adults are associated with an
increased risk of FA; however, conflicting results have been reported.

Our results showing increased prevalence among females are consistent
with findings of a Swedish cohort study of more than 1 million children.
The noted positive associations between adiposity, cesarean delivery, and
parental history of FA and the prevalence of study-defined FA are consistent with the findings of prior investigations. Similarly, the
observed inverse association between birth order and the prevalence of
study-defined FA is consistent with the findings of prior studies. Although emerging evidence suggests that exposure to dogs in early life
reduces the risk of FA, our study showed that exposure to dogs in in-
fancy was associated with an increased prevalence of study-defined FA, an
association that needs further corroboration. Similarly, the observed
increased prevalence of study-defined FA among overweight children
compared to those with normal BMI-for-age needs to be corroborated.
However, a plausible explanation is reverse causation where malnutrition
in children with FA could lead to growth impairment and overweight.

On the other hand, prior studies investigating the effect of breastfeeding
on the development of allergic diseases, including FA, reported conflicting
conclusions, with some studies suggesting protective effect, others
showing no effect, and a few suspecting that breastfeeding could even
increase the risk of developing allergic diseases. Our report showed no
association between breastfeeding and study-defined FA.

IgE-mediated inflammatory mechanisms predispose individuals to
and link the development of asthma, rhinitis, eczema, and FA. Prior
studies have shown that FA is associated with an increased risk of asthma,
rhinitis, and eczema. In this report, we assessed whether FA is asso-
ciated with the single occurrence and the coexistence of allergic diseases.
The results of this study showed that study-defined FA was not statistically
significantly associated with an increased prevalence of asthma only or
rhinitis only. However, study-defined FA was strongly associated with an
elevated prevalence of eczema only, which further highlights that FA and
eczema are closely related. On the other hand, study-defined FA showed
strong associations with having more than one allergic disease, an
observation that has been previously reported. Moreover, we demon-
strated that study-defined FA is associated with increased severity of
asthma, rhinitis, and eczema symptoms. Therefore, FA might contribute to
the chronicity and severity of allergic diseases. Nevertheless, it is
essentially to indicate that our analysis aimed to assess concurrent associ-
ations rather than to determine temporal associations.

A major strength of the current study is the representative and large
study sample, which allowed for the estimation of FA prevalence among
schoolchildren throughout Kuwait. A limitation to our study is the lack of
the use of the gold standard of OFC to ascertain FA status. However, we
have applied robust symptom-based criteria that are commonly used in
clinical settings. Moreover, the applied FA ascertainment criteria have
been published previously and have provided results comparable to
those of investigations using the gold standard for clinical diagnosis,
which is a further indication of the robustness of our FA definition. The
observed sex difference between the estimated prevalence of
parent-reported anaphylaxis (3.9%) among children with study-defined
FA and the estimated prevalence of anaphylaxis in the SchoolNuts
study (9.7%) is an indication that parent-report of anaphylaxis and
syncope could have led to unreliable estimates. Another potential limi-
tation to our study is the inaccuracy of parent-/guardian-reported weight
and height of their children, which could have led to the misclassifica-
tion of children into BMI-for-age groups. However, the estimated prevalence of overweight (25.4%) and obesity (28.8%) in the current report did not
substantially differ from that in a previous investigation conducted among schoolchildren aged 6–18 years in Kuwait that used objective weight and height measurements (overweight: 21.6% and obesity: 30.5%). Data on race/ethnicity of participants was not collected, which could be an important factor in FA. Rather, information on nationality (Kuwaiti vs non-Kuwaiti), a variable that could partially account for the race/ethnicity effect, was available and analysis comparing the two population groups showed that children of Kuwaiti nationality (4.1%, 142/3,459) and non-Kuwaiti nationality (4.3%, 12/379) had similar prevalence estimates of study-defined FA (see Online Supplementary, Table S1). Moreover, the determination of temporal associations between study-defined FA and the coexistence and the severity of allergic diseases was hampered by the cross-sectional nature of our study, in which concurrent data were collected. Selection bias could also be a concern in large population-based cross-sectional studies; however, the possibility of selection bias affecting the results of our study is low because the response proportion was high (i.e., 73.9%). Moreover, since this study was conducted among older children, the effect of recall bias on the evaluated associations cannot be excluded, which can either overestimate or underestimate the measure of association.

Conclusions

The findings of this study indicate that FA is common among schoolchildren in Kuwait, which mirrors prevalence estimates reported in Western nations. Common risk factors for FA identified in our study included the female sex, underweight and adiposity, cesarean section delivery, exposure to dogs in infancy, and parental history of FA, whereas increased birth order was associated with a lower prevalence of FA. Moreover, we demonstrated that FA is associated with the coexistence and the severity of asthma, rhinitis, and eczema. Therefore, FA is a common problem among schoolchildren in Kuwait that potentially links the comanifestations of asthma, rhinitis, and eczema and contributes to their chronicity and severity.

Ethics approval and consent to participate

The study was approved by the Standing Committee for Coordination of Health and Medical Research, Ministry of Health, Kuwait (no. 2016/451). Written informed consent was obtained from the parents or legal guardians to enroll children in the study.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

AHZ conceived, designed, and planned the study; obtained funding; supervised the conduct of the research; analyzed and interpreted the data; and drafted the manuscript. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

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