



Epidemiology of Anaphylaxis Induced by Food: Incidence, Trends, Natural History, and Bias

Food anaphylaxis epidemiology

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Abstract

Purpose of the Review We present an updated information on the epidemiology of food-induced anaphylaxis based on meta-analyses and epidemiology studies published in the last 5 to 10 years. Our review covers incidence, trends, natural history (recurrence and deaths), differences by geographic region, foods involved, and demographic and ethnic distributions.

Recent Findings Various studies and meta-analyses worldwide report a high frequency of food-induced anaphylaxis in childhood and adolescence and an increase in rates of anaphylaxis managed in health care settings. Major efforts have been made to determine whether the frequency of food anaphylaxis and associated trends is distributed in the same way between countries and ethnic groups (high rates in second-generation immigrants in Western countries).

Summary Food is the main cause of anaphylaxis in childhood and adolescence, although important methodological problems prevent us from concluding that there has been a true increase in food-related anaphylaxis in the last 15 years. Deaths due to food anaphylaxis are very rare but appear more frequently in adolescence. Publications from Central and South America, Asia, and Africa are needed to complete the picture of food anaphylaxis worldwide.

Introduction

Publications mainly from developed countries show an increase in the frequency of anaphylaxis caused by foods during the last 15 years [1–3], consistent with an increase in the frequency of food allergy in the same geographical areas [4]. The data reported are from population-based studies, such as national clinical-administrative datasets of admissions or emergency department data [5–7, 8•, 9] and registries covering allergy departments in several European countries [10]. Data have also been collected from different clinical settings in the same geographic area [11, 12•, 13•, 14•] and through meta-analyses [15••, 16••, 17••]. The increase mostly affects children and adolescents, since food allergy is predominantly a disease of pediatric and adolescent populations [8•, 11, 15••, 17••]. A recent systematic review found recurrence of food-induced anaphylaxis to be more frequent than anaphylaxis of other causes [18••]. Conversely, a

meta-analysis reported that fatal anaphylaxis due to foods is less frequent than anaphylaxis of other causes (<0.1 deaths per million people) [19••]. Also unresolved is the issue of the characteristics of anaphylaxis in countries other than those mentioned above, although several population-based studies from Asia [20, 21] have been published in the last 5 years. Similarly, it is unknown whether the increase in food anaphylaxis is true or the result of more frequent diagnosis and recording because of higher awareness of the severity of anaphylaxis among the general population and physicians [22].

The present review addresses these questions. Where available, we have used published systematic reviews and meta-analyses complemented with population-based studies published after the systematic review date, mainly studies from the last 5 years.

Incidence and Prevalence of Anaphylaxis Due to Foods

Foods are the most frequent cause of anaphylaxis in children and young adults, as confirmed in several population-based studies [14•, 22]. Two meta-analyses have addressed the incidence and prevalence of anaphylaxis caused by food using two different perspectives. Umasunthar et al. [15••] estimated the incidence of food anaphylaxis between people with food allergy, while Wang et al. [17••] estimated the incidence of anaphylaxis and anaphylaxis triggered by several causes in children.

Umasunthar et al. [15••] estimated the incidence of food anaphylaxis, using an estimated prevalence of food allergy of 3% overall and 3.9% for patients aged 0–19 years. In the case of food anaphylaxis diagnosed by physicians, which accounts for over 19.9 million person-years, the authors estimated the incidence to be 0.14 per 100 person-years overall, 0.20 in those aged 0–19 years, and 0.37 in those aged 0–4 years. The authors observed a marked variation between the studies, although the incidence was low in all

groups, with the highest value in the preschool group aged 0–4 years. The estimated pooled incidence validity can be called into question owing to the considerable heterogeneity of the meta-analyses, which was almost always higher than 95%, and possible over-estimation, because many of the enrolled patients came from specialist allergy clinics. However, the value was lower than in studies based on self-reported anaphylaxis.

In their systematic review, Wang et al. [17••] assessed the incidence of anaphylaxis and incidence of food-induced anaphylaxis in the pediatric population (0–19 years) using mainly registry databases from hospital and/or emergency departments. They did not estimate pooled statistics, given the marked heterogeneity of the studies selected. Seventeen studies reported the incidence of food-induced anaphylaxis, ranging from 1 to 77 per 100,000 person-years, while prevalence ranged from 0.3 to 1.2% in 4 studies.

In their prospective cohort study of adolescents aged 16 years in Stockholm, Sweden, Vetander et al. [23•] estimated the incidence of anaphylaxis within 12 months prior to the 16-year assessment to be 761 episodes per 100 000 person-years (95% CI, 488–1133), according to the definition of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN). This rate was compared with previously published rates (6.6–8.7 to 124.5 episodes per 100 000 person-years) [1–3]. Interestingly, adolescents with anaphylaxis were sensitized to hazelnut and peanut storage proteins, whereas those who experienced nonanaphylactic reactions were predominantly sensitized to birch pollen homologs from peanut and hazelnut. Another relevant observation was the difference in the overall incidence: 761 vs 254 in adolescents who attended a health care facility, thus indicating how the incidence of anaphylaxis can be underestimated when data are from health care settings instead of from studies where the anaphylaxis episodes occurred in the community.

Table 1 shows data from two more recent American studies [14•, 24].

These studies conclude that reported figures vary widely, probably because of differences in the definitions of anaphylaxis, settings, coding systems used to extract data, dietary habits throughout the world, and age of the study population. Likewise, food-induced anaphylaxis is much more frequent in the pediatric population, with the highest incidence rates reported in patients aged 0–4 years.

In almost all studies, the predominance of males is constant until puberty (male–female ratio 1.6:1) [6, 8•]. After age 15–18 years, the difference changes, with the highest percentages reported for females [25].

Trends in the Frequency of Food-Induced Anaphylaxis

Many studies from developed countries generally show an increase in the incidence of food-induced anaphylaxis, which may be related to the increased frequency of food allergy reported in several studies during the last 20 years [26–37] (Table 2).

In their meta-analysis, Umasunthar et al. [15••] found an increase in the incidence rate of coded food anaphylaxis, which was higher in patients aged 0–19 years (0.31) and 0–4 years (1.35) than in the total food-allergic

Table 1 Incidence and prevalence of food anaphylaxis in two published meta-analyses and two recent population-based studies

Author, country, year	Design	Population	Subpopulation	Incidence
Umasunthar, Metha-analysis, 2014	Systematic review	People with food allergy diagnosed by a physician Estimate based on whole population	Overall 0–19 years 0–4 years 0–19 years 0–4 years Overall	0.14 per 100 person-years (95% CI 0.05–0.35; range 0.01–1.28) 0.20 (95% CI 0.09–0.43; range 0.01–2.55) 0.37 (95% CI 0.01–17.07; range 0.03–7.03) 200 × 0.39 = 78 per 100,000 person-years 370 × 0.39 = 144.3 per 100,000 person-years 140 × 0.33 = 46.2 per 100,000 person-years
Wang, Metha-analysis, 2019	Systematic review	Children in general population	Incidence rate Prevalence	1 to 77 per 100,000 person-years Prevalence ranged from 0.3 to 1.2% in 4 studies
Vetander, Sweden, 2016	Prospective cohort study	Adolescents aged 16 years	Overall incidence rate Incidence rate for adolescents seeking health care	761/100,000 person-years (95% CI 488–1133) 254/100,000 person-years (95% CI 110–500)
Lee, USA, 2017	Retrospective observational study of a national clinical-administrative dataset of admissions	All ages	Incidence rate	15.54/100,000 person-years

Table 2 Trends in food-induced anaphylaxis in studies from throughout the world

Author	Study period	Type of study	Age groups	Annual rate increase	Annual percentage increase
Umasunthar, Meta-analysis, 2014,	1992–2012	Systematic review and meta-analysis	All age groups with food anaphylaxis	In the total food-allergic population –0.25 (range 0.05–1.28) In 0- to 19-year-olds 0.31 (range 0.03–2.55) In 0- to 4-year-olds 1.35 (range 0.23–7.03) For peanut allergy 0.18 (range 0.11–0.30)	
Lin, USA, 2008	1996–2006	Retrospective observational study of a clinical-administrative dataset of admissions in New York State	All age groups with food anaphylaxis		
Liew, Australia, 2009		Retrospective observational study of a national clinical-administrative dataset of admissions	All age groups with food anaphylaxis		Overall 350%
Rudders, USA, 2014	2000–2009	Clinical-administrative dataset of admissions	Children	0.60 per 1000 to 1.26 Increases in all age groups, except the 0- to 2-year group	
Dyer, (Illinois) USA, 2015	2008–2012	Retrospective observational study of a clinical-administrative dataset of admissions	Pediatric population		ED visits, 29.3% Admission, 17.2% Hispanic children, 44.3% Children with public insurance, 30.28% The greatest proportionate increase occurred in patients aged 5–14 and 15–29 years
Mullins, Australia, 2015	1998–1999 to 2011–2012	Retrospective observational study of a national clinical-administrative dataset of admissions	All age groups with food anaphylaxis		

Table 2 (continued)

Author	Study period	Type of study	Age groups	Annual rate increase	Annual percentage increase
Mullins, Australia, 2015	1998–2012	Retrospective observational study of a national clinical-administrative dataset of admissions	All age groups with food anaphylaxis		Overall, 280% 5- to 14-year age group, 430%
Nocerino, Italy, 2015	2006–2011	Retrospective observational study of a national clinical-administrative dataset of admissions	Children		Highest increase in those aged 5–14 years
Turner, UK, 2015		Retrospective observational study of a national clinical-administrative dataset of admissions and data from UK Registry of Fatal Anaphylaxis	All age groups with food anaphylaxis		Highest increase was in the 0- to 14-year age group
Lee, USA, 2017	2001–2010	Retrospective observational study of a regional epidemiologic registry of health providers in Olmsted County (Rochester)	All age groups with food anaphylaxis	Incidence rate ratio of 1.098 (95% CI, 1.048–1.150), ($p < .001$)	Yearly 9.8% increase in the incidence rate for patients with food as the suspected trigger
Motosue, USA, 2017	2015–2014	Retrospective observational study of a national clinical-administrative dataset of emergency department visits	All age groups with food anaphylaxis		124% overall, significant for all age-groups except patients > 64 years The increase was higher in the 5- to 17-year group (285%) and 18- to 34-year group (150%)

Table 2 (continued)

Author	Study period	Type of study	Age groups	Annual rate increase	Annual percentage increase
Wang, Hong Kong, 2017	2001–2015	Retrospective observational study of a national clinical-administrative dataset of admissions	All age groups with food anaphylaxis	Overall 1.16 (1.11–1.22) Age groups 0–4 years: 1.15 (1.07–1.24) 5–14 years: 1.21 (1.13–1.29) 15–18 years: 1.06 (0.96–1.16)	
Motosue, USA, 2018		Retrospective observational study of a national clinical-administrative dataset of emergency department visits	Children		Highest increase (413%) was seen in adolescents (age 13–17 years)

Table 2 (continued)

Author	Study period	Type of study	Age groups	Annual rate increase	Annual percentage increase
Motosue, USA, 2018	2005–2014	Retrospective observational study of a national clinical-administrative dataset of emergency department visits	Children younger than 18 years		Over the years, emergency department rates of food-induced anaphylaxis increased in all age groups, with the highest rate of increase during the study period seen in adolescents aged 13–17 years (413%; $p < 0.001$) 0–2 years, $p < 0.001$, 147.1% 3–6 years $p < 0.001$, 151.0% 7–12 years $p < 0.001$, 230.9% 13–17 years $p < 0.001$, 412.8% Tree nut, 373% Milk (only 0.2 years) Peanut, $p < 0.001$, 194.6% Shellfish/fish, $p < 0.001$, 66.9% Tree nuts/seeds, $p < 0.001$, 373.0% Milk, $p < 0.001$, 152.5% Section 1.2 Egg, $p < 0.001$, 324.9% Proportion of ICU admissions decreased (–45.03%, $p = 0.001$)

Table 2 (continued)

Author	Study period	Type of study	Age groups	Annual rate increase	Annual percentage increase
Michelson, USA, 2020	2008–2016	Retrospective observational study of a national clinical-administrative dataset of emergency department visits	All age groups with food anaphylaxis	The incidence of idiopathic and food-related anaphylaxis increased steadily over the study period. However, the authors do not report data The incidence of anaphylaxis overall increased in adults (<i>IRR</i> 1.91 [95% <i>CI</i> , 1.73–2.10]) and in children (<i>IRR</i> 3.23 [95% <i>CI</i> , 2.56–3.90])	
Poirot, USA, 2020	2000–2014	Retrospective death record review and analysis of inpatient hospital discharges and emergency department visits in New York City residents	All age groups with food anaphylaxis	Rates of hospitalizations increased from 16.5/1,000,000 person-years during 2000–2003 to 34.0/1,000,000 during 2011–2014. Emergency department visit rates increased from 35.6/1,000,000 person-years during 2005–2010 to 73.8/1,000,000 during 2011–2014	Annual increase, 5.7% Annual increase in patients younger than 15 years, 6.6% Total and annual increase in patients aged 15–59 years, 6.6%
Baseggio, UK, 2021	2008–2018	Retrospective observational study of a clinical-administrative dataset of admissions	All age groups with food anaphylaxis	Total increase in patients aged younger than 15 years, 339% Total increase in patients aged 15–59 years, 214% Total increase for those aged 60 years or older, 78%	Annual increase, 5.7% Annual increase in patients younger than 15 years, 6.6% Total and annual increase in patients aged 15–59 years, 6.6%

population (0.25). Again, the considerable heterogeneity of the studies means that the increase must be interpreted with caution.

Using a clinical-administrative dataset of visits to the emergency department and to the hospital, Dyer et al. [32] found the incidence rate of food-induced anaphylaxis to be increased in the pediatric population of Illinois (USA) during 2008–2012. Emergency department visits increased annually by an average of 29.3% and admissions by 17.2%. Increases in both health settings were observed in all the study groups, although the greatest annual percentage increase was recorded in Hispanic children and children with public insurance.

In the USA, Rudders et al. [34] reported that admission for anaphylaxis due to food increased two-fold in the period 2000–2008 (0.60 per 1000 to 1.26 of hospitalizations per 1000 total hospitalizations).

Baseggio et al. [8•] analyzed the trends of admissions in the UK due to anaphylaxis induced by food between 1998 and 2018 using a national admissions database of the National Health Service. During this period, the annual increase was 5.7%; the highest increase was in individuals younger than 15 years (total increase 339%, annual increase 6.6%), while the increase in those aged 15–59 years was 5.9% and 214% annually and in total, respectively.

Motosue et al. [5] assessed trends in visits to the emergency department in the USA between 2005 and 2014 using administrative data for private and public insurance enrollees. During the study period, the frequency of food-induced anaphylaxis increased by 124% in patients overall; the difference was significant for all age groups except those older than 64 years. The increase was higher in individuals aged 5–17 years (285%) and 18–34 years (150%). Cow's milk and eggs were predominant in children aged 0 to 2 years compared with children aged >3 years. The same authors [6] extended the study to adolescents and children (under 18 years) and found the highest increase in adolescents aged 13–17 years (413%) for anaphylaxis triggered by tree nuts.

In Olmsted County in Rochester (USA), Lee et al. [14•] found a 9.8% increase per year in the incidence rate for patients whose suspected cause was food.

Data from non-Western countries are much sparser. Although fewer studies from Asia have been published in the last 5 years, researchers from Hong Kong [21] and Korea [20], who used a similar methodology to that commented on above, confirmed increases in the frequency of anaphylaxis [27], with the largest increase observed in the 0- to 9-year age group, suggesting that these increases were due to food-induced anaphylaxis.

During the last 20 years, several studies [28] from Australia [29, 30], the USA [31–34], the UK [7], and Spain [9] have studied age groups where the increases are higher. For the period 2004–2011, Mullins et al. [30] found an overall increase in admission rates (1.8-fold, 280%), with the highest increase in the 5- to 14-year age group (3.3-fold, 430%), while Tejedor et al. [9] found the highest increase to be in the 5- to 9-year age group. In the UK, Turner et al. [7] reported the highest increase to be in the 0- to 14-year age group. Based on a clinical administrative dataset of the Ministry of Health in Italy, Nocerino et al. [35] found the greatest increase to be in patients aged 5–14 years. Again, based on a national administrative dataset, Mullins et al. [30] extended this

maximal increase to age 29 years (5–14 and 15–29 years). Finally, using clinical administrative data, Motosue et al. [6] reported the highest increase in emergency department visits due to food-induced anaphylaxis (413%) in patients aged 13–17 years.

The classic explanations for this increase are that adolescence is the life stage during which responsibility is transferred from parents, perceptions of danger with respect to risk behavior are lower, adherence to self-care is poor, peer pressure leads individuals to hide their illness, and communication with health care professionals is poor [28].

We must determine whether this increase is real or due to bias. The increase may be associated with the reported increase in food allergy, with this relationship acting as stronger evidence of an increase in the frequency of anaphylaxis due to food. According to the American Centers for Disease Control and Prevention, rates of pediatric food allergy increased by 50% in the period 1997–2011 [6]. In the UK, a cross-sectional study performed with different cut-points in the same geographical area by Venter et al. [38] revealed an increase in food allergy between 1993–1994 and 1997–1999, but not in 2004. In the USA, Sicherer et al. [39] conducted phone surveys in 1997, 2002, and 2004, observing an increase in self-reported peanut and/or tree nut anaphylaxis from 0.6 to 2.1%, but only among children. However, as Baseggio et al. and other authors report [8•, 37, 40], the increases are not parallel in the UK and other countries.

Recurrence of Anaphylaxis

Tejedor et al. [18••] conducted a systematic review and meta-analysis of recurrence of anaphylaxis. For cohort and cross-sectional studies, the frequency of recurrence was higher in the case of food (hazard ratio, 11.44 [95% CI, 1.58–83.08]; and prevalence rate ratio, 1.80 [95% CI, 1.15–2.83]) than for the remaining causes of anaphylaxis. Likewise, the incidence recurrence rate and the prevalence rate ratio varied from 5.8 to 17.09 per 100 person-years and from 8.97 to 84.62%, respectively.

In this review, the observation that the of anaphylaxis in patients with a strong atopic background (mainly food, but also exercise and unknown causes) is associated with more frequent recurrences is supported by the presence of asthma as a moderate risk factor for recurrence (*HR*, 1.52). Atopy is a well-recognized risk factor for asthma, mainly at younger ages. While the meta-analysis of asthma as a risk factor comprised 5 studies, analyses related to the main causes of anaphylaxis comprised 3 studies, thus, limiting the certainty of the results of risk factors for recurrence.

Anaphylaxis related to a history of food allergy may recur more frequently than other causes of anaphylaxis because of a marked predisposition to new sensitization to other allergens or cross-reactivity between food allergens or an unknown allergen source.

Fatal Food-Induced Anaphylaxis

In their systematic review on the incidence of deaths due to anaphylaxis (46 studies and 16,541 deaths), Perez-Codesido et al. [19••] found the crude food-induced anaphylaxis mortality rate to be lower than for the remaining main causes of anaphylaxis. In this review, the range of the mortality rate for anaphylaxis due to food (0.002–0.29 per 1 million person-years) was smaller than for deaths due to drugs (range 0.004–0.56) or Hymenoptera venom (range 0.02–0.61). Oral intake may be less dangerous than parenteral intake, for the following reasons: (1) the number of human tryptase-containing mast cells from the small bowel mucosa is lower than that of connective tissue-type mast cells located at other sites; (2) younger age may better compensate for the hemodynamic changes induced by anaphylaxis in older patients [41, 42].

In a previous meta-analysis, Umasunthar et al. [43] found that the crude mortality rate for anaphylaxis due to food was 1.81 per million person-years when the prevalence of food allergy was 3%. The extrapolated estimation of the crude anaphylaxis death rate in the general population is 0.045 per million person-years, which is well within the ranges reported in food-induced fatal anaphylaxis studies in the systematic review of Perez-Codesido et al. [19••] (0.02–0.29). However, both the meta-analysis of Umasunthar et al. [43] and the systematic review of Perez-Codesido et al. [19••] were subject to considerable heterogeneity ($I^2 > 85\%$), which limits the strength of a pooled estimation.

Studies from Australia and the UK reported a similar incidence of fatal anaphylaxis due to food, although in the USA, the lower death rate may be associated with poorer accessibility to the hospital system due to the lower number of people with health insurance [22]. Nevertheless, in both cases, the number of deaths in patients admitted with food anaphylaxis does not follow these trends [44].

The meta-analysis of Perez-Codesido et al. [19••] did not reveal an increase in the crude yearly mortality rate for anaphylaxis during the study period among people who died from food-induced anaphylaxis. However, several recent studies in Australia have reported a positive trend toward an increase in the anaphylaxis mortality rate (6.2% per year, predominantly for food-induced anaphylaxis in the period 1997 to 2013) [30]. Conversely, in their recent report of admissions for anaphylaxis in the British National Health Service, Baseggio et al. [8•] reported a decrease in deaths due to food-anaphylaxis between 1998 and 2018 (incidence rate ratio, 0.93; 95% *CI*, 0.90–0.96). In any case, the lack of an increase in deaths due to food anaphylaxis, despite the increase in the frequency of food anaphylaxis, can be explained by the growing awareness among patients, and in the general population, of the risk of severe reactions to foods to which patients are allergic [7].

This incidence rate of fatal food-induced anaphylaxis can be underestimated, since episodes may be underdiagnosed, miscoded, or classed as being of unknown cause [44].

The highest risk of fatal food-induced anaphylaxis has been noted in adolescence and young adulthood (twofold increase in risk in the 14- to 17-year

age group compared with the 0- to 2-year age group and a peak in the second and third decades of life) [8•, 26, 45, 46]. Evidence for this fragility in adolescence is weak. The classic explanation that adolescents take greater risks [28, 47] has been questioned by some authors [8•], given that the increase in risk extends to midadulthood (the fourth decade of life), thus pointing to a physiologic vulnerability whose nature is not explained.

Also important, a significant number of cases of fatal food-induced anaphylaxis occur in patients who had previously experienced episodes of food allergy triggered by the same food [29, 30]. Likewise, in fatal food-induced anaphylaxis, a high proportion of deaths are due to bronchospasm or laryngeal angioedema followed by circulatory collapse resulting from hypoxia and respiratory arrest [48]. This observation is explained by the presence of asthma in more than two-thirds of asthma patients who died of food anaphylaxis.

The high frequency of asthma among people who die of food-induced anaphylaxis has led us to consider asthma a risk factor for fatal anaphylaxis, especially if the asthma is poorly controlled. However, in the UK Fatal Anaphylaxis Registry, no evidence of poorly controlled asthma is found in most cases, and a large proportion of asthma is also found between food-allergic people. Therefore, asthma has a low positive predictive value for fatal anaphylaxis [22, 44].

Tree nuts and peanut have classically been considered the most frequent causes of fatal anaphylaxis (55–87% of deaths) [49, 50]. However, in the UK Fatal Anaphylaxis Registry [8•], cow's milk is the most frequent food-related cause of death (26% in children and 5% in adults). In Australia, seafood accounts for 50% of cases of fatal food-induced anaphylaxis [30], and in France, goat and sheep's milk are responsible for 13% of deaths [51]. In the UK, deaths due to peanut have been decreasing compared with an increase in deaths due to milk, a food with a high-protein content [8•], thus potentially explaining why even very low amounts of milk can cause severe episodes of anaphylaxis. In the European Anaphylaxis Registry of Anaphylaxis [10], the most frequently reported causes of fatal food-induced anaphylaxis in children and adolescents were cow's milk, hazelnut, cashew, and peanut.

Many authors emphasize eggs as an infrequent cause of death or state directly that they are not a cause of death [10]. However, in an article from Spain, eggs were found to be a cause of death [52].

Differences Between Populations

Baseggio et al. [53••] performed a systematic review of the distribution of foods triggering anaphylaxis episodes throughout the world. The most frequent causes were peanut, tree nuts, cow's milk, and crustaceans. The studies reviewed were studies of individual institutions or regional/national registries of cases. The researchers found common foods as the cause of anaphylaxis in different geographic areas, whereas other, less common foods appeared as major causes in only 1 or 2 regions. Likewise, they reported the proportions of anaphylaxis compared with the pooled prevalence of food

allergy estimated in the meta-analysis for the main foods. In Europe, crustaceans and cow's milk caused anaphylaxis in adults more frequently than peanut. Hazelnut and some fruits caused anaphylaxis less frequently than peanuts; the authors hypothesized that this was because hazelnut and fruits are the cause of pollen–food allergy syndrome. Finally, fish and crustaceans were frequent causes of anaphylaxis in adults in Asia. In southern Europe, sensitization to lipid transfer protein is a major cause of anaphylaxis. In the rest of Europe, fruit allergy is associated with sensitization to birch pollen. In China, lipid transfer protein is also a cause of anaphylaxis, although sensitization is related to cross-reactivity to mugwort pollen.

Various foods are responsible for anaphylaxis in the different age groups in childhood and adolescence and in different ways in different geographic areas. In Hong Kong, hen's egg only appeared as the cause in patients aged 0–4 years, while crustaceans were only observed in patients aged 15–19 years [21]. Wheat, seafood, and vegetables were the common foods in Korean adults [54, 55], while in a study from Japan, where children accounted for 70% of patients, the most important foods were cow's milk, hen's eggs, and wheat [56]. Peanut and tree nuts are commoner in Europe than in Asia. In a combined study of pediatric intensive care units in the USA and Canada, eggs, milk, and tree nuts/seeds were responsible for anaphylaxis in children with a younger median age (2.2, 3.2, and 5.6 years, respectively), while peanuts, fruit/vegetables, and crustaceans were causes of anaphylaxis in older children (6, 11, and 13.4 years, respectively) [46]. Peanut and tree nuts were the common triggers of food anaphylaxis for patients seen in the pediatric emergency department in the USA [5, 34]. In the European Anaphylaxis Registry [10], cow's milk and hen's egg are the most frequent causes in the first 2 years of life. In the same registry [10], cashew and hazelnut appeared as the trigger in the preschool group, while peanut was a trigger in the period from infancy to young adulthood.

Wheat is reported as the main cause of anaphylaxis in several Asian countries [27]. It is the third cause of food allergy in Japanese children, with onset of episodes during the first year of life [56, 57]. Buckwheat and wheat have been described as major allergens or as the main causes of anaphylaxis in adolescents and adults in Japan and Korea and northern China, respectively [55–58].

Several studies from the UK, USA, and Australia have found ethnic differences within their geographical areas [22]. African American race was a relevant risk factor for fatal food-induced anaphylaxis in the USA [59]. African American adults with food allergy had more severe episodes and more visits to the emergency department than White adults, even after adjusting for several sociodemographic factors (e.g., household income, educational level) [40, 59]. Similar observations have been made in the pediatric population in the USA for the African American and the White populations. It is unclear whether these findings are due to inequality in access to the health system, genetic or environmental causes, or as yet unknown factors [22, 44]. In the UK Fatal Anaphylaxis Registry, males in families from Africa, Middle East, and the Far East are over-represented [60]. A higher prevalence of peanut allergy was reported in the Australian HealthNuts study of infants of parents born in Asia than in the infants of parents born in Australia [61], after accounting for

differences in food introduction practices and key characteristics of household socioeconomic level [32, 40, 62].

Differences in food anaphylaxis rates have also been reported between rural and urban populations [63]. An analysis of the Healthcare Cost and Utilization Project data for New York and Florida for the period 2009–2014 found that emergency visits due to food anaphylaxis were higher in urban than in rural settings (12.3/100,000 vs. 4.6/100,000) [64].

Bias and Weaknesses

Turner et al. [22] address the question of whether bias affects studies on the epidemiology of anaphylaxis, thus diminishing the validity of reported findings.

One such bias is selection bias [22]. Anaphylaxis episodes occur in the community, and many episodes do not reach health care facilities for treatment. Studies often report data from health insurance company-based discharge or emergency department data at national level, with the result that incidence rates are often underestimated.

Selection bias affects the frequency of the different severities of anaphylaxis episodes, with over-representation of severe episodes and under-representation of the least severe episodes. Indeed, cases of fatal anaphylaxis may not reach the emergency department of primary care clinics. The incidence of anaphylaxis can increase if the threshold for seeking medical help decreases [5].

Many studies are retrospective and therefore subject to registry and recall bias. Comparative analysis of trends can be affected by registry bias if the criteria for admitting a patient with anaphylaxis to a hospital ward differ between hospital systems or there are settings where patients do not appear in hospital registries (e.g., observation units in emergency departments).

Studies are also subject to information bias. Coding errors occur in regional clinical-administrative datasets of discharges in the following cases: when episodes of anaphylaxis are erroneously entered as asthma, urticaria, or other; when the cause is coded as unknown; when coding routines differ depending on the country (e.g., collection of symptoms or not, different comprehensibility); and when clinicians use different definitions of anaphylaxis [22].

The consequences of bias for the analysis of trends at different cut-points or in different geographic areas can be partially attenuated if the studies are based on a similar methodology, although this does not resolve the effects of different coding routines in different geographic areas or the effect of differences in awareness of the presence of anaphylaxis at different times [42, 63].

Ideally, studies should be based on unselected populations; however, the number of cases collected may be low, and confidence in the case definition may raise doubts about the external validity of the studies [8•]. At least 2 studies with these characteristics have been published. One was a telephone survey conducted in the USA and the second was a cohort study conducted in Stockholm (Sweden) in a general adolescent population. Both studies

reported increased prevalence and incidence rates of anaphylaxis due to food [23•, 65•].

The information presented above leads us to ask whether anaphylaxis, including food-induced anaphylaxis, is underreported and underdiagnosed or whether the incremental trends toward a higher presence of anaphylaxis due to food are true [5, 44]. The most robust support for the increase in the frequency of anaphylaxis is the increase in the frequency of food allergy in countries where an increase in food-induced anaphylaxis is reported [6], although studies from the same location did not find the same increases for anaphylaxis and food allergy during the same periods [8•].

Despite these problems, registry and clinical-administrative data remain the most utilized and valuable sources of information on the epidemiology of anaphylaxis [22].

Conclusions and Future Perspectives

The evidence supporting current knowledge on the epidemiology of anaphylaxis cannot explain with sufficient confidence whether the rates in the different countries or in the increased trends in anaphylaxis due to food are accurate or result from confounders that have not yet been identified. More studies are necessary in the general population and in the community. However, if such studies have not been performed to date, it may be because they are difficult to perform and may not provide reliable data. If studies on trends in anaphylaxis in geographical areas other than in Western countries follow the same methodology, they will be unable to determine whether an increase in the frequency of food-induced anaphylaxis is true. However, they will help to assess how environmental causes can modulate the frequency of food-induced anaphylaxis.

Declarations

Conflict of Interest

The authors declare no competing interests.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

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