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Article type : Review

The Global Burden of Illness of Peanut Allergy: A Comprehensive Literature Review

Running Title: Burden of Peanut Allergy

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Short running title: 24 characters (<50 characters max)

Review text word count: 5220/4500 max (not including abstract, figure legends, refs)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ALL.14666

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Accepted Article

Abstract word count: 188/200 max (unstructured)

Figures and tables: 4 tables/6 figures/10 total (up to 10 max)

Supplemental figures and tables: 2 tables/1 figure

Keywords 5/5 max

References: 157/200 max

Sponsor: Aimmune Therapeutics

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ACKNOWLEDGEMENTS

This narrative review was funded by Aimmune Therapeutics. Editorial assistance and medical writing support were provided by The Curry Rockefeller Group, LLC and was funded by Aimmune Therapeutics.

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ABSTRACT

Peanut allergy (PA) currently affects approximately 2% of the general population of Western nations and may be increasing in prevalence. Patients with PA and their families/caregivers bear a considerable burden of self-management to avoid accidental peanut exposure and to administer emergency medication (adrenaline) if needed. Compared with other food allergies, PA is associated with higher rates of accidental exposure, severe reactions, and potentially fatal anaphylaxis. Approximately 7-14% of patients with PA experience accidental peanut exposure annually, and one-third to one-half may experience anaphylaxis, although fatalities are rare.

These risks impose considerably high healthcare utilisation and economic costs for patients with PA and restrictions on daily activities. Measures to accommodate patients with PA are often inadequate, with inconsistent standards for food labelling and inadequate safety policies in public establishments such as restaurants and schools. Children with PA are often bullied, resulting in sadness, humiliation, and anxiety. These factors cumulatively contribute to significantly reduced health-related quality of life for patients with PA and families/caregivers. Such factors also provide essential context for risk/benefit assessments of new PA therapies. This narrative review comprehensively assessed the various factors comprising the burden of PA.

Keywords: Accidental exposure, anaphylaxis, burden, health-related quality of life, peanut allergy

INTRODUCTION

Peanut allergy (PA) is one of the most common food allergies among children in Western nations,[1] and is often a lifelong condition.[2] Onset of PA typically occurs in early childhood,[3-6] and is associated with more severe reactions than other food allergies.[7] In contrast to food allergies such as milk, egg, wheat, and soy that resolve in childhood or adolescence in approximately half to the majority of cases,[8,9] PA persists into adulthood in approximately 75-80% of children.[2,10]

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Until recently, the recommended management strategy for PA was limited to the combination of strict allergen avoidance along with an action plan, including having an adrenaline autoinjector (AAI) on hand in case of accidental exposure and reaction to peanut,[11,12] which is sometimes referred to as an avoidance management strategy.[13] However, the 2018 European Academy of Allergy and Clinical Immunology (EAACI) Guidelines for management of food allergy recommended oral immunotherapy (OIT) as a treatment option to increase the reaction threshold in children with PA from around 4-5 years of age (strength/evidence level/grade of recommendation: strong/1/A) (Supplemental Table 1).[14] EAACI guidelines further stated that post-discontinuation effectiveness of OIT is suggested, but not yet confirmed.

The combined factors of the risk of potentially life-threatening and often traumatic accidental allergic reactions, lifelong persistence of PA in the majority of individuals, responsibility for self-management of risks, and the lack of any approved treatments for this condition, all contribute to a significant burden of illness associated with PA.[15,16] Multiple studies have investigated specific aspects of the burden of PA, such as impact on health-related quality of life (HRQoL),[17-19] risks of accidental exposures to peanut,[20] and costs of self-management of PA.[21] However, comprehensive reviews that assess these various factors together to provide an updated and holistic perspective on the burden of PA are lacking. Such perspectives are particularly needed in light of recent evidence that PA incidence and prevalence may be increasing,[8,22] thus potentially adding to the societal burden of PA.

These perspectives are particularly relevant due to recent advances in PA management, which pose new choices and important questions for clinicians, patients with PA, and their caregivers. Recent clinical trials have demonstrated the benefit of introducing peanut to children at a young age to reduce the risk of developing PA,[23] prompting the publication of US, British, and Australasian guidelines for early introduction of peanut to infants/at-risk infants.[24-26] In addition, the novel oral immunotherapy Peanut (*Arachis hypogaea*) Allergen Powder-dnfp, formerly known as AR101, was recently approved to mitigate allergic reactions that may occur with accidental exposure to peanuts in individuals 4-17 years of age with a confirmed diagnosis of PA.[27,28] Other immunotherapies are in phase 2 and 3

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development.[29-31] A complete and accurate assessment of the current burden of self-managed PA is needed to allow for full consideration of the role of emerging and future management options.

Objective

This article will review in comprehensive narrative format the impact of the risks of PA and the burden of self-management on peanut-allergic children, adolescents, and their families.

Methods

Narrative review vs. systematic review

This narrative review was designed to assess the latest data concerning the burden of PA from a broad and multifaceted perspective, including impacts in socioeconomic, clinical, psychosocial, and HRQoL domains. Because narrative reviews are generally comprehensive and cover a wider range of issues within a given topic, as compared to the narrow focus and prescribed methods of a systematic review, the use of a systematic or meta-analysis review method was deemed impractical for the purpose of assessing the spectrum of factors associated with PA burden. Additionally, since multiple individual searches were required for each topic, using consistent, precise selection/elimination criteria across topics would have inherently resulted in the omission of several publications that were critical to our report.

We searched the United States National Institute for Biotechnology Information/National Institutes of Health/National Library of Medicine PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) for studies pertaining to the burden of PA in the following main keyword/topic areas: peanut allergy prevalence and incidence, accidental exposures, anaphylaxis and severe reactions, healthcare utilisation, economic costs, mortality, comorbidities, burden of peanut allergy on the individual and family (including requirements of disease self-management), and peanut allergy impact on HRQoL. The searches for each topic area, search terms used for each, and main results of each search are illustrated in Supplemental Figure 1. Initial searches were limited to data published within the past 2 years. If these data were insufficient, we conducted a second search within a 10-year time frame. We

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also incorporated articles as appropriate if publications retrieved during our searches pointed to essential prior studies.

RESULTS

Peanut Allergy Prevalence And Incidence

Estimates of PA prevalence have varied in part due to the different methods utilised for determining its presence, ranging from self-report to skin prick test (SPT), peanut-specific immunoglobulin E (psIgE) testing, and oral food challenge (OFC), as well as different thresholds for each test, and the age cohorts and regional populations studied. Some evidence also suggests incidence and prevalence of PA may be increasing, thus introducing a further challenge to accurate assessment.[8,32] Studies reporting prevalence of PA published since 2010 are listed in Table 1.

Overall, studies have generally reported PA prevalence rates between 1% and 2% in Western nations (Table 1). Incidence and prevalence of PA appear to be less common in Asia and other global areas, although epidemiological studies of PA in non-Western regions have been sparse (Table 1).[22] One cross-sectional, multicenter study reported a PA prevalence of 0.8% in South African children based on SPT and OFC,[33] and a cross-sectional study in Kuwaiti schoolchildren aged 11-14 years reported a PA prevalence of 1.3% based on clinical history.[34] A retrospective, single-center cohort study found that among 98 Singaporean children presenting with anaphylaxis, peanut was the most common trigger of anaphylactic events, although no cases of peanut-triggered anaphylaxis were documented in a similar study conducted 15 years earlier, possibly indicating effects of changes in dietary habits.[35,36] In both studies, anaphylaxis cases were indicated by hospital and emergency room discharge codes and confirmed by presence of clinical symptoms; however, the later study used the 2008 Sampson criteria for diagnosis, while these criteria were not available for the earlier study.[35,36]

Some, but not all, data also indicate that PA incidence and prevalence may be increasing in Western nations.[3,37,38] A longitudinal national US claims database study found that annual incidence of PA in one-year-old children had increased from 1.7% in 2001 to 5.2% in 2017.[39] A recent study in a representative US population of over 40,000 individuals found that PA impacts 2.2% of children and

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1.8% of adults.[40,41] In addition, a retrospective cohort study of children aged 0-6 years in the Australian Capital Territory reported increasing incidences of PA (children born in 2001, 0.73%; children born in 2004, 1.15%).[42]

Among prevalence studies, a nationwide US study found a 3-fold increase in self-reported PA prevalence in children between 1997 (0.4%) and 2008 (1.4%),[37] although actual prevalence figures may be inflated in studies only considering self-reported PA.[8,43] A nationwide English study of clinician-recorded PA diagnosis found that while incidence remained stable, the prevalence of PA doubled, from 2001 (0.24 per 1000 patients) to 2005 (0.51 per 1000 patients).[38] More recently, a three-decade, retrospective UK medical records database study found that point prevalence per 100,000 had risen from 31 to 202 in the total population, and from 116 to 635 in children from 2000 to 2015.[44] In addition, this study found that incidence of PA overall in the UK had more than doubled, from 8.6 to 18.2 per 100, 000, between 2000 and 2015. However, stable PA prevalence has been reported in two Canadian studies for the periods of 2000 to 2007 in Montreal[45] and 2010 to 2017 across Canada[46] and in a study conducted on the Isle of Wight, UK between the late 1990s and 2004.[47]

HEALTHCARE BURDEN

Risks of Accidental Exposure, Severe Reactions, and Anaphylaxis

Even with adherence to standard self-management behaviors,[14,16] risk of accidental exposure to peanut is still high among individuals with PA. The widespread use of peanuts in various foods makes it particularly difficult to avoid peanut exposure in the home, where children play, or at school.[7] Data on the rate of accidental reactions in patients with PA have varied, likely due to variations in study design, geographic region, and decade of study (Table 2).[6,20,41,48-53]

Data on the frequency of anaphylaxis in patients with PA are limited, in part because of varying definitions of anaphylaxis used. Multiple studies in Western nations have reported that severe allergic

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reactions due to peanut occur more frequently than to other food allergies.[40,54] A nationwide US study on food allergies in children (n=38,408) found that a history of severe reactions was more common in children with PA (59.2%) versus all other food allergies (42.3% rate of severe reactions overall).[40] Similarly, a nationwide 2009-2010 US survey study in 38,480 children found that a significantly higher percentage of children with PA (n=754) had experienced a severe reaction to peanut versus children with food allergy in general (n=2464) (53.7% vs. 41.0%; $P<0.001$).[7] Among US adults with PA, 68% report at least one severe peanut-allergic reaction versus a 51% overall rate of any severe food-allergic reactions among all US adults with food allergy.[41] The Australian SchoolNuts Study, which included 547 adolescents aged 10 to 14 years with possible food allergy, found that 38.6% of all confirmed anaphylaxis episodes and 30.6% of unconfirmed anaphylaxis episodes were reactions to peanut, the highest percentages of any food causes.[55]

Studies in the US and Canada have reported that 11% to 17% of accidental exposures were severe (Table 2).[20,50,51] A cross-sectional nationwide US study in 754 children with PA reported an anaphylaxis rate of 14.2%, compared with 8.1% in children with other food allergies[7], and a UK clinical practice database study found a considerably lower anaphylaxis rate of 1.2% of all patients (children and children) with PA versus 0.007% of matched controls.[44] Another US study reported that anaphylaxis occurred in approximately 35% of 525 children over a 5-year period,[6] and a smaller study (n=83) reported a 5-year rate of reactions with "potentially life-threatening symptoms" in approximately 52% of children (Table 2).[53] Accidental exposures causing anaphylaxis frequently occur in children whose initial reactions leading to diagnosis were mild (Figure 1),[6,53] demonstrating the unpredictable nature of PA reaction severity.[56] While varying methodologies of reporting reactions and varying definitions of anaphylaxis make it difficult to put a finite number on the frequency of anaphylaxis to peanut, it is evident that severe and accidental reactions are common in patients with PA. Several studies also relied on self-report, which is prone to recall bias and misclassification. More studies are needed that examine current, consistent, and well-validated criteria for the diagnosis of anaphylaxis.

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Healthcare Utilisation

In the European Anaphylaxis Registry, peanut is the most common trigger involved in anaphylaxis cases in both children and adults, accounting for 27.2% and 18.0% of food-related anaphylaxis cases, respectively.[54,33] Peanut is also the most common food trigger involved in most studies of paediatric emergency department (ED) admissions overall and in paediatric intensive care unit (ICU) admissions in North America; peanut is the second most common trigger, after milk, in France.[57,58] Anaphylaxis to peanut is also associated with high rates of hospital admission following ED visits, compared with other food-related and non-food-related causes of anaphylaxis.[59] Recent US survey data show that 23% of children[40] and 20% of adults[41] with PA reported an ED visit in the past year due to a food-allergic reaction. A healthcare utilisation study in the UK demonstrated that compared to matched control groups (normal and with/without an atopic condition) patients with PA had a greater number of contacts (per person–year) with primary care providers, inpatient care, prescriptions, outpatient care, and accident and emergency admissions.[60]

An epidemiological study in the US, Canada, and Mexico of paediatric anaphylaxis ICU admissions between 2010 and 2015 (n=1989) found that peanut was the most frequent trigger, accounting for 39% of such cases (Figure 2).[57] In addition, a study of paediatric ED visits and hospital admissions due to food-induced anaphylaxis in Illinois between 2008 and 2012 found that such cases had increased significantly over the period ($P< 0.005$), with a 30% average annual increase observed for peanut-induced events (Figure 3).[61] A nationwide Italian study found that the rate of hospital admissions for food-induced anaphylaxis in children had increased from 0.001% in 2001 to 0.005% in 2011 ($P<0.05$), and that while peanut exposure was a less frequent cause than milk and eggs, it was the cause of 1 out of every 4 deaths that occurred in patients aged >14 years.[62]

Although sparse, these utilisation data support and confirm the studies discussed in the previous section showing relatively high rates of anaphylaxis and severe reactions despite their diversity of methodology.

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Economic Burden

The economic burden of PA includes both direct and indirect costs, each of which have been investigated in several studies.

Direct medical costs

Among US studies, a retrospective national US government healthcare database analysis of the annual direct costs of food allergy, including PA, over the years 2006 and 2007 estimated that total annual medical costs were $225 million (2007 US dollars), with office visits accounting for just over half of the cost; the rest of the cost was split among ED visits, inpatient and outpatient visits, ambulance transfers, and AAIs.[63] A survey of US caregivers of children with food allergy estimated direct medical costs of $4.3 billion annually (or $724 per child).[64] The caregivers also reported a willingness to pay $3504 per year per child for a safe and effective treatment that would allow the child to eat all foods; that total cost was estimated at $20.8 billion annually, a number similar to the total estimated indirect costs spent on children with food allergy ($20.5 billion). The total annual economic burden of food allergy was estimated to be $24.8 billion, which combined direct ($4.3 billion) and indirect costs.[64] A 2013 pan-European, case-control survey study conducted among participants in the EuroPrevall study (n=1411) found that the mean costs of health care over the previous year for adults and children with possible food allergy (symptoms unconfirmed by psIgE testing) were I$2016 and I$2197 versus I$1089 and I$863 for controls, respectively.[65]

Among studies that assessed the costs of PA specifically, a 2017 white paper found that patients with PA averaged approximately 1.25 medical services per patient in 2016 based on an analysis of nationwide US medical insurance claims.[66] On average, patients with PA were charged $236.73 per patient for services over the 2016 year, with insurance covering $100.11. A US study assessed value-based pricing for an AAI, which is substantially higher in the US than most other countries, for community-based anaphylaxis management in patients with PA.[21] This study found that given the average pharmacy AAI cost of $715 in 2016, combined with 2018 reported costs for ED visits and hospitalisations for anaphylaxis symptoms, the cost of anaphylaxis preparedness and treatment in

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those prescribed an AAI over an 80-year time horizon was $25,478 (95% CI: $25,399-$25,447) versus $654 (95% CI: $685-$743) for those not prescribed an AAI. Assuming that AAI prescription reduced anaphylaxis fatality risk by 10- to 100-fold, the estimated cost-effective price range for AAI was $24 to $264, indicating that AAI at its then-current US price was not cost-effective. A retrospective cohort study of PA costs among patients with PA in the UK (n=15,483), reported per-person annual incremental healthcare costs versus healthy controls of £333, ranging up to £392 for those prescribed an AAI, and £662 per year for those with history of anaphylaxis; total excess costs of PA in the UK were between £33 and £44 million in 2015.[60] The average cost of an AAI in the UK in 2017 was £25.80 (approximately US$32.10).[67] Comparable studies of PA costs in regions/countries other than the US and UK are lacking. The available studies rely on modelling and reflect vastly disparate healthcare costs in different countries; thus, defining the exact costs of PA across countries remains difficult. However, the consistent finding among these studies is that PA raises healthcare costs.

Indirect medical costs

A Swedish case-control study demonstrated that indirect costs of food allergy were significantly higher in families with food-allergic children (excluding adolescents) compared with controls.[68] The US retrospective, government healthcare database study mentioned above also estimated annual indirect costs (e.g. lost work productivity and earnings) of food allergy including PA for 2006-2007 to be $115 million (2007 US dollars).[63] A cross-sectional US survey study[64] estimated annual lost labor productivity due to food allergy at $773 million, or $130 per child, associated with accompanying child to medical visits; $5.5 billion, or $931 per child, in annual out-of-pocket costs, including special diets/allergen-free foods, changes in childcare, and changes in schools; and annual opportunity costs due to forgone labor market activities, at $14 billion, or $2399 per child. While these studies have limitations, similar to those analysing direct costs, an overall trend towards increased indirect costs is apparent.

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Mortality

While rates of fatal anaphylaxis due to peanut are low, peanut is among the most frequent food allergens implicated in fatal anaphylaxis. This finding has been documented in the US,[69-71] the UK,[72,73] Australia,[74] and France.[75] A 2013 meta-analysis of data on fatal food-related anaphylaxis found that the incidence of peanut-induced mortalities was 2.13 per million person–years (95% CI: 1.09, 4.16; I-squared=86.4%; *P* <0.001), which was higher than the rate for all food allergies (1.81 per million person–years [95% CI: 0.94, 3.45; I-squared=94.8%; *P*<0.001]).[76] UK data showed that deaths from food-related anaphylaxis usually occurred in allergic people whose previous reactions had been mild, underlining the unpredictability of reaction severity, although presence of asthma and asthma exacerbation were identified as mortality risk factors.[73] A 2018 meta-analysis of 32 published studies of food-related anaphylaxis, which found that peanut and tree nuts were the leading triggers of fatal anaphylaxis, also showed that a history of asthma in young adults was an important risk factor for fatality.[77]

Comorbidities

Comorbid conditions including allergic rhinitis, atopic dermatitis, and asthma, as well as other food allergies are very common in patients with PA (Table 3)[4,6]; in the French MIRABEL study, only 5% of individuals had no associated allergic comorbidity.[4] Comorbid tree nut allergy is particularly common in patients with PA, with reported prevalence ranging from approximately 16% to 50%.[7,78] In tree nut–allergic patients, reported concomitant PA ranges from 20% to 68%.[79] Increased number of food allergies tends to increase the burden due to the added requirements of vigilance and dietary restriction.[80]

THE BURDEN OF PEANUT ALLERGY ON THE INDIVIDUAL

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Dietary Restrictions

The primary strategies for allergen avoidance in patients with PA and their families are diet modification and restrictive eating habits, which has a substantial impact on quality of life (QoL).[18] These strategies also carry the risks of nutritional deficiency and compromised growth in young children, particularly if parents exclude a wider-than-necessary range of foods without expert nutritional consultation.[81-83] Individuals with PA often avoid tree nuts, in part because of concern over cross-reactivity or contamination.[49] However, studies that investigated rates of coexistence of nut allergies have shown that performance of SPT or basophil activation tests or OFCs for various nuts in children with one or more PA or other nut allergies could result in relief of dietary restrictions.[84,85] In the PRONUTS study, use of OFC to confirm tolerance of specific nuts in children with ≥1 nut allergy led to a median of 9 nuts being introduced into the diets of study participants.[85]

Reading Food Labels: Precautionary Allergen Labels

Mandatory requirements for allergen labelling in food items are well established in developed and developing countries and are typically clear and useful.[86] However, *precautionary* allergen labelling is not legally required in most countries, is mostly unregulated, and may be confusing for consumers.[86] In a US study of prepackaged food labelling just under half of products included had a "may contain" type of advisory label.[87] A 2017 study from France found that of more than 17,000 food products, 1% included peanut in the ingredient list, yet 13% of products contained a precautionary statement listing peanut.[88] In addition, an investigation by the Food Standards Agency in the UK found that approximately 20% of food samples in England contained an undeclared allergen, the majority of which were peanuts.[89] In a longitudinal, prospective cohort study in the Netherlands, among 157 patients with food allergy, including 71% with PA, 73 reported 151 accidental reactions to an allergen, of which 118 (78%) could be attributed to a specific product.[90] Of the 51 food products that fulfilled criteria for further analysis, 19 (37%) contained 1 to 4 allergens (including peanut) that were unidentified in the product labelling.

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Several studies have shown that using unregulated language in advisory statements on food labels may create uncertainty for consumers. A US-based study showed that only 4.5% of products with advisory labelling specific to peanuts tested positive for peanut residue, further unnecessarily restricting diet choices.[91] In addition, shoppers increasingly ignore labels,[92] with up to 40% of US and Canadian consumers who either have a food allergy or care for a food-allergic child stating they had purchased food despite the product's precautionary labelling, in one study (Supplemental Table 2).[93] The French MIRABEL study found that accidental exposure peanut doses eliciting reactions were <100 mg in 44.3% of study participants with PA; however, such data have not been incorporated into clear and universal labelling regulations.[4] The quantity of accidentally ingested peanut leading to symptoms in patients with PA appears to vary widely and is not well studied.

The lack of consensus for standard labelling impairs the ability of healthcare professionals to provide an effective management approach, and may indirectly impact emotional adjustment, social interactions, and coping strategies,[94-97] causing increased anxiety and impaired QoL.[98] Recent recommendations from The National Academies of Sciences, Engineering, and Medicine (NASEM) highlighted the importance of evaluating and improving food labels with allergen information.[99]

Eating at Restaurants

Eating food made outside of the home can also impact patients with PA, as peanut is a common ingredient in many dishes. The 2017 NASEM consensus report recommended that patients and their parents be guided to always inform restaurants (e.g. servers, managers, cooks) of food allergies to minimise risk of exposure.[99] The European Commission of the European Union also issued legislation effective December 2014 including "mandatory allergen information for non-prepacked food, including in restaurants and cafes."[100] In 2019, the European Federation of Allergy and Airways Diseases Patients' Associations released a report calling for additional improvements to food labelling and safety measures at restaurants.[101]

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A survey of children with peanut- and tree nut allergy who experienced a reaction due to exposure at a restaurant (dine-in or takeout) found that most reactions (81%) were due to accidental exposure in children who had already been diagnosed; yet allergic individuals or their parents alerted restaurant personnel about the allergy less than half (45%) of the time.[102] Surveys of restaurant workers in the US, UK, Turkey, and Malaysia, have demonstrated a poor understanding of food allergies and appropriate measures for avoiding allergens.[103-109] A UK interview study found that individuals with food allergy strongly preferred written information to be provided in restaurants.[110] Respondents further reported they practiced avoidance as a last resort if uncertain.

Restrictions on Daily Activities

The risk of accidental exposure posed by PA extensively impacts daily activities, which may include playdates at friends' homes, attendance at daycare or afterschool care, parties and sports events, and camp and sleepovers.[111]

Travel

Individuals with PA must take extra precautions in trip planning. A survey of this population in the UK highlighted several such considerations, including ability to understand the language at the destination, perceived experience on airlines, accessibility to medical care, familiarity with the destination, and avoiding unfamiliar cuisines.[112]

An international study of 3273 respondents with peanut and/or tree nut allergy from 11 countries found that 349 reactions to peanuts or tree nuts occurred aboard flights, with 13.3% of respondents receiving adrenaline for their reactions.[113] In addition, flight crews were notified of the reactions in

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only 50.1% of cases. However, 69% of respondents made preflight accommodation requests (55% of reactors vs. 71.6% of nonreactors; $P<0.001$).

School

European meta-analysis data indicate that food allergy affects 4%-7% of primary school children, and approximately 8-20% of paediatric food-related accidental reactions and anaphylaxis reactions may occur at school.[114] Peanut was the most common trigger among 105 cases of food-induced anaphylaxis (25% of cases) at school documented in a French national allergy database,[115] and was the second most common food trigger of anaphylaxis (16%), after tree nuts (23%), occurring in school settings in one German study (n=87 anaphylaxis cases).[116] [115]A US study of all food-allergic reactions due to accidental exposure at school found that 25% to 29% of reactions were attributed to peanut.[117] In a survey study of parents of children with PA or tree nut allergy in the US Peanut and Tree Nut Registry (n=4586), 16% of respondents reported a reaction at daycare, preschool, or elementary school.[118] Of the 124 total reactions (115 to peanut), 65 (52.4%) were severe and 71 (57.3%) were treated with adrenaline. A further study in this registry population (n=5149) also found that as children got older, school was increasingly the setting for accidental exposures subsequent to the child's first reaction (Figure 4).[48]

Multiple studies in various countries have examined potential strategies for schools to address the risks of food allergies, such as becoming "peanut-free" and making adrenaline available to school staff, with some controversy.[115,116,119-127] A survey of school nurses in Massachusetts found that 10.3% of schools do not permit peanuts to be sent in from home, 91.1% had peanut-free tables, and 65.6% had peanut-free classrooms.[128] However, a study investigating the impact of peanut-free schools on the PA-related burden and QoL of parents demonstrated no difference compared with schools that are not peanut-free.[129]

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Emotional Impact

Living with food allergy can lead to fear and anxiety not only regarding the risk of exposure and reaction to the allergen,[111] but also fear of using a prescribed AAI, possibly related to uncertainty of how and when to use it and past or anticipated traumatic experiences of severe reactions [19,130-132] In those with PA, factors such as comorbid illnesses and experience of PA may also play a role. The MIRABEL study in 785 children with PA found that higher anxiety scores (n= 401 evaluated for anxiety) were observed in patients with atopic dermatitis (P=0.003), both atopic dermatitis and asthma (P=0.032), and those who had received strict avoidance advice (P<0.001).[4] Dietary avoidance itself may also be a source of anxiety and stress.[18,133]

Bullying, teasing, and taunting because of food allergy have been reported among children with food allergy in studies at rates ranging from 16% to 71%, causing substantial adverse emotional impact.[134] Data specifically on bullying in children and adolescents with PA is scant. One survey study of children and adults with food allergy included 287 individuals with PA.[135] In this study, 24.1% reported having been bullied, harassed, or teased because of their food allergy by a variety of perpetrators (Figure 5A). After excluding children younger than 5 years, the rate increased to 35.2%. The great majority of those bullied, teased, or harassed (85.9%) reported physical acts of bullying such as having the allergen waved in their face (Figure 5B); nonphysical acts included verbal teasing and exclusion. The most common reported emotional effects of the bullying were sadness and depression, embarrassment and humiliation, and nervousness and anxiety (Figure 5C).

Impact on Health-Related Quality of Life/Quality of Life

Multiple studies have demonstrated adverse impacts of food allergy on HRQoL and QoL in people with food allergies and their parents/caregivers.[132,136,137] Several studies also evaluated the effects of PA specifically on HRQoL, which is of particular interest since PA is associated with relatively high rates of prevalence, accidental exposures, severe reactions and anaphylaxis, as discussed above.[17-19,80]

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A recent study surveyed parents of children aged <13 years with PA (n=717), sesame allergy (n=34), or seafood allergy (n=42) using the Food Allergy Quality of Life Questionnaire—Parent Form.[80] Mean QoL scores (higher scores=worse QoL) were similar for PA (2.53) and sesame allergy (2.56), but scores were significantly worse for PA (but not sesame allergy) compared to seafood allergy (1.97; 0.55 difference, 95% CI: 0.13, 0.98). An older study compared QoL of children with PA (n=20; mean age 9.0 years) and diabetes mellitus (n=20; mean age 10.4 years) using a QoL questionnaire developed for the study (which has since been validated)[138] and an adapted Vespid Allergy Quality of Life questionnaire.[17] In this study, mean scores were significantly higher (worse) in children with PA versus those with diabetes in both questionnaires (54.9 for PA vs 46.4 for diabetes; P=0.004 [novel questionnaire] and 54.3 for PA vs 34.5 for diabetes; $P \leq 0.001$ [adapted Vespid questionnaire]) (Figure 6). The children with PA were also reported to experience significant anxiety in a wide range of settings.[17]

A study in 46 families that included a child with clinically confirmed PA, and which used validated QoL and anxiety and stress scales, reported significantly worse scores for physical HRQoL ($P<0.05$), QoL within school ($P<0.01$), general QoL ($P<0.05$), and greater separation anxiety ($P<0.05$) in children with PA than in their siblings without PA.[18] Mothers had significantly worse scores for psychological and physical health, and higher levels of anxiety and stress than fathers. However, another study, which examined HRQoL, anxiety, and stress levels in 51 families including a child with PA, found that many measures did not significantly differ from population norms.[19] This study also found that parental stress and child anxiety levels varied with clinical history, and that both parent and child perceptions of their own HRQoL were affected by each other's anxiety and stress levels. Children's QoL was also adversely affected by length of time since diagnosis and the experience of having to self-inject or receive an AAI injection.

Depending on the management strategies employed by children with PA and their families, the impact of PA on QoL is variable.[139] Further, management of PA by paediatric allergy specialists has been

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shown to slightly improve QoL,[140] demonstrating a crucial role for allergists and immunologists in helping allergic children and their families manage this burden.

CONCLUSIONS

The incidence and prevalence of PA appear to be increasing, and rates of accidental exposure in patients with PA are high, despite extensive efforts at avoidance. Patients with PA and their families experience significant psychosocial and economic ramifications from PA allergy, resulting in a negative impact on HRQoL/QoL. Multiple new approaches and initiatives towards better understanding of PA risks and improved PA management are clearly needed (Table 4). Introduction of peanut to children at a young age may reduce the risk of developing PA,[23] and international guidelines for the use of this approach have been provided.[24-26] However, such prevention practices do not address those with PA or who develop PA despite this new guidance. While the approval of the first oral immunotherapy product for PA[27] is a major advance, the ultimate benefit of this therapy and other new treatments will likely depend on multiple factors including baseline disease severity, the cost-effectiveness of immunotherapies versus adrenaline, effects of immunotherapy on QoL, and the ability to induce sustained unresponsiveness.[15] Continued research into the burden of PA remains essential to provide perspectives for current and future developments in PA management.

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CONFLICT OF INTEREST STATEMENT

JAL reports receiving research funding from and serving as an advisor to Aimmune Therapeutics and serving as an advisor to DBV Technologies and Covis Pharma.

RG reports receiving grants from the National Institutes of Health (NIH), Stanford University, and Aimmune Therapeutics; serving as a medical consultant/advisor for DBV technologies, Aimmune, Before Brands, Pfizer, Mylan, and Kaleo, Inc,; and receiving grants from the NIH, Allergy and Asthma Network, Food Allergy Research & Education, Rho Inc, Northwestern University Clinical and Translational Sciences Institute, Thermo Fisher, United Health Group, Mylan, and the National Confectioners Association.

RK is a consultant for Aimmune Therapeutics.

TH is a consultant for Aimmune Therapeutics.

ST is an employee of Aimmune Therapeutics.

DPM is a member of the Board of Directors for the Canadian Society of Allergy and Clinical Immunology; serves on the Editorial Board of the Journal of Food Allergy. He has provided consultation and speaker services for Pfizer, ALK, Aimmune, Merck, Covis and Pediapharm and has been part of an advisory board for ALK, Pfizer and Bausch Health.

GP has provided consultation and speaker services for Aimmune Therapeutics, Bausch and Lomb, Stallergenes, ALK-Abello; serves as a medical consultant/advisor for Bausch and Lomb.

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TABLES

Table 1. Peanut Allergy Population-Based Prevalence Estimates (Published 2010 to Present)

Study	n	Age cohort (mean age, y)	Study Period	Region	Criteria for PA (Study Type)	PA Prevalence Estimate(s), %
Liu et al, 2010[141] (NHANES 2005-2006)	8203	Children and adults (NR)	2005-2006	US	psIgE; age-based clinical criteria for likely FA (in-person survey interview/mobile lab testing)	1.3, overall; 1.8 children aged 1-5 y; 2.7, children aged 6-19 y; 0.9, adults aged 20-59 y; 0.3, adults aged ≥60 y
Sicherer et al, 2010[37]	13,534	Children and adults (NR)	2008	US	Self-reported reaction/symptoms (random telephone survey)	0.8 overall; 1.4, children
Ben-Shoshan et al, 2010[142]	9667	Children and adults (NR)	2008-2009	Canada	Perceived: self-report; Probable: self-report + convincing history or PD; Confirmed: self-report + convincing history and PD based on specified criteria (telephone survey)	1.0, perceived; 0.9, probable; 0.6 confirmed[b]
Gupta et al, 2011[143]	38,480	Children (8.5)	2009-2010	US	Self-reported reaction/symptoms (online survey)	2.0 overall; ranging in paediatric subgroups from 1.4 in children aged 0-2 y and ≥14 y , to 2.8 in children

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						aged 3-5 y
Osborne et al, 2011[144] (HealthNuts)	2848	12-month old infants (1.7)	2007-2010	Melbourne, Australia	SPT, wheal size ≥1mm+ OFC (clinic examination)	3.0 overall
Kotz et al, 2011[38]	2,958,366	Children and adults (NR)	2005	England	GP-recorded diagnosis (database search)	0.5 per 1000 patients
McGowan et al, 2013[145] (NHANES 2007-2010)	20,686	Children and adults (NR)	2013	US	Self-reported FA, 30-day food consumption, demographic/clinical predictors of FA (in-person survey, respondent dietary diary)	1.0 overall; 1.2, children; 0,9 adults
Nwaru et al, 2014[a114]	NR	Children and adults (NR)	2000-2012	Europe	Self-report, SPT, OFC, psIgE, PA clinical history (various)	Point prevalence: 1.7, self-report; 1.7, SPT; 8.6, psIge; 0.2, FC positive; 1.6, FC or PA history; lifetime prevalence: 0.4
Bunyavanich et al, 2014[43]	616	Children aged 7-10 (7.9)	NR	Eastern Mass, US	Self-report; psIgE; psIgE + AAI prescription; psIge, ≥14 KU/L; psIgE ≥14 KU/L + AAI prescription (in-person survey)	4.6, self-report; 5.0, psIgE; 4.9, psIgE + AAI prescription; 2.9 psIgE, ≥14 KU/L; 2.0, psIgE ≥14 KU/L + AAI prescription
Dyer et al, 2015[7]	38,480	Children	2009-2010	US	Convincing history, PD (online survey)	2.0 (76.0% confirmed by PD)
Peters et al,	139	4-year-old	2011-	Melbourne,	SPT, wheal size ≥1 mm + OFC	1.9 overall

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2017[c146] (HealthNuts)		children (4.3)	2014	Australia	(clinic examination)	
Bedolla-Barajas et al, 2017[147]	756	Children aged 6-7	2014	Guadalajara, Mexico	Probable: self-report of reaction; Convincing: self-report + observation of skin, respiratory, and/or gastrointestinal reactions ≤ 2 hours after peanut ingestion; Systemic: a convincing reaction (above) involving ≥2 organ systems	Probable: 1.8; convincing: 1.1; systemic: 0.4%
Kim et al, 2017[148]	29,842	Children aged 6-16	2015	Korea	Self-report + detailed history of symptoms	0.22 overall
Sasaki et al, 2018[149] (SchoolNuts)	9816	Children aged 10-14 (NR)	2011-2014	Melbourne, Australia	Self-report + psIgE + OFC (clinic examination)	2.7 overall
Gupta et al, 2018[40]	38,408	Children (NR)	2015-2016	US	Self-report + convincing history (online survey)	2.2 overall
Lieberman et al, 2018[150]	NR	Children aged 4-17	2017	US	Longitudinal analysis of PA diagnosis codes/services (healthcare claims database)	2.2 overall
Gonzalez-	365	Children aged	2015-	Honduras	OFC of children showing	0.8 overall

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González et al, 2018[151]		1-18	2016		sensitisation	
Ziyab, 2019[34]	3864	Children aged 11-14 (NR)	2016-2017	Kuwait	Self-report + convincing history (child- and parent-completed questionnaires)	1.3 overall
Botha et al, 2019[33]	1583	Children aged 1 to 3 (NR)	NR	South Africa	Self-report + SPT, ≥1mm, + OFC	0.8 overall[d]
Gupta et al, 2019[41]	40,443	Adults (46.6)	2015-2016	US	Self-report, convincing history (online survey)	1.8 overall; ranging by age cohorts from 2.9, 30-39 y to 0.8, ≥60 y
Clarke et al, 2019[46] (S2S)	15,322	Children and adults (NR)	2016-2017	Canada	Perceived: self-report; Probable: self-report + convincing history and/or physician diagnosis (telephone survey)	Perceived: 1.4 overall, 3.5 children, 1.0 adults; probable: 1.2 overall, 3.2 children, 0.8 adults
Simons et al, 2019[152]	3,455	Children aged 0 to3	2008-2012	Canada	SPT, not consuming peanut at least once per month, convincing history (In-clinic SPT)	At age 3.0 years: Possible: 2.7, overall; probable: 1.8 overall

[a]Meta-analysis of 48 studies conducted in various European countries and employing diverse methods. [b]More than half of physicians failed to respond to requests for confirmatory data. [c]This study was an update of the HealthNuts cohort reported by Osborne et al, 2011 (line 5 of

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this table) to assess rate of peanut allergy at age 4 in subjects reported to have peanut allergy at age 1 (n=156[144]; 139 participated in follow-up). [d]This study examined urban and rural cohorts and found 0 prevalence of peanut allergy in rural children.

AAI, adrenaline auto-injector; FA, food allergy; GP, general practitioner; Mass., Massachusetts; NHANES, National Health and Nutrition Examination Survey; NR, not reported; OFC, oral food challenge; PA, peanut allergy; PD, physician diagnosis; psIgE, peanut-specific immunoglobulin E; SPT, skin prick test; US, United States; y, years.

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Table 2. Studies Reporting Reactions to Peanut Due to Accidental Exposures (Following Initial Reaction)

Study	n	Age Cohort (mean/median age, y)	Region	Methods	Follow-Up Period	Accidental Exposure Prevalence or Incidence (following initial reaction)	Severe Reaction/ Anaphylaxis Rate (initial or subsequent reactions)
Sicherer et al, 1998[52]	102	Children (median, 7.4)	US	In-clinic questionnaire survey	5.4 y median	55% of subjects; average of 2 per subject	21% of subjects, first reaction; 15% of subjects, subsequent reactions[a]
Sicherer et al, 2001[48]	4685	Children (median, 5)	US	Postal questionnaire survey, food allergy registry	Cross-sectional	47.5% of subjects	NR
Vander Leek et al, 2000[53]	83	Children (median, 5.9)	US	Longitudinal telephone follow up single centre study	5 y	60% of subjects; 0.33 reactions per year	51.7% of subjects
Yu et al, 2006[51]	252	Children (mean, 8.1)	Canada	Postal questionnaire survey, single centre	244 patient–years	14.3% annual incidence	11.4% of accidental exposures were severe
Ben-Shoshan et al, 2010[142]	9667	Adults and children (NR)	Canada	Random telephone questionnaire survey	Cross-sectional	73.7% of all subjects; 84.8% of adults, 56.7% of children	91.1% of all subjects; 91.8% of adults, 90.0% of

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							children[b]
Nguyen-Lu et al, 2012[50]	1411	Children (mean, 7.1)	Canada	Longitudinal postal questionnaire survey, multicentre	5 y/2227 patient–years	12.5% annual incidence	17.3% of accidental exposures were severe
Neumann-Sunshine et al, 2012[49]	782	Children (NR)	US	Retrospective chart review, single centre	5.3 y median /4,526 patient–years	7.3% annual incidence	Severe reaction rates: 1.0%-1.6% of subjects per year[c]
Cherkaoui et al, 2015[20]	1941	Children (6.2)	Canada	Postal questionnaire survey, multicentre	10 y/4589 patient–years	12.4% annual incidence	15.0% of accidental exposures were severe
Leickly et al, 2018[6]	1070	Children (NR)	US	In-clinic interview, multicentre	5 y	21.3% of subjects[d]	34.9% of subjects; 33.9% of accidental exposures involved anaphylaxis
Gupta et al, 2019	~728[e]	Adults (NR)	US	Online questionnaire survey	Cross-sectional	NR	67.8% of subjects

[a]Reactions including all 3 of skin, gastrointestinal, and respiratory symptoms. [b]Moderate or severe reaction; percent of subjects with an accidental exposure; [c]Annual rates of post-diagnosis accidental exposures: with lower respiratory symptoms, 1.5%; resulting in a severe reaction: 1.6%; receiving treatment in the emergency department, 1.0%; receiving treatment with epinephrine, 1.1%. [d]Rate among 525 children who returned for at least one clinic visit following initial interview. [e]Estimated from reported peanut allergy prevalence rate of 1.8% among 40,443 adults who completed surveys.

NR, not reported; US, United States; y, years.

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Table 3. Selected Studies Reporting Comorbidities in Children With Peanut Allergy

Comorbidity	Studies, % Participants With Comorbidity					
	Neumann-Sunshine et al, 2012[49] (n=782)	Deschildre et al, 2015[4] (n=785)	Dyer et al, 2015[7] (n=754)	Leickly et al, 2018[6] (n=1070)	Johnston et al, 2019[153] (n=496)	Fleisher et al, 2019[31] (n=356)
Atopic dermatitis	70.8	66	NR	65	62	61.2
Allergic rhinitis	57.3	49	NR	NR	72	55.9
Asthma	55.8	58	NR	41	53	47.5
EoE	3.1	NR	NR	NR	NR	NR
Other food allergies						
Any	93.1[a]	62	NR	68.7	66	NR
Tree nuts	87.6	NR	15.6	NR	NR	NR
Milk	35.7	NR	10.8	19.9	NR	NR
Soy	13.2	NR	3.6	NR	NR	NR
Egg	39.5	NR	8.5	40.2	NR	NR
Wheat	11.0	NR	3.6	NR	NR	NR
Sesame	23.3	NR	3.0	NR	NR	NR
Other legume	4.1	NR	NR	NR	NR	NR
Other	40.8	NR	NR	NR	NR	NR

[a]Avoiding other foods whether a food allergy had been diagnosed or not.

EoE, eosinophilic oesophagitis; NR, not reported.

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Table 4. The State of Knowledge on the Burden of Peanut Allergy and Future Needs: An Overall Assessment

Area of Assessment	Current Knowledge and Needs
What is known	• PA affects 1% to 2% of the general population, and appears to be increasing in prevalence and incidence, in Western nations • PA is typically lifelong and is associated with high rates of severe reactions and anaphylaxis due to accidental exposures, compared with other food allergies • Peanut is among the most frequent allergens implicated in documented cases of fatal food-related anaphylactic reactions • PA is associated with high rates of healthcare utilisation and costs • The risks of PA impose restrictions in multiple activities of daily living for patients, parents, and caregivers, including food shopping, dining out, socializing, schooling, and travel • Management of PA risks in consumer food labelling, and accommodations at schools, restaurants, and travel are inconsistent and often inadequate • Bullying of children with PA is common, causing emotional impacts including sadness, humiliation, and social isolation • QOL is significantly reduced for patients with PA, parents, and caregivers, possibly more so than in other chronic diseases
What is likely	• The incidence of PA may increase in regions other than Western/advanced nations as they adopt Western styles of diet and pediatric nutrition management • Costs of future PA treatments may meet with acceptance if they approximate the current costs of AAIs • Recent guidelines for prevention of PA in infants may stabilise or decrease PA prevalence and incidence
What is needed	• Improved and more consistent methodology for study of PA epidemiology • More and better data on PA epidemiology from geographic regions other than Western/advanced countries • More and better data on the healthcare utilisation and costs of PA from regions/countries other than the US and UK

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	• Standardized, clear, and evidence-based food-labelling for peanut content • Increased knowledge/studies on the amount of peanut in foods that will cause reactions, and the circumstances of/risk factors for accidental reactions (e.g. where they occur) • Improved and more consistent standards for accommodations for individuals with PA at public establishments such as restaurants, schools, and travel conveyances • More accurate QOL instruments adapted specifically for PA including those that may measure the impacts of treatment of PA on QOL • Treatments that reduce the risk of severe reactions due to accidental exposure to peanut and may alleviate the burden of PA • Further studies to assess peanut OIT efficacy and safety, establish validated protocols for optimal dosing and duration of therapy, and assess impact on QOL and cost effectiveness.

PA, peanut allergy; OIT, oral immunotherapy; QOL, quality of life.

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FIGURE LEGENDS

Figure 1. History and nature of reactions to peanut from a single-centre study in 83 children with peanut allergy followed for 5 years. Approximately one-third of subjects who had non-life-threatening first reactions (19 of 61; 31.1%), and more than half of those who had life-threatening first reactions (12 of 22; 54.5%), subsequently experienced a/another potentially life-threatening reaction. All reactions subsequent to first reaction were from accidental exposure (as opposed to reactions occurring during food challenges).[53]

Reproduced with permission from Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *J Pediatr.* 2000;137(6):749-755.

Figure 2. A study of all anaphylaxis admissions to North American (United States, Canada, and Mexico) paediatric intensive care units between 2010 and 2015 (N=1989) found that peanut was the most common trigger.[57] FA, food allergy; Hx, history.

Reproduced with permission from Ramsey NB, Guffey D, Anagnostou K, Coleman NE, Davis CM. Epidemiology of Anaphylaxis in Critically Ill Children in the United States and Canada. *J Allergy Clin Immunol Pract*. 2019;7:2241-2249.

Figure 3. From an Illinois (United States) state hospital association database study of emergency department (ED) visits or hospitalisations for food-induced anaphylaxis in Illinois hospitals from 2008 to 2012 (n=1893; 10.9 ED visits or hospitalisations per 100,000 children). A. Rates of ED visits and hospital admissions due to food-induced anaphylaxis by food allergen trigger. B. Annual percent increase in ED visits from 2008 to 2012. Asterisk indicates a statistically significant increase from 2008 to 2012 ($P < 0.005$).[61]

Reproduced with permission from Dyer AA, Lau CH, Smith TL, Smith BM, Gupta RS. Pediatric emergency department visits and hospitalizations due to food-induced anaphylaxis in Illinois. *Ann Allergy Asthma Immunol.* 2015;115(1):56-62.

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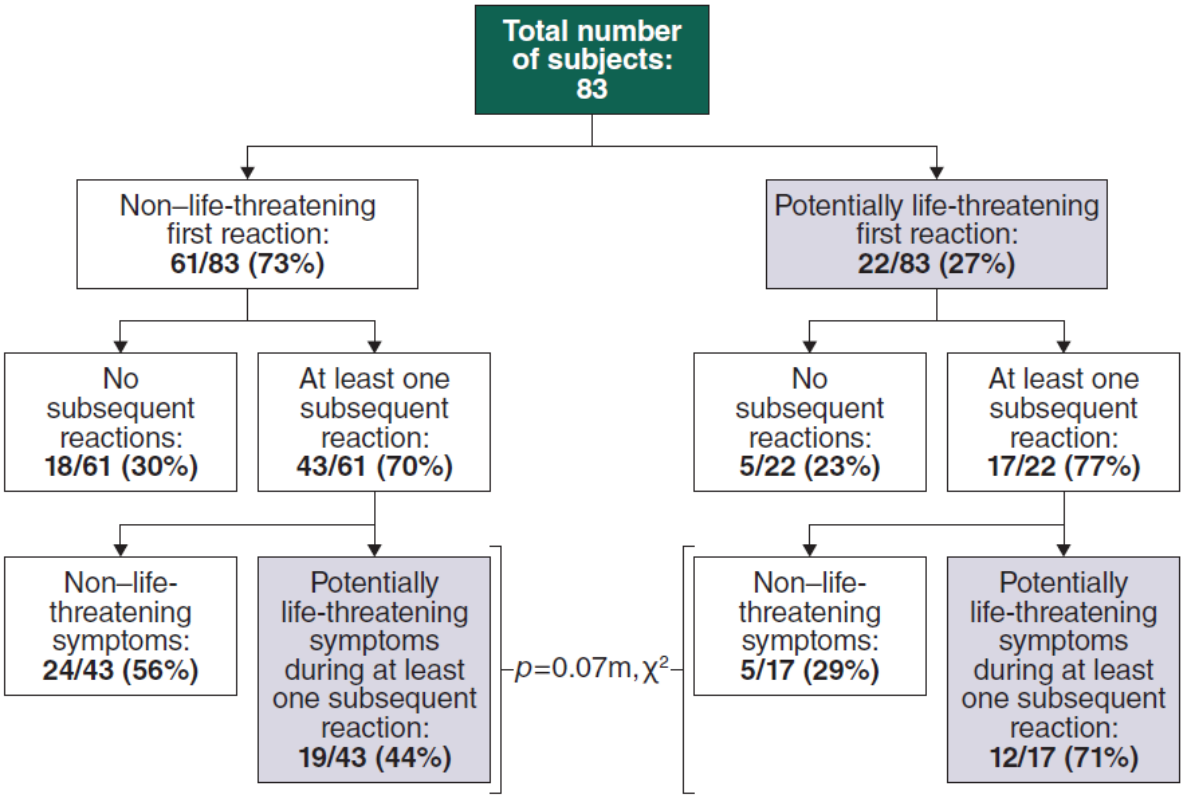
Figure 4. Settings of first and subsequent reactions among 5149 registrants in a peanut and tree-nut allergy registry, of whom 89% were children (aged <18 years), 68% had isolated peanut allergy, and 23% had both peanut and tree-nut allergy. Accidental exposures to peanut subsequent to the first reaction occurred increasingly at school settings. "Other" locations include workplace, stores, malls, sporting event sites, transportation vehicles, and houses of worship .[48]
Reproduced with permission from Sicherer SH, Furlong TJ, Munoz-Furlong A, Burks AW, Sampson HA. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. 2001;108(1):128-132.

Figure 5. Bullying: respondents who reported having been bullied because of their/their child's food allergy (n=85) from a survey study in 353 individuals with food allergy, including 287 (81.3%) with peanut allergy. Panel A describes the perpetrators of the bullying. Panel B describes the types of physical bullying. Panel C shows the reported emotional effects of bullying. For each parameter, respondents could select more than one perpetrator, type of bullying, and emotional effect.[135]
Reproduced with permission from Lieberman JA, Weiss C, Furlong TJ, Sicherer M, Sicherer SH. Bullying among pediatric patients with food allergy. *Ann Allergy Asthma Immunol*. 2010;105(4):282-286.

Figure 6. Scores on specific questionnaire items in **s**tudy comparing quality of life in children with peanut allergy (blue bars; n=20) and diabetes mellitus (orange bars; n=20). A. Fear of eating peanuts/having a hypoglycemic event; B. Chance of having a bad reaction and getting very sick; C. I have to be very careful about what I eat; D. I must take care when eating in a restaurant.[17]

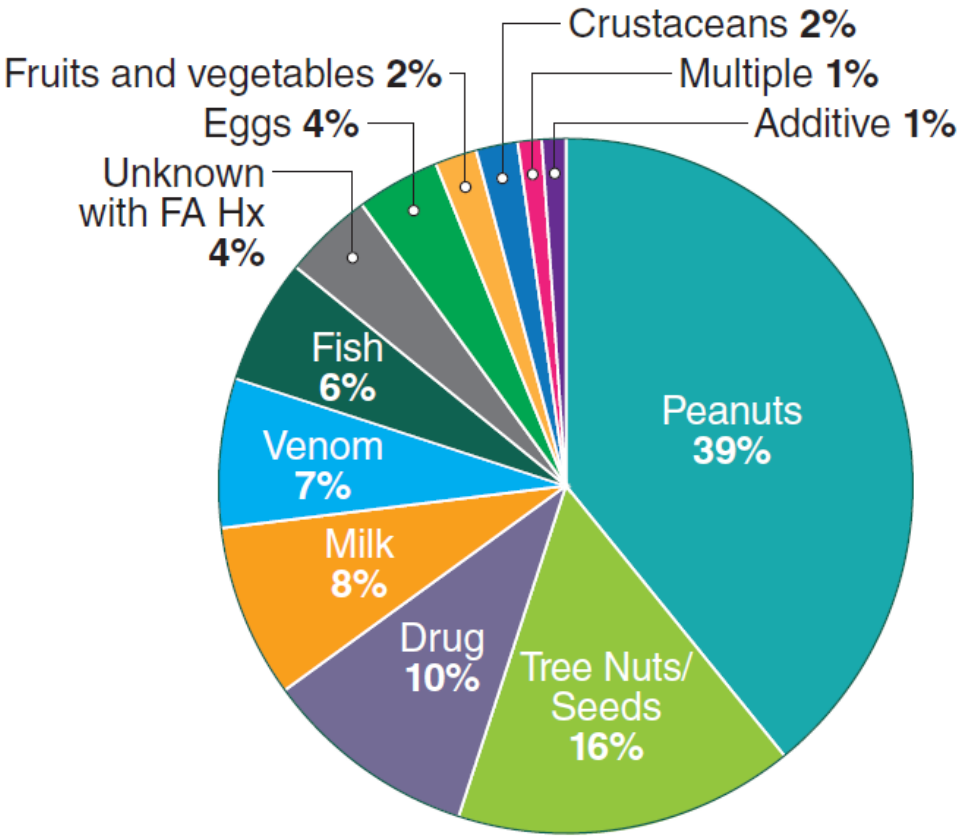
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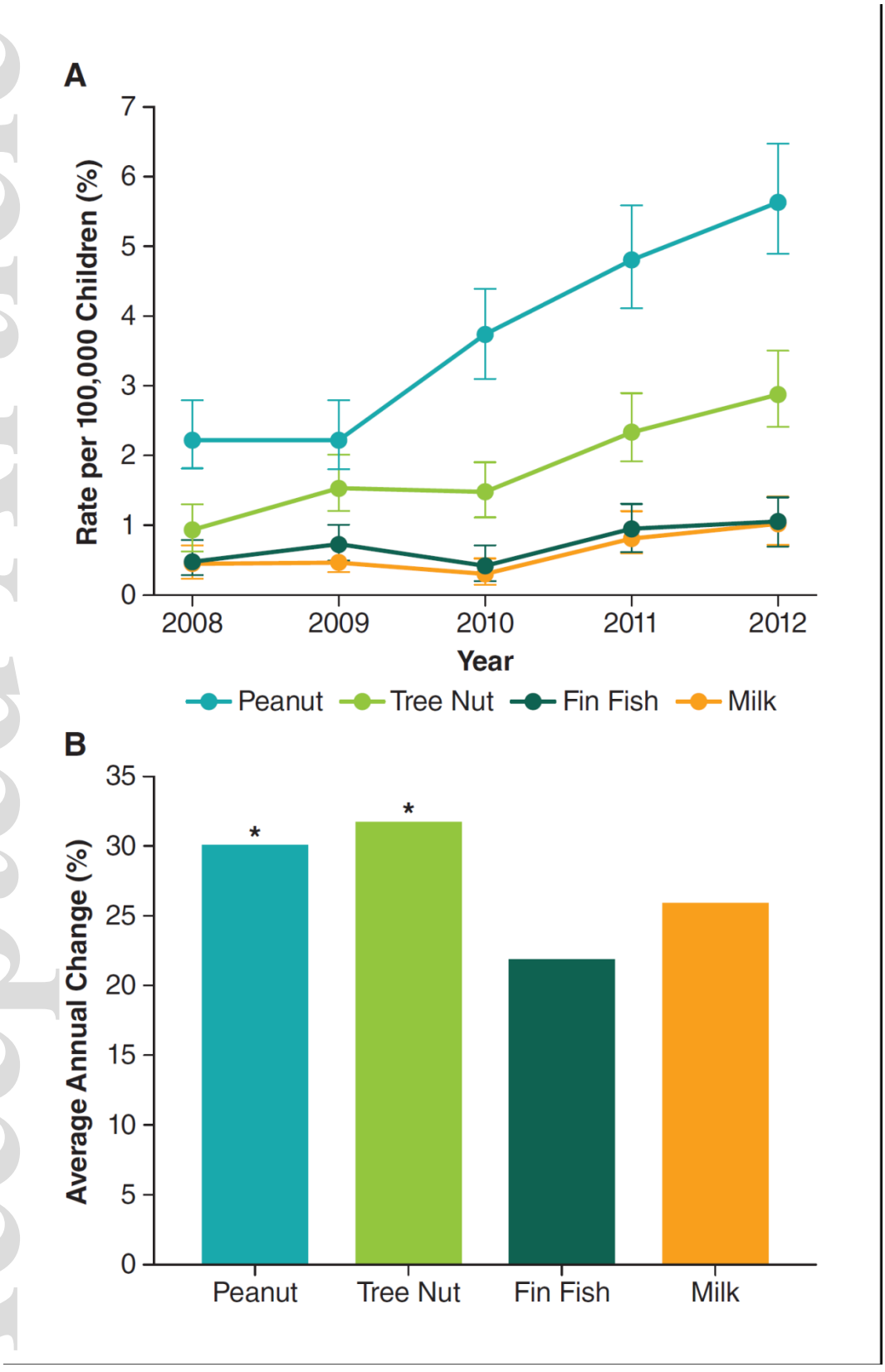
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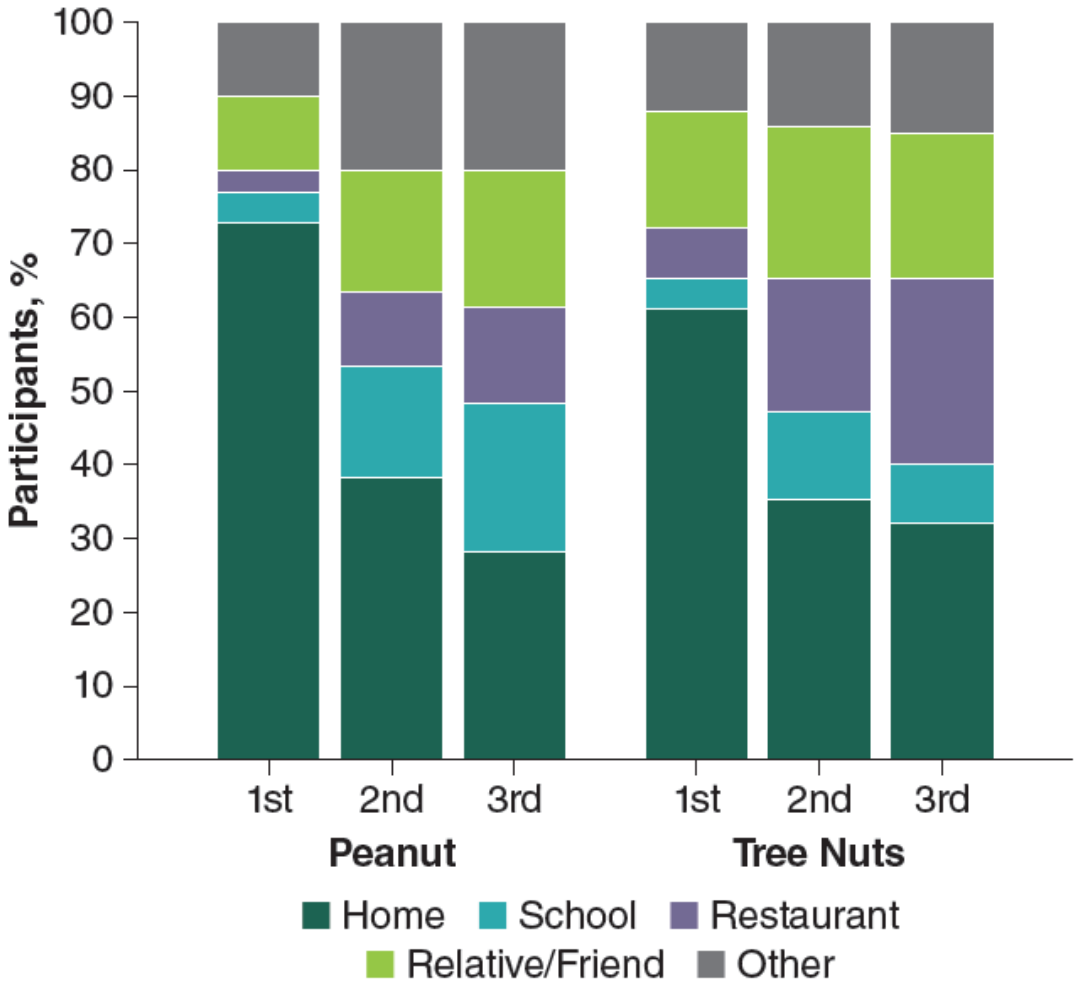
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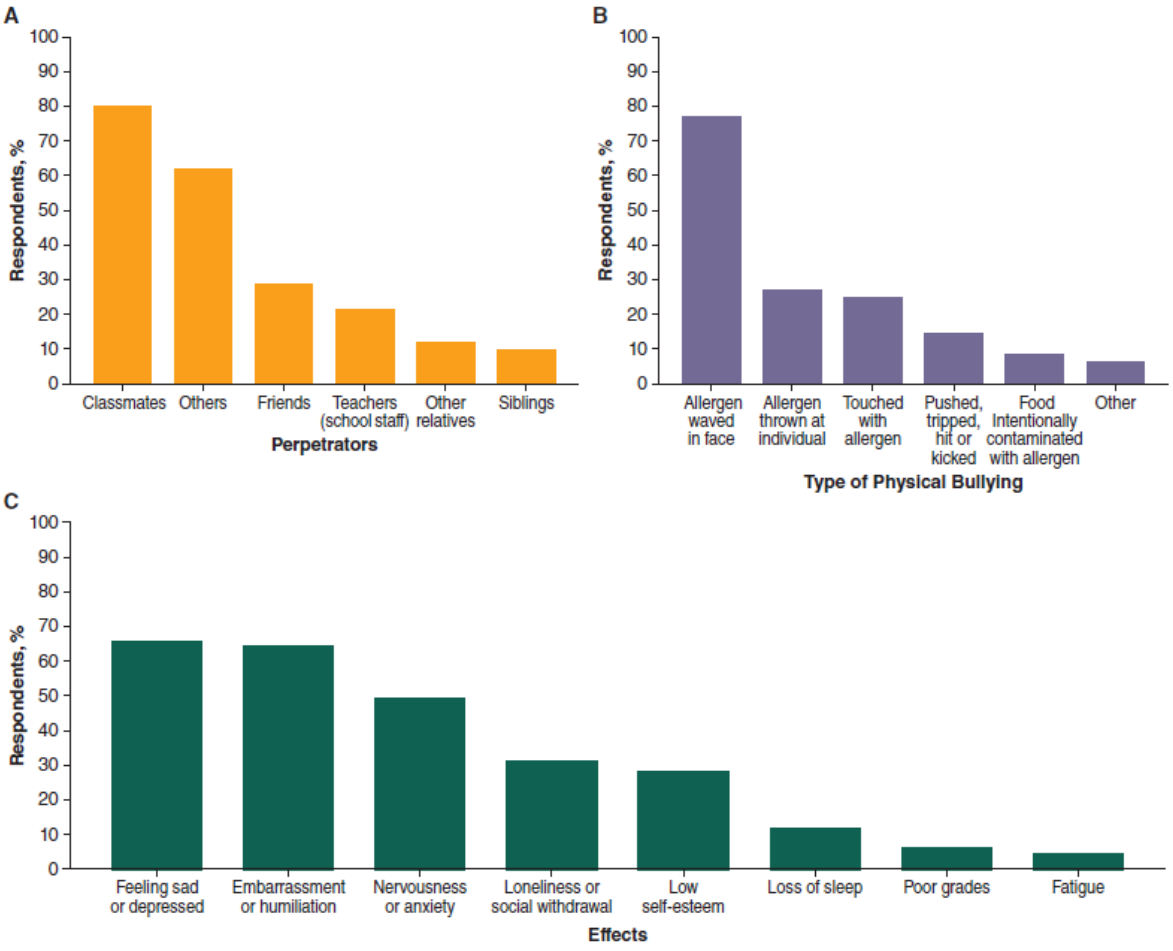
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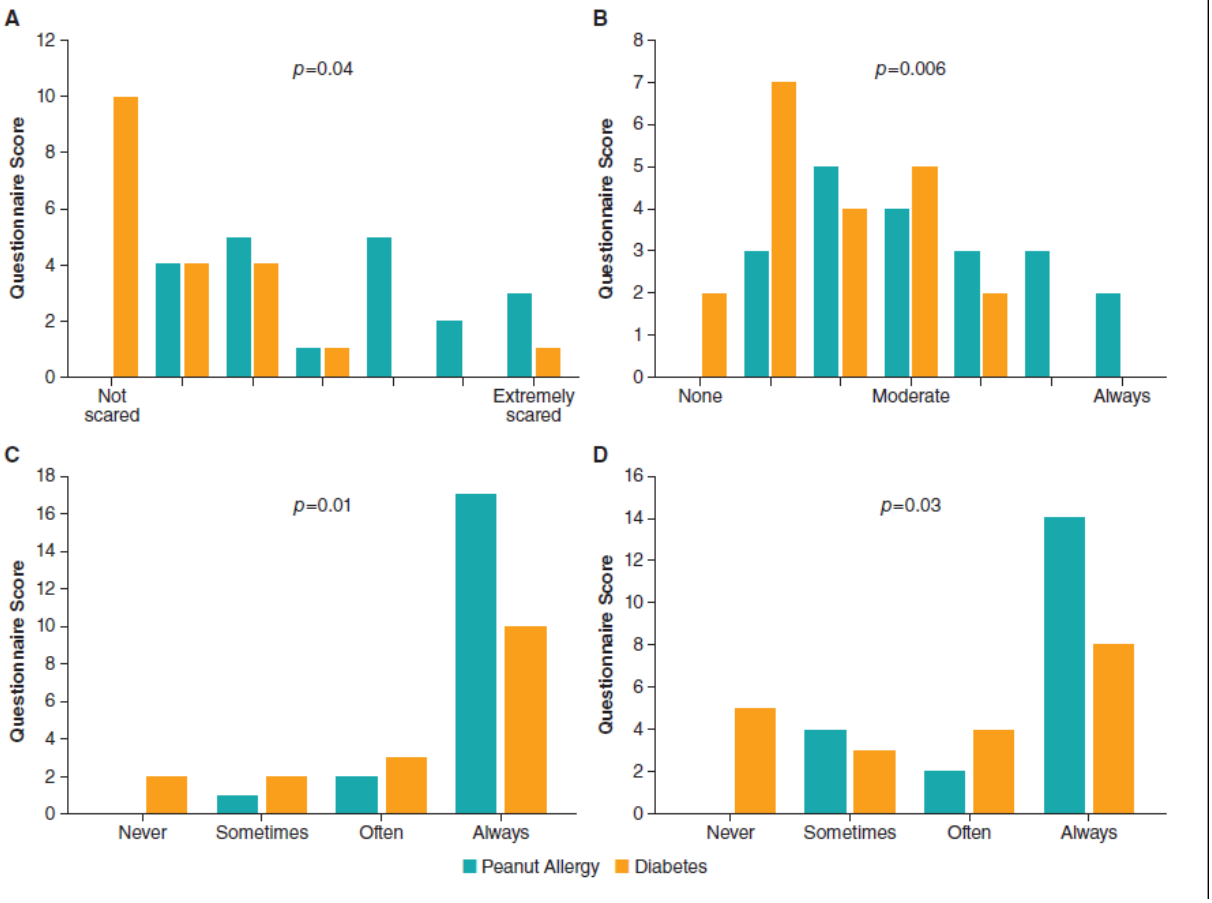
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Supporting information

Elucidating the α-Gal syndrome at the molecular allergen level

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Material and methods

Patient cohort

Patients with symptoms of delayed allergic reactions following mammalian meat consumption attended the Allergy Unit at Södersjukhuset in Stockholm. They were examined and diagnosed by the same allergologist with many years of experience in food allergy. Blood samples were drawn for analysis of allergen-specific IgE antibodies. Diagnosis of mammalian meat allergy was defined as symptoms after mammalian meat consumption and IgE to α-Gal (≥0.1 kU_A/L) measured by ImmunoCAP. In total, 138 patients were enrolled in the study. All patients answered a detailed questionnaire regarding the onset of symptoms. Anaphylaxis was defined as a severe, usually rapid onset and potentially life-threatening systemic hypersensitivity reaction from several organ systems, always including respiratory and / or cardiovascular manifestations. In addition, symptoms from the skin, mucous membranes, gastrointestinal tract and the central nervous system are usually seen [1].

Atopy was defined as IgE antibodies to one or more of the inhalant allergen molecules from birch, hazelnut, timothy grass, and mugwort pollen (Bet v 1, Cor a 1.01, Phl p 1, Phl p 11, Phl p 2, Phl p 5, Phl p 6, Art v 1, Art v 3), and from cat, dog and horse (Fel d 1, Fel d 4, Can f 1, Can f 2, Can f 4, Can f 5, Can f 6, Equ c 1) and from mites and mold (Der f 1, Der f 2, Der p 1, Der p 2, Cla h 8). Patients were diagnosed with airborne allergy if they were atopic and had airway symptoms after exposure to birch, timothy or furry animals.

One-hundred and twenty-five of the patients had previously been characterized based on analysis of allergen extracts by ImmunoCAP and symptoms [2]. The study was approved by the local ethics committee (Ethical permit No 2011/1604-31/2, 2018/2483-32),

performed in accordance with the declaration of Helsinki, and all patients gave their written informed consent.

ImmunoCAP and ISAC IgE determination

Serum samples were tested by ImmunoCAP and the updated ISAC^{112} (Thermo Fisher AB, Uppsala, Sweden). Total IgE and allergen-specific IgE antibody reactivity to α-Gal (bovine thyroglobulin, o215), birch, timothy, cat (e1) and dog (e5) were analyzed by ImmunoCAP. The cutoff for total IgE was ≥2 kU/L and for allergen-specific IgE ≥0.1 kU_A/L. The updated ISAC^{112} was used for determining IgE reactivity against allergen molecules. The chip contains 112 allergen molecules from 48 allergen sources, including α-Gal (the same bovine thyroglobulin molecule as on ImmunoCAP). Analysis was performed according to the manufacturer's instructions [3]. The results were evaluated using Phadia Microarray Image Analysis (MIA) software. The cutoff for IgE detection was set at 0.3 ISAC standardized units (ISU) with a scale ranging from Low (0.3–3 ISU-E), Moderate to High (3–15 ISU-E), and Very High (> 15 ISU-E).

Statistical analysis

Statistical analysis was performed with GraphPad Prism, version 6 (GraphPad software, La Jolla, CA, USA). Measurements of IgE antibodies were compared using Mann-Whitney U tests. Frequencies were compared using Fisher's exact test. Spearman's rank correlation was used to calculate the strength and direction of an association between two variables. A P-value of less than 0.05 was considered significant.

Results

Table S1. Patient characteristics.

Parameter	
Sex (M:F)	68:70
Age (median years, min-max)	48.5 (17-76)
α-Gal IgE (median kU_A/L, min-max)	16.0 (0.26-144.0)
Total IgE (median kU/L, min-max)	121.5 (8.6-3600.0)
Percentage α-Gal IgE of total IgE (median, min-max)	14 (0.0-66.0)
A/O blood group (percentage)	97.6%
Frequency anaphylaxis	47.8%
Frequency angioedema	60.1%
Frequency urticaria	90.5%
Frequency GI symptoms	74.6%

Table S2. Explanatory list of allergen abbreviations.

Protein group	**Allergen source**	**Allergen molecules**
Foods	Cow's milk (*Bos domesticus*)	Bos d 4, Bos d lactoferrin
Foods	Chicken (*Gallus domesticus*)	Gal d 1
Foods	Wheat (*Triticum aestivum*)	Tri a 19
Foods	Kiwi (*Actinidia deliciosa*)	Act d 1, 2, 8
Foods/PR-10	Celery (*Apium graveolens*)	Api g 1
Foods/PR-10	Apple (*Malus domestica*)	Mal d 1
Foods	Peach (*Prunus persica*)	Pru p 1, 3
Grass pollen	Timothy (*Phleum pratense*)	Phl p 1, 2, 4, 5, 6, 7, 11, 12
Grass pollen/CCD	Bermuda grass (*Cynodon dactylon*)	Cyn d 1
Tree pollen	Birch (*Betula verrucosa*)	Bet v 1, 2, 4
Tree pollen/PR-10	Hazel (*Corylus avellana)*	Cor a 1.0101
Tree pollen/PR-10	Alder (*Alnus glutinosa*)	Aln g 1
Tree pollen/CCD	Japanese cedar (*Cryptomeria japonica*)	Cry j 1
Tree pollen/CCD	Cypress (*Cupressus arizonica*)	Cup a 1
Tree pollen	Olive (*Olea europaea)*	Ole e 1, 9
Tree pollen	Plane (*Platanus acerifolia*)	Pla a 3
PR-10 proteins	Peanut (*Arachis hypogaea*)	Ara h 8
PR-10 proteins	Soy bean (*Glycine max*)	Gly m 4
PR-10 proteins	Celery (*Apium graveolens*)	Api g 1
PR-10 proteins	Peach (*Prunus persica*)	Pru p 1
PR-10 proteins	Birch (*Betula verrucosa*)	Bet v 1
Furry animals	Dog (*Canis familiaris*)	Can f 1, 2, 3, 4, 5, 6b
Furry animals	Horse (*Equus caballus*)	Equ c 1, 3
Furry animals	Cat (*Felix domesticus*)	Fel d 1, 2, 4
Furry animals	Mouse (*Mus musculus*)	Mus m 1
Nuts and seeds	Cashew nut (*Anacardium occidentale*)	Ana o 2
Nuts and seeds	Brazil nut (*Bertholletia excelsa*)	Ber e 1
Nuts and seeds/PR-10	Hazelnut (*Corylus avellana*)	Cor a 1.0401
Nuts and seeds	Walnut (*Juglans regia*)	Jug r 3
CCDs	Bromelain	MUXF3
CCDs	Timothy (*Phleum pratense*)	Phl p 4
Legumes	Peanut (*Arachis hypogaea*)	Ara h 1, 2, 3, 8, 9
Legumes	Soy bean (*Glycine max*)	Gly m 4, 5, 6
Weed pollen	Mugwort (*Artemisia vulgaris*)	Art v 1, 3
Weed pollen	Goosefoot (*Chenopodium album*)	Che a 1
Weed pollen	Mercury (*Mercurialis annua*)	Mer a 1
Weed pollen	Wall pellitory (*Parietaria judaica*)	Par j 2
Weed pollen	Saltwort (*Salsola kali*)	Sal k 1
Mites	Blomia (*Blomia tropicalis*)	Blo t 5
Mites	Dermatophagoides (*Dermatophagoides farinae*)	Der f 1, 2
Mites	Dermatophagoides (*Dermatophagoides pteronyssinus*)	Der p 1, 2, 10, 23
Mites	Lepidoglyphus (*Lepidoglyphus destructor*)	Lep d 2
Latex	Latex (*Hevea brasiliensis*)	Hev b 5, 6, 8
Sea food	Cod (*Gadus callarias*)	Gad c 1

Sea food	Shrimp (*Penaeus monodon*)	Pen m 1, 2
Tropomyosin	Shrimp (*Penaeus monodon*)	Pen m 1
Tropomyosin	Dermatophagoides (*Dermatophagoides pteronyssinus*)	Der p 10
Tropomyosin	Cockroach (*Blattella germanica*)	Bla g 7
Tropomyosin	Anisakis (*Anisakis simplex*)	Ani s 3
Fungi	Alternaria (*Alternaria alternate*)	Alt a 1, 6
Fungi	Aspergillus (*Aspergillus fumigatus*)	Asp f 1, 3, 6
Fungi	Cladosporium (*Cladosporium herbarum*)	Cla h 8
Insects	Cockroach (*Blattella germanica*)	Bla g 1, 7

Table S3. Sensitization frequencies (≥0.3 ISU) among the different allergen sources and families.

Protein group	**Included components**	**Nr of positive patients**
Foods	Lactoferrin, Gal d 1, Bos d 4, Tri a 19, Act d 1,2,8, Api g 1, Mal d 1, Pru p 1,3	55 (40%)
Grass pollen	Phl p 1,2,4,5,6,7,11,12, Cyn d 1	46 (33%)
Tree pollen	Bet v 1,2,4, Cor a 1.0101, Aln g 1, Cry j 1, Cup a 1, Ole e 1,9, Pla a 3	46 (33%)
PR-10 proteins	Cor a 1.0401,1.0101, Ara h 8, Gly m 4, Act d 8, Api g 1, Mal d 1, Pru p 1, Aln g 1, Bet v 1	43 (31%)
Animals	Can f 1,2,3,4,5,6b, Equ c 1,3, Fel d 1,2,4, Mus m 1	37 (27%)
Nuts and seeds	Ana o 2, Ber e 1, Cor a 1.0401, Jug r 3	34 (25%)
CCDs	Cry j 1, Cup a 1, Cyn d 1, MUXF3, Phl p 4	31 (23%)
Legumes	Ara h 1,2,3,8,9, Gly m 4,5,6	25 (18%)
Weed pollen	Art v 1,3, Che a 1, Mer a 1, Par j 2, Sal k 1	21 (15%)
Mites	Blo t 5, Der f 1,2, Der p 1,2,10,23, Lep d 2	17 (12%)
Latex	Hev b 5,6,8	10 (7%)
Sea food	Gad c 1, Pen m 1,2	7 (5%)
Tropomyosin	Pen m 1, Der p 10, Bla g 7, Ani s 3	5 (4%)
Fungi	Alt a 1,6, Asp f 1,3,6, Cla h 8	5 (4%)
Insects	Bla g 1,7	4 (3%)

References

1. Non-commercial website of the Drug Therapeutic Committee and the Health and Medical Care Administration of Region Stockholm providing drug information to health care professionals. Available from: www.janusinfo.se. Accessed May 22, 2020.
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3. van Hage M, Schmid-Grendelmeier P, Skevaki C, et al. Performance evaluation of ImmunoCAP® ISAC 112: a multi-site study. *Clin Chem Lab Med*. 2017;55(4):571-577.