INTRODUCTION

Peanut allergy (PA) is one of the most common food allergies among children in Western nations and is often a lifelong condition. Onset of PA typically occurs in early childhood and is associated with more severe reactions than other food allergies. 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, PA persists into adulthood in approximately 75%–80% of children.

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 auto-injector (AAI) on hand in case of accidental exposure and reaction to peanut, which is sometimes referred to as an avoidance management strategy. 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) (Table S1).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 peanut20 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 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.

1.1 | 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.

1.2 | Methods

1.2.1 | 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 utilization, 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 Figure S1. 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 also incorporated articles as appropriate if publications retrieved during our searches pointed to essential prior studies.

2 | RESULTS

2.1 | Peanut allergy prevalence and incidence

Estimates of PA prevalence have varied in part due to the different methods utilized for determining its presence, ranging from self-report to skin prick test (SPT), peanut-specific immunoglobulin E (pS1gE) 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, multicentre 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-centre 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
| 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         | pslgE: 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, confirmed9 |
| 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 aged 3–5 y |
| Osborne et al (2011)144       | 2848   | 12-month-old infants (1.7) | 2007–2010    | Melbourne, Australia | SPT, wheal size ≥1 mm + 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       | 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)144a        | NR     | Children and adults (NR) | 2000–2012    | Europe     | Self-report, SPT, OFC, pslgE, PA clinical history (various)                                  | Point prevalence: 1.7, self-report: 1.7, SPT; 8.6, pslgE; 0.2, FC positive; 1.6, FC or PA history; lifetime prevalence: 0.4 |
| Bunyavanich et al (2014)143   | 616    | Children aged 7–10 (7.9) | NR           | Eastern Mass, US | Self-report; pslgE; pslgE + AAI prescription; pslgE, ≥14 KU/L; pslgE ≥14 KU/L + AAI prescription (in-person survey) | 4.6, self-report; 5.0, pslgE; 4.9, pslgE + AAI prescription; 2.9, pslgE, ≥14 KU/L; 2.0, pslgE ≥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 (2017)146c       | 139    | 4-year-old children (4.3) | 2011–2014    | Melbourne, Australia | SPT, wheal size ≥1 mm + OFC (clinic examination)                                               | 1.9 overall                                                                                 |
| 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 h 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        | 9816   | Children aged 10–14 (NR) | 2011–2014    | Melbourne, Australia | Self-report + pslgE + OFC (clinic examination)                                               | 2.7 overall                                                                                 |

(Continues)
Table 1 (Continued)

| Study                     | n         | Age cohort (mean age, y) | Study period | Region      | Criteria for PA (study type)                                                                 | PA prevalence estimate(s), % |
|---------------------------|-----------|--------------------------|--------------|-------------|-----------------------------------------------------------------------------------------------|-----------------------------|
| Gupta et al (2018)        | 38,408    | Children (NR)            | 2015–2016    | US          | Self-report + convincing history (online survey)                                                | 2.2 overall                 |
| Lieberman et al (2018)    | NR        | Children aged 4–17       | 2017         | US          | Longitudinal analysis of PA diagnosis codes/services (healthcare claims database)              | 2.2 overall                 |
| Gonzalez-González et al (2018) | 365      | Children aged 1–18       | 2015–2016    | Honduras    | OFC of children showing sensitization                                                            | 0.8 overall                 |
| Ziyab (2019)              | 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)        | 1583      | Children aged 1 to 3 (NR)| NR           | South Africa| Self-report + SPT, ≥1mm, + OFC                                                                  | 0.8 overall                 |
| Gupta et al (2019)        | 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 (2020)       | 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 (2020)       | 3,455     | Children aged 0–3        | 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 |
**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)  | 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 |
| Sicherer et al (2001)  | 4685 | Children (median, 5)            | US     | Postal questionnaire survey, food allergy registry | Cross-sectional  | 47.5% of subjects                                                              | NR                                                                  |
| Vander Leek et al (2000) | 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)        | 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) | 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 children          |
| Nguyen-Lu et al (2012) | 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) | 782  | Children (NR)                   | US     | Retrospective chart review, single centre     | 5.3 y median /4526 patient-years | 7.3% annual incidence                                                            | Severe reaction rates: 1.0%–1.6% of subjects per year              |
| Cherkawi et al (2015)  | 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)   | 1070 | Children (NR)                   | US     | In-clinic interview, multicentre              | 5 y              | 21.3% of subjects                                                               | 34.9% of subjects; 33.9% of accidental exposures involved anaphylaxis |
| Gupta et al (2019)     | ~728 | Adults (NR)                     | US     | Online questionnaire survey                   | Cross-sectional  | NR                                                                              | 67.8% of subjects                                                   |

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

*Reactions including all 3 of skin, gastrointestinal and respiratory symptoms.

Moderate or severe reaction; per cent of subjects with an accidental exposure.

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%.

Rate among 525 children who returned for at least one clinic visit following initial interview.

Estimated from reported peanut allergy prevalence rate of 1.8% among 40,443 adults who completed surveys.
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 1-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 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.5,43 A nationwide US 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 Montreal45 and 2010 to 2017 across Canada46 and in a study conducted on the Isle of Wight, UK between the late 1990s and 2004.47

3 | HEALTHCARE BURDEN

3.1 | Risks of accidental exposure, severe reactions and anaphylaxis

Even with adherence to standard self-management behaviours,34,16 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 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%) vs 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 vs children with food allergy in general (n = 2464) (53.7% vs 41.0%; p < .001).7 Among US adults with PA, 68% report at least one severe peanut-allergic reaction vs 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 10–14 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%–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 adults) with PA vs 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).6,53,54 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.

3.2 | Healthcare utilization

In the European Anaphylaxis Registry, peanut is the most common trigger involved in anaphylaxis cases in both children and adolescents, accounting for 26.3% and 18.3% of food-related anaphylaxis cases, respectively.54 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 children40 and 20% of adults41 with PA reported an ED visit in the past year due to a food-allergic reaction. A healthcare utilization 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,
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). 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 < .005), with a 30% average annual increase observed for peanut-induced events (Figure 3). 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 < .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.

Although sparse, these utilization 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.

### 3.3 | Economic burden

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

#### 3.3.1 | 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. A survey of US caregivers of children with food allergy estimated direct medical costs of $4.3 billion annually (or $724 per child). 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.
A 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 pIgE testing) were $2016 and $2197 vs $1089 and $863 for controls,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 hospitalizations for anaphylaxis symptoms, the cost of anaphylaxis preparedness and treatment in those prescribed an AAI over an 80-year time horizon was $25,478 (95% CI: $25,399–$25,447) vs $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–$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 vs 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.

3.3.2 | 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 (eg 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 study64 estimated annual lost labour 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 labour 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.

3.4 | 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 Australia74 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; I² = 86.4%; p < .001), which was higher than the rate for all food allergies (1.81 per million person-years [95% CI: 0.94–3.45; I² = 94.8%; p < .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. 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.

### 3.5 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). In the French MIRABEL study, only 5% of individuals had no associated allergic comorbidity. Comorbid tree nut allergy is particularly common in patients with PA, with reported prevalence ranging from approximately 16%–50%. In tree nut-allergic patients, reported concomitant PA ranges from 20% to 68%. Increased number of food allergies tends to increase the burden due to the added requirements of vigilance and dietary restriction.

### TABLE 3 Selected studies reporting comorbidities in children with peanut allergy

| Comorbidity     | Neumann-Sunshine et al (2012) | Deschildre et al (2015) | Dyer et al (2015) | Leickly et al (2018) | Johnston et al (2019) | Fleisher et al (2019) |
|-----------------|-------------------------------|-------------------------|-------------------|---------------------|-----------------------|----------------------|
|                 | (n = 782)                     | (n = 785)               | (n = 754)         | (n = 1070)          | (n = 496)             | (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                          | 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                   |

Abbreviations: EoE, eosinophilic oesophagitis; NR, not reported.

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

### 4 THE BURDEN OF PEANUT ALLERGY ON THE INDIVIDUAL

#### 4.1 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). 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. Individuals with PA often avoid tree nuts, in part because of concern over cross-reactivity or contamination. 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. In the PRONUTS study, the 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.

#### 4.1.1 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. However, precautionary allergen labelling is not legally required in most countries, is mostly unregulated and may be confusing for consumers. In a US study of prepackaged food, labelling for just under half of products included had a ‘may contain’ type of advisory label. 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. 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 1–4 allergens (including peanut) that were unidentified in the product labelling.

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 (Table S2).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

4.1.2 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 (eg servers, managers, cooks) of food allergies to minimize 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

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.

4.2 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

4.2.1 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 only 50.1% of cases. However, 69%

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. Reproduced with permission from Sicherer et al48
of respondents made preflight accommodation requests (55% of reactors vs. 71.6% of nonreactors; p < .001).

4.2.2 | 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. 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 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). A US study of all food-allergic reactions due to accidental exposure at school found that 25%–29% of reactions were attributed to peanut. 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. 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).

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. 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. 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.

![Figure 5](image-url) 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. Reproduced with permission from Lieberman et al.
4.3 | Emotional impact

Living with food allergy can lead to fear and anxiety not only regarding the risk of exposure and reaction to the allergen, 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. 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 \((n = 401 \text{ evaluated for anxiety})\) were observed in patients with atopic dermatitis \((p = .003)\), both atopic dermatitis and asthma \((p = .032)\), and those who had received strict avoidance advice \((p < .001)\). Dietary avoidance itself may also be a source of anxiety and stress.

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. Data specifically on bullying in children and adolescents with PA are scant. One survey study of children and adults with food allergy included 287 individuals with PA. In this study, 24.1% reported having been bullied, harassed or teased because of their food allergy by a variety of perpetrators. 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; 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.

4.4 | 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. 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.

**FIGURE 6** Scores on specific questionnaire items in study 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 hypoglycaemic 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.
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%–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 utilization 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 paediatric 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 stabilize 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 utilization and costs of PA from regions/countries other than the US and UK |
|                    | 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 (eg 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. |

Abbreviations: OIT, oral immunotherapy; PA, peanut allergy; QoL, quality of life.

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. 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 with 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) and an adapted Vespid Allergy Quality of Life questionnaire. In this study, mean scores were significantly higher (worse) in children with PA vs those with diabetes in both questionnaires (54.9 for PA vs 46.4 for diabetes; p = .004 [novel questionnaire] and 54.3 for PA vs 34.5 for diabetes; p = .001 [adapted Vespid questionnaire]) (Figure 6). The children with PA were also reported to experience significant anxiety in a wide range of settings.

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 < .05), QoL within school (p < .01), general QoL (p < .05) and greater separation anxiety (p < .05) in children with PA than in their siblings without PA. 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. 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. Further, management of PA by paediatric allergy specialists has been shown to slightly improve QoL, demonstrating a crucial role for allergists and immunologists in helping allergic children and their families manage this burden.
5 | 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 PA27 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 vs 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

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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