

Food Allergy: Temporal Trends and Determinants

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Abstract This review summarizes studies discussing temporal trends in the prevalence of food allergy as well as potential factors associated with the development of food allergy. In addition, we will address the potential hypotheses accounting for the apparent increase in food allergy prevalence. Studies suggest increased prevalence of food allergy. However, relatively little is known about its pathogenesis. This review aims to assess temporal trends in the prevalence of food allergy and discuss potential genetic, environmental, and demographic determinants. The search strategy examined the medical literature database MEDLINE (using PubMed) for the time period of January 1, 2002 to January 31, 2012. In recent decades, the prevalence of food allergy in general has increased by 0.60 % [95 % confidence interval (CI), 0.59 %–0.61 %] and the prevalence of peanut allergy by 0.027 % (95 % CI, 0.026 %–0.028 %), but it has now likely stabilized in developed countries. Genes, the environment, and demographic characteristics play a role in the pathogenesis of food allergy. Numerous environmental and demographic factors as well as gene-environment interactions may account for this increase in prevalence,

but further studies are required to tease out their relative contribution.

Keywords Food allergy · Temporal trends · Determinants · Prevalence · Genetic factors · Environmental factors · Demographic factors · Hygiene hypothesis

Introduction

A recent US study estimated that the economic burden of allergic reactions related to food allergy was half a billion dollars in 2007 and that ambulatory visits accounted for more than half of the costs [1]. Food allergy in infancy increases the risk of not only other allergic diseases (“atopic march”), but also allergy to other foods (“food allergen march”) [2]. The fact that individuals with food allergy face food and social restrictions due to the potentially life-threatening nature of their disease inevitably impacts upon their quality of life [3, 4]. Thus, it is crucial that patients with severe food allergy are correctly identified, carefully followed, and appropriately managed.

It is generally accepted that food allergy affects up to 2.5 % of the adult population and 6–8 % of children less than 3 years of age [5–8]. However, these initial estimates are based on studies conducted three decades ago in relatively small communities [8, 9], were based on self-report without any requirements for physician diagnosis with appropriate testing and do not represent a nation-wide sample. Further, the diagnostic algorithm (for those individuals who were evaluated by a physician) did not consistently include confirmatory tests for IgE-mediated reactions such as skin prick test (SPT) and specific IgE levels [10] and instead used elimination diets (i.e., exclusion diets to specific foods) that have inherent difficulties (regarding choice of the elimination

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diet and the patient's compliance) [11]. In addition, only those reporting food-related adverse reactions were included in these studies, while those never exposed to the food were not further investigated. The disparity between estimates based solely on self-report versus those involving confirmatory testing is exemplified in a recent random telephone survey conducted in Turkey. Individuals reporting food allergy were invited for a clinical investigation that included a double blind placebo controlled food challenge (DBPCFC). It was found that the lifetime prevalence of self-reported food allergy was 9.50 % (95 % CI, 8.94 %–10.00 %), decreasing to 0.30 % (95 % CI, 0.17 %–0.36 %) after the incorporation of clinical investigations, and to as low as 0.10 % (95 % CI, 0.05 %–0.18 %) based on DBPCFC only [12]. Given the complexity of the diagnosis of food allergy and potential disparities between studies using self-report and those using diagnostic algorithms, it is not surprising that temporal trends in food allergy are hard to interpret. In addition, genetic and environmental factors that differ between countries may be responsible for different temporal changes. This review aims to address these important issues and highlight knowledge gaps related to the development of food allergy.

Search Strategy and Study Selection

The search strategy examined the medical literature database MEDLINE (using PubMed) for the time period of January 1, 2002 to January 31, 2012 with the keywords “food allergy”, “prevalence,” “genes,” environmental factors (“season”, “drugs”, “microbial exposure”, “mode of delivery”, “food consumption”, “route of exposure”, “day care attendance”, “pet ownership”, “food processing”, “omega-3 fatty acids”, “vitamin D” and “breastfeeding”)

and demographic factors (“age”, “sex”, “race/ethnicity”, “socioeconomic status”, “education”, “maternal age at delivery”, “household size”, “birth order”, “immigrant”, “obesity”, “diabetes”, “geography” and “atopy”) and included abstracts written in English in which access to full text was possible.

For the current report, all titles and abstracts of identified articles were screened. Regarding the study design, all observational study designs were included, i.e. population-based, cross-sectional, case-control and cohort studies. We then performed a meta-analysis that included all studies assessing temporal trends in food allergy (Fig. 1) using STATA® version 12 (StataCorp LP, College Station, TX).

Is the Prevalence of Food Allergy Increasing?

Only a few studies have explored this question. Most of these studies rely on self-report of food allergy by patients [13–17] or physician recorded diagnosis [18]; some include confirmatory testing [19–26] and only one study has evaluated the change in prevalence across time through the use of food challenge in all participants [22]. One study addressed the change in incidence in peanut allergy and sensitization rather than prevalence [23] and another study assessed prevalence in a selective population consisting of those referred to an allergist for diagnosis and hence is not representative of the general population, although likely indicative of an increased food allergy burden [24]. The majority of studies have assessed peanut allergy) [13–15, 18–21, 25, 26] and only four assessed all food allergies (Table 1) [16, 17, 22, 24].

Four US studies, replicating the same methodology, compared the prevalence of self-reported food allergy across

Fig. 1 Temporal trends of peanut allergy prevalence. Forest plot of the meta-analysis of peanut allergy temporal trends with 95 % confidence intervals. The square size represents the weight of the study; the dashed line gives the pooled estimate. UKa=first study in UK, UKb=second study in UK (as indicated in Table 1)

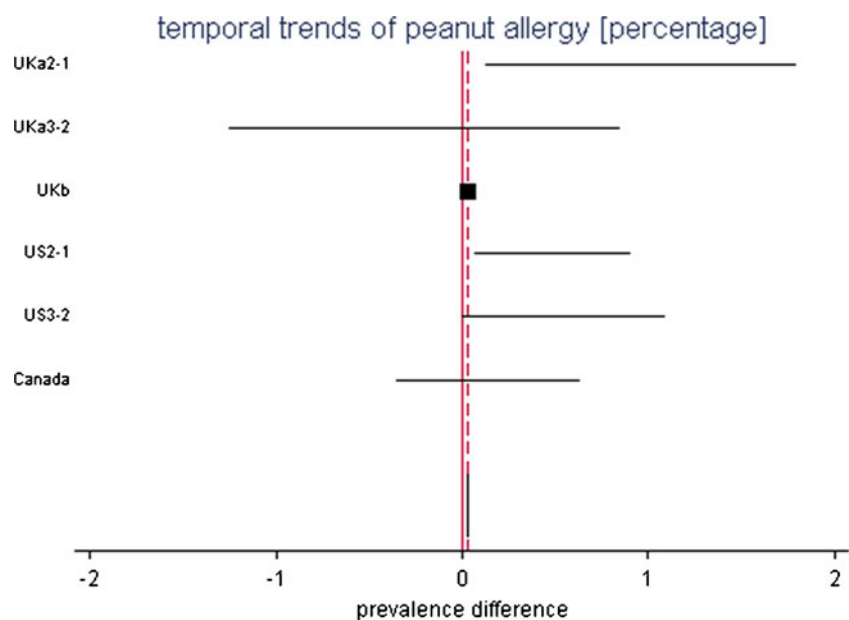


Table 1 Studies assessing temporal trends in food allergy prevalence

Country	Study 1 Numerator/ denominator Prevalence (%) Year (ref)	Study 2 Numerator/ denominator Prevalence (%) Year (ref)	Study 3 Numerator/ denominator Prevalence (%) Year (ref)	Data collection method	Difference in prevalence between studies (2–1)	Difference in prevalence between studies (3–2)	Difference in prevalence between studies (3–1)	Comments
Peanut								
UKa	6/1218 0.5 % 1989 [19]	18/1246 1.5 % 1994/96 [20]	11/891 1.2 % 2001/02 [21]	Self report, SPT, FC	0.95 (0.1–1.8)	–0.21 (–1.28–0.86)	0.74 (–0.18–1.66)	Cohort of children (4 years of age) born on the Isle of Wight in 1989 (study 1), between 1994 and 1996 (study 2) and 2001–2002 (study 3)
UKb	11,700/48,750,000 0.24 % 2001 [18]	25,700/50,392,157 0.51 % 2005 [18]		Physicians	0.027 (0.03–0.028)			General practitioners recorded diagnosis of peanut allergy in England between 2001 and 2005
US	12/2998 0.4 % 1997 [15]	26/3127 0.8 % 2002 [14]	40/2915 1.4 % 2008 [13]	Self report	0.48 (0.05–0.91)	0.54 (–0.02–1.10)	0.99 (0.48–1.50)	Children (less than 18 years of age) based on a random digital phone survey of US population in 1997, 2002 and 2008
Canada	64/4255 1.50 % 2000/02 [25]	82/5031 1.62 % 2005/07 [26]		Self report, SPT, IgE, FC	0.13 (–0.38–0.63)			Montreal school children 5–9 years of age
Incidence estimates for peanut								
Australia	191/26,137 0.73 % 2001 [23]	653/26,137 2.5 % 2007 [23]		Self report, SPT	1.77 (1.54–1.99)			The estimated minimum incidences of peanut allergy and sensitization by age 72 months in Australian Capital Territory
All foods								
Korea	1639/40,429 4.05 % 1995 [16]	2043/42,202 4.84 % 2000 [16]*		Self report	0.8 (0.5–0.07)			A survey on random samples of school children 6 to 14 years of age at two time points, 1995 and 2000 throughout Korea
Australia	11/55 20 % 1995 [24]	138/240 57.5 % 2006 [24]		Self report, SPT	37.5 (24.09–50.9)			Retrospective analysis of records (1,489 children aged 0–5 years) referred to community-based allergists practicing in the Australian Capital Territory
US	2,300,000/69,696,970 3.3 % 1997 [17]	3,000,000/76,923,077 3.9 % 2007 [17]		Self report	0.6 (0.59–0.66)			National Health Interview Survey (NHIS) for the years 1997–2007. Nationwide representative sample of households, using a multistage probability sampling design for children under 18 years of age
China	11/314 3.7 % 1999 [22]	31/401 7.7 % 2009 [22]		FC	4.22 (0.63–7.82)			10-year period from 1999 to 2009 infants

*Food allergy reported to be diagnosed by physician. (The lifetime prevalence of food allergy was not significantly different from 1995 to 2000)

SPT, Skin Prick Test; FC, Food Challenge

5- to 10-year periods. They suggested that the prevalence of food allergy in general and peanut allergy in particular had increased significantly over a 10-year period [13–15, 17]. Studies conducted by our group and others combining clinical history with positive confirmatory tests suggested that the prevalence of peanut allergy might have stabilized in recent years although it is still higher than in previous reports [21, 26]. This is in line with the most recent US estimates suggesting no substantial increase in the prevalence of peanut allergy between 2002 and 2008 [13]. However, studies conducted over longer periods of time in other countries establish a true increase in the prevalence of food allergy. A Chinese study enrolled infants randomly when receiving a well-baby check up. Open challenges were performed in all with either a history or SPTs suggesting food allergy. Although the rate of parent-reported food allergy increased from 13.70 % (1999 study) to 16.70 % (2009 study), (95 % CI for the difference crossing 0), positive SPT response was significantly higher in 2009 (18.0 %) than in 1999 (9.90 %) and the prevalence of confirmed food allergy (based on food challenge) increased markedly from 3.50 % (1999 study) to 7.70 % (2009 study) [22]. In conclusion, overall there is a 0.027 % increase in the prevalence of peanut allergy (95 % CI, 0.026 %–0.028 %, $I^2=61.20$ %) and a 0.60 % (95 % CI, 0.59 %–0.61 %, $I^2=66.80$ %) increase in the prevalence of all food allergies over the last 10 years (Figs. 1, 2). Based on current evidence, it is likely that in developed countries, the increase has reached a plateau during the last five years, while in other countries, the prevalence continues to increase. A potential explanation for this observation might be a relative lack of change in life style and other environmental factors in the US, Canada, and the UK in contrast to ongoing changes in other countries such as China and Korea.

What Are the Factors Associated with the Development of Food Allergy?

Processes leading to the development of tolerance versus allergy are affected by genetic, environmental, and demographic factors and potentially by gene-environment interactions. Given the relatively rapid temporal changes in food allergy prevalence over the last two decades, it is likely that factors related to the environment are playing the most important role in the development of food allergy, although very few studies have actually examined the relative contribution of each of the factors.

Genetic Effects

Animal models have clearly shown that there is a genetic selection for susceptibility/resistance to oral tolerance. (Table 2) [27]. In humans, it was shown that siblings

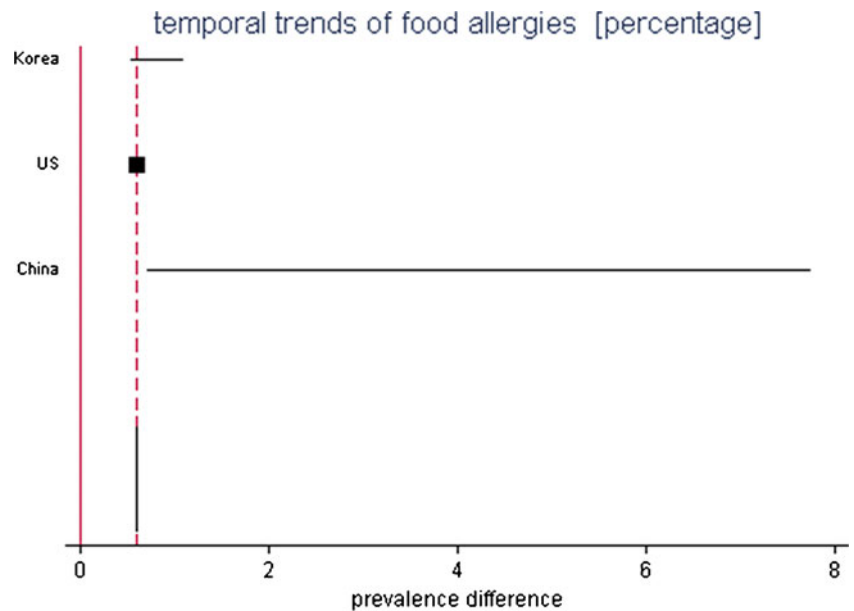
of an individual with food allergy are at increased risk, while monozygotic (MZ) twin studies reinforce the premise of gene-environment interactions. In a large study on all children born from April 2001 to March 2006 in one province of southeast Finland, it was found that up to the age of 4 years, the incidence of any positive food allergy test (SPT, specific IgE levels or a food challenge) was threefold higher if both parents reported having an allergic manifestation and twofold higher if either mother or father had such a manifestation when compared with children whose parents did not report any of these conditions [28]. In a study on 581 nuclear families (2,004 subjects) in Chicago, it was reported that food allergy in the index child was a significant and independent predictor of food allergy in other siblings [odds ratios (OR) 2.60, 95 % CI, 1.20–5.60]. There were significant and positive associations among family members (father-offspring, mother-offspring, index-other siblings) for total IgE and specific IgE to all the nine major food allergens (sesame, peanut, wheat, milk, egg white, soy, walnut, shrimp and cod fish) [29]. In China, zygosity-specific concordance rates and ORs for sensitization to food allergens in 826 Chinese twin pairs [472 MZ and 354 dizygotic (DZ)] aged 12–28 years were assessed. This study revealed that concordance rates and risk of sensitization in one twin given the presence versus absence of sensitization in the other twin were higher in MZ twins compared to DZ twins. However, a large number of MZ twins were discordant for sensitization to common allergens, implying also non-genetic factors [30]. These results are in line with other studies in the US [31] and Europe [32] suggesting a high risk for clinical food allergy and not only sensitization in MZ versus DZ twins.

Several genes have been implicated in the pathogenesis of food allergy (Table 2). These include genes contributing to an impaired anatomical barrier [e.g., Filaggrin [33, 34] and Serine Protease Inhibitor Kazal type 5 (SPINK5) [35, 36]] and genes involved in innate [including Nucleotide-binding domain and Leucine-rich Repeat-containing family Pyrin domain containing 3 (NLRP3), [37] Toll Like Receptor 9 (TLR9), [38] CD14 [39] and Thymic Stromal-Derived Lymphopoietin (TSLP) [38]] and adaptive immunity [e.g., HLA alleles [40–43], interleukin 4 (IL4) [44], IL12 and its receptor (IL12R) [38], IL-10 [45–47], and IL-13 [48]], the Signal Transducer and Activator of Transcription 6 (STAT-6) [49] and Forkhead box P3 (FOXP3) gene [50].

Environmental Effects

Season. It is suggested that food allergy is more common in those born in the fall or winter [51–53] potentially due to reduced UV-B exposure and subsequent lower levels of vitamin D generation during a vulnerable period of immune development (Table 3). It was reported that children younger than 5 years born in the fall or winter had a 53 % higher

Fig. 2 Temporal trends of food allergy prevalence. Forest plot of the meta-analysis of food allergy temporal trends with 95 % confidence intervals. The square size represents the weight of the study; the dashed line gives the pooled estimate



odds of food allergy compared with controls [51]. However, it is also possible that this association is due to confounders unrelated to vitamin D status such as higher rates of eczema in the winter that might be associated with increased risk of food allergy [51, 52] or adjuvant effects of winter time infection on the development of food allergy [51, 53].

Drugs. A single study in humans suggested that proton pump inhibitors raise the risk of food allergy by reducing the peptic digestion of food allergens and by increasing mucosal permeability and atrophic gastritis [54]. In an observational cohort study of 152 adult patients from a gastroenterological clinic with no history of atopy or allergy who received H2-receptor blockers or proton pump inhibitors for three months, 10 % showed a boost of pre-existing IgE antibodies and 15 % de novo IgE formation toward numerous digestion-labile dietary compounds, like milk and potato. The relative risk to develop food-specific IgE after anti-acid therapy was 10.50 (95 % CI, 1.44–76.48). The authors also found that five months after stopping treatment, food-specific IgE could still be measured in 6 % of the patients [54].

Microbial Exposure. Immune responses mediated by Th2 cells are considered to play a major role in the pathogenesis of food allergies. Several hypotheses suggested a pivotal role of the microbacterial environment in the pathogenesis of Th2 responses emphasizing the route of antigen exposure as the crucial factor in the development of allergic reactions [55].

Microbial organisms may be relevant to the development of allergy in several ways:

- (1) Bacteria can enhance the integrity of the intestinal barrier [56].

- (2) It is suggested that low-level activation of microbial pattern recognition receptors (PRRs) caused by low-level pathogen exposure results in allergen presentation in the absence of IL-12, leading to Th2 lymphocyte development and allergic sensitization [57]. In contrast, pathogen-associated molecular patterns induce high-level PRRs activation that results in allergen presentation with IL-12 secretion, leading to Th1/T reg responses to allergen, without allergic sensitization [58–63]. However, while certain infections are suggested to be protective [64, 65], this has not been substantiated in the majority of studies [58, 66–81]. Further, certain parasites [82] and viral infections [60], mainly by respiratory viruses [66, 83, 84], are reported to be associated with a high risk for food allergy.

These hypotheses led to recent studies exploring the potential role of probiotics, i.e. microorganisms (bacteria, yeast) that exert a beneficial effect on host health, on the development of food allergy [58]. However, the data do not yet enable any clear conclusion regarding the potential beneficial effects of probiotics on the prevention or treatment of allergy in general and food allergy in particular [58, 80, 81].

Mode of Delivery. It has been postulated that as the caesarean delivered infant does not pass through the birth canal, he or she is not inoculated with the bifidogenic microflora of the mother's vagina [61, 62] or that certain strains of bacteria (e.g., higher levels of *C. difficile*) are more prone to colonize the newborn gut in home versus hospital-based deliveries [85]. These may lead to skewing of the immune response in favor of Th2 lymphocytes and lead to an increased risk for food allergy [78, 86–92]. However, other

Table 2 Genes implicated in the pathogenesis of food allergy

Group	Name of gene	Comments	Reference number
Barrier genes	Filaggrin	Increased risk of developing allergic sensitization and food allergy independently of the presence of atopic dermatitis OR: 1.9; (95 % CI, 1.4, 2.6).	[34]
	SPINK5	AA or AG genotype displayed a significantly higher prevalence of food allergy (20/91 subjects) than did those with the GG genotype (1/26 subjects; AA+AG vs GG, $P=0.03$).	[36]
Innate immunity genes	NLRP3: SNPs (rs4612666 and rs10754558)	NLRP3 controls the activity of inflammasomes.	[37]
	NLRP3 SNPs (rs4612666 and rs10754558)	NLRP3 SNPs (rs4612666 and rs10754558) were significantly associated with susceptibility to food-induced anaphylaxis ($P=0.00086$ and $P=0.00068$, respectively).	[38]
	TLR	Exclusive breast-feeding duration significantly increased the risk of FS in a dose-responsive manner in children carrying the <i>TLR9</i> -rs352140 TT genotype, with ORs of 3.3 (95 % CI, 1.0–10.9) and 13.2 (95 % CI, 3.0–57.3) for children breast-fed less than 4 months and breast-fed 4 or more months, respectively.	[39]
	CD-14	CD14 gene codes a lipopolysaccharide receptor. Patients with food allergy had a 4-fold increased odds of having the TT genotype versus carriers of the C allele compared with control subjects (OR=3.9; 95 % CI, 1.5, 10.3).	[38]
Adaptive immunity	TSLP	Exclusive breast-feeding duration significantly increased the risk of food sensitivity in a dose-responsive manner in children carrying the <i>TSLP</i> C/T/T genotype, with ORs of 2.2 (95 % CI, 1.3–3.7) and 3.1 (1.7–5.8).	[40]
	HLA-II	In children with cow milk allergy, HLA (DRI15)-DQB1*0602 haplotype was associated with high levels of beta-lactoglobulin-specific total IgG ($p<0.001$) and IgG4 ($p<0.001$) and alpha-casein-specific total IgG ($p=0.003$) and IgG4 ($p=0.002$), but not among control subjects. (DRI1/10)-DQB1*0501 was associated with lower levels of beta-lactoglobulin-specific total IgG ($p<0.001$) and IgG4 ($p<0.001$), ovalbumin-specific total IgG ($p=0.002$) and IgG4 ($p<0.001$), particularly in control subjects ($p<0.001$). No association between 7 DQ and 18 DR allele groups and peanut allergy.	[41]
	IL12R	Latex-fruit allergy is associated with HLA-DQB1*0201, DRB1*0301, and *0901, as well as with HLA-DR functional group E. DRB1 (*) 13 and DQB1 (*) 06 were both increased in frequency in the nut allergy patients over both the atopic and blood donor controls. However, none of these increased frequencies were significant when corrected for the number of comparisons undertaken.	[42]
	STAT6	Children who were ever breast-fed ($n=739$), including exclusively breast-fed children, were at a 1.5 (95 % CI, 1.1–2.1; $P=0.019$) times higher risk of FS than never breast-fed children ($n=231$). This association was significantly modified by rs425648 in the IL-12 receptor $\beta 1$ gene (IL12RB1; P for interaction=0.0007): breast-feeding increased the risk of FS (odds ratio, 2.0; 95 % CI, 1.4–3.1; $P=0.0005$) in children carrying the GG genotype but decreased the risk (odds ratio, 0.6; 95 % CI, 0.3–1.4; $P=0.252$) in children carrying the GT/TT genotype.	[38]
	FOXP3	Key transcription factor involved in both IL-4- and IL-13-mediated biological responses. Dinucleotide repeat polymorphism of the STAT6 exon 1 (13/15-CT repeat heterozygosity and the 15GT repeat homozygosity) was higher in children in the Japanese population with allergic diseases (bronchial asthma, atopic dermatitis and/or food-related anaphylaxis) compared to controls ($P=0.0158$).	[49]
	IL10	This gene is located on the X-chromosome and encodes a transcription factor that directs T cells toward a regulatory phenotype. Five FOXP3 SNPs (rs5906761, rs2294021, rs2294019, rs6609857 and rs3761548) were significantly associated with sensitization to egg at ages 1 and 2 and with sensitization to indoor allergens at age 2 ($P<0.05$). Rs5906761 and rs2294021 were associated with remission of sensitization to food allergens in boys.	[50]
	IL4	IL-10 A-1082 G gene polymorphism is associated with food allergy susceptibility (OR=2.5; 95 % CI, 1.0–6.4 vs atopic control subjects).	[47]
	III2	A significant interaction between IL4 gene polymorphism (rs2243250) and vitamin D deficiency ($p(\text{interaction})=0.003$, $p(\text{FDR})=0.10$) was found: Vitamin D deficiency increased the risk of food sensitivity among children carrying CC/CT genotypes (OR=1.79, 95%CI: 1.15–2.77).	[44]
	IL13	Breast-feeding increased the risk of food sensitization (odds ratio, 2.0; 95 % CI, 1.4–3.1; $P=0.0005$) in children carrying the GG genotype in IL-12 receptor $\beta 1$ gene but decreased the risk (odds ratio, 0.6; 95 % CI, 0.3–1.4; $P=0.252$) in children carrying the GT/TT genotype.	[38]
		The IL-13 promoter - 1055 TT genotype, a polymorphism that results in an increase in IL-13 protein production associated with increased odds of food sensitization (OR=of 3.49; 95 % CI, 1.52–8.02).	[48]

OR, odds ratio; CI, confidence interval; SPINK5, Serine Protease Inhibitor Kazal type 5; NLRP3, NLR (Nucleotide-binding domain and Leucine-rich Repeat-containing) family Pyrin domain containing 3; TLR, Toll Like Receptors; TSLP, Thymic Stromal-Derived Lymphopoietin; FS, Food Sensitization; SNP, Single-Nucleotide Polymorphism; STAT-6, Signal Transducers and Activators of Transcription 6; FOXP3, Forkhead box P3; IL, Interleukin

Table 3 Environmental factors associated with food allergy

Factor	Study	Type of study	Effect	Reference number
Season	Vassallo MF	Case control	Children younger than 5 years born in fall or winter had a 53 % higher odds of food allergy compared to controls.	[51]
	Kim J	Cohort	Children who were born during autumn had a higher prevalence than those born during spring ($p=0.005$) [aRR=3.48].	[52]
	Mullins RJ	Case control	Autumn/winter births were more common than spring/summer births among food allergy patients (57 % vs. 43 %; $p<0.001$).	[53]
Drugs	Untersmayr E	Cohort	Among 152 non-atopic adults treated with H2-receptor blockers or proton pump inhibitors for 3 months, the relative risk of developing food-specific IgE toward numerous digestion-labile dietary compounds, such as milk, potato, celery, carrots, apple, orange, wheat, and rye flour was 10.5 (95 % CI: 1.44–76.48).	[54]
	Gourbeyre P	Review of case control and cohort studies	No clear conclusion regarding beneficial effects of probiotics on the prevention or treatment of allergy.	[58]
Microbial exposure	Sidorchuk A	Birth cohort	Seropositivity to cytomegalovirus alone, i.e., without seropositivity to EBV, was related to IgE antibodies to airborne and food allergens (adjusted odds ratio, 1.8; 95 % CI, 1.2–2.9).	[60]
	Jartti T	Cross sectional	The OR for food allergen sensitization in those with sole rhinovirus was 2.02 (95 % CI: 1.08–3.78).	[66]
	Michos A	Cross sectional	Despite the higher burden of exposure to the battery of the infectious agents tested among Roma children, no protective effect for allergic disease development was evident.	[67]
	Mai XM	Birth cohort	Antibiotic use during the first year of life was not associated with food hypersensitivity at the age of 4 years.	[68]
	Pinelli E	Cross sectional	There was an associations between positive <i>Ascaris</i> IgG ELISA results (ratio ≥ 1.0) and food allergen sensitization OR=2.95 (1.47–5.89).	[82]
	Eifan AO	Birth cohort	No significant association was found between positive tuberculin skin test and food sensitization	[69]
	Konturek PC	Case control	The prevalence of Hp infection among adults with proven food allergy was 33.3 % and it was significantly lower than that in the control group (40 %).	[64]
	Bacciglu A	Case control	SPT positivity was similar between Hpi (+) and Hp (–) subjects.	[70]
	Bernsen RM	Case control	No evidence for any protective effects from MMR diseases for the development of atopy. The authors found a statistically significant positive association between measles infection and 'any atopic disorder' [OR (95 % CI): 1.77 (1.20–2.61)] in the MMR-vaccinated group.	[71]
	Bernsen RM	Case control	In the unvaccinated group, there were no significant associations between pertussis infections and atopic disorders. In the vaccinated group, there was a positive association between pertussis infections and food allergy (OR=2.68, 95 % CI, 1.48–4.85)	[72]
	Kummeling I	Birth cohort	Specific IgE for foods was not associated with antibiotic exposure.	[73]
	Bernsen BM	Case control	No indication for a higher risk of reported physician-diagnosed atopic disorders at primary school aged children (8 to 12 years of age) after Hib vaccination in the first year of life.	[74]
	Kolho KL	Case control	The difference in the number of children with an elevated serum IgE level for CM in Hp positive and negative children was not significant.	[75]
	Resch A	Cross sectional	No association between viral infections and food sensitization.	[76]
	Schauer U	Birth cohort	A positive test for IgE for common food allergens was noted in 14 out of 42 (33 %) RSV children and in 2 out of 84 (2.3 %) children in the control group.	[83]
	Silverberg JI	Case control	No association between wild-type varicella zoster infection up to 8 years of age and food sensitization.	[77]
	Keski-Nisula L	Birth cohort	No significant association between food sensitization and duration of ruptured membranes in labor.	[78]
	Matheson MC	Cohort	No association between any childhood immunization (Diphtheria, Tetanus, Pertussis, Polio, Smallpox) and food allergy.	[79]

Table 3 (continued)

Factor	Study	Type of study	Effect	Reference number
Mode of delivery	Kukkonen K	Randomized controlled trial	Probiotic treatment compared with placebo showed no effect on the cumulative incidence of allergic diseases but tended to reduce IgE-associated (atopic) diseases (OR=0.71; 95 % CI, 0.50–1.00; P=0.052).	[80]
	Taylor AL	Randomized controlled trial	The presence of <i>Lactobacillus</i> at 6 months of age was associated with increased risk of subsequent cow's milk sensitization (P=0.012).	[81]
	Nakajima K	Cohort	Weak patterns of association were observed between the risk of food allergies and immunization against diphtheria (OR=1.5, 95 % CI, 1.0–2.1), polio (OR=1.4, 95 % CI, 1.00–2.1) and tetanus (OR=1.30, 95 % CI, 0.99–1.70).	[65]
	Gustafsson D	Cohort	The OR for food allergic reactions in those with repeated colds was 2.45(95 % CI, 1.45–4.14).	[84]
	Van Nimwegen FA	Cohort	Decreased risk of sensitization to food allergens in vaginal home delivery compared with vaginal hospital delivery (OR, 0.52; 95 % CI, 0.35–0.77) was only found for children with atopic parents. No association was found with cesarean section.	[85]
	Keski-Nisula L	Cohort	Children of allergic parents delivered by cesarean section had significantly lower risk of food sensitization compared to those born vaginally (OR=0.18, 95 % CI, 0.046–0.68; P<0.012).	[78]
	Roduit C	Cohort	The association between cesarean section and food and inhalant sensitization at the age of 8 years was significant only in children of non-allergic parents (OR=2.14; 95 % CI, 1.16–3.98).	[86]
	Metsala J	Nested case control	Cesarean section (OR=1.18, 95 % CI, 1.10–1.27) was associated with increased risk for diagnosed CMA.	[87]
	Sánchez-Valverde F	Cohort	IgE-mediated CMA is associated with cesarean delivery (OR=2.14, 95 % CI, 1.02–4.49).	[88]
	Eggesbo M	Cohort	Confirmed/probable CMA/CMPF was twice as common among children who had been delivered by a cesarean section compared with children who had been vaginally delivered (OR=2.5, 95 % CI, 0.8–7.5).	[92]
Food consumption (quantity and timing)	Eggesbo M	Cohort	Among children whose mothers were allergic, cesarean section was associated with a 7-fold increased risk of parentally perceived reactions to egg, fish, or nuts (odds ratio, 7.0; CI, 1.8–28; P=0.005) although the association was significant for confirmed food allergies.	[89]
	Laubereau B	Cohort	Infants born by cesarean section (147/865, 17 %) had a greater risk of sensitization to food allergens (aOR=2.06, 95 % CI 1.123 to 3.80).	[90]
	Negele K	Cohort	Allergic sensitization defined as at least one specific IgE $\geq$ 0.70 kU/l against food allergens [OR=1.64, 95 % CI, 1.03–2.63] was increased in those with cesarean section.	[91]
	Kvenshagen B	Cohort	No increased risk for food allergy in the first 2 years of life in children delivered by cesarean section.	[93]
	Sausenthaler S	Cohort	High maternal intake of celery (OR=1.85, 95 % CI, 1.18–2.89) and citrus fruit (OR=1.73, 95 % CI, 1.18–2.53) during pregnancy increased the risk of sensitization to food allergens (specific IgE $\geq$ 0.35KU/L).	[94]
	Poole JA	Cohort	After adjusting for breastfeeding duration, introduction of rice cereal, family history of allergy, and history of food allergy before 6 months of age, age at initial exposure to cereal grains continued to be strongly associated with wheat allergy ($\geq$ 7 months: OR=3.8, 95 % CI, 1.18–12.28).	[96]
	Fox AT	Cohort	A dose-response relationship was observed between environmental (nonoral) peanut exposure and the development of peanut allergy [OR for environmental consumption of more than 15 g in cases (defined as SPT>8 mm, IgE>15 od positive DBPCFC) vs high risk controls (those already diagnosed with egg allergy):22.81(95 % CI, 8.9–58.6)], which was strongest for peanut butter. No effect of maternal peanut consumption during pregnancy or lactation was observed.	[111]
	Du Toit G	Case control	After adjustment for atopy, other food allergies, age, and sex, the RR for peanut allergy in the UK vs Israel is 5.8 (95 % CI, 2.8–11.8), and largest and most significant difference in weaning between the UK and Israel was observed in the age of introduction of peanut (P<0.0001). By 9 months of age, 69 % of Israelis were eating peanut compared with only 10 % of UK infants.	[112]

Table 3 (continued)

Factor	Study	Type of study	Effect	Reference number
	Katz Y	Cohort	The OR was 19.3 (95 % CI, 6.0–62.1) for development of IgE mediated CMA among infants with exposure to cow milk protein at the age of 15 days or more ($P<0.001$) vs those introduced to cow milk protein before 15 days.	[97]
	Kuo HC	Cohort	The percentage of food sensitization (especially to milk protein) was significantly lower in those fed hypoallergenic formula than in those fed cow milk based formula at 36 months (12.7 vs. 23.4 %, $p=0.048$). However, occurrence of allergic diseases during the first 3 years of life was not correlated with food allergen sensitization, parental atopy or feeding types.	[98]
	Joseph CL	Cohort	Early feeding reduced the risk of peanut sensitization among children with a parental history of asthma/allergy: OR=0.2 (95 % CI, 0.1–0.7); $P=0.0071$. The relationship also became significant for egg when a cut-off for IgE of ≥ 0.70 IU/mL was used [OR=0.5 (95 % CI, 0.3, 0.9)].	[99]
	Koplin JJ	Case control	Introduction of cooked egg at age 4 to 6 months vs later exposure reduced the risk of egg allergy [OR=0.2 (95 % CI, 0.06–0.71)].	[100]
	Nwaru BI	Birth cohort	After adjustment for potential confounders, late introduction of potatoes (>4 months), oats (>5 months), rye (>7 months), wheat (>6 months), meat (>5.5 months), fish (>8.2 months), and eggs (>10.5 months) was associated with sensitization to any food allergen. Late introduction of egg and wheat was associated with increased OR for egg and wheat allergy (2.26 (1.25, 4.08) and 3.51 (1.58, 7.81) respectively).	[101]
	Zutavern A	Birth cohort	There was an increased risk for food sensitization when solid food was introduced beyond 4 months into the child's diet (OR=2.15, 95 % CI, 1.28–3.62).	[102]
	Kull I	Birth cohort	Regular fish consumption during the first year of life was associated with a reduced risk for allergic sensitization to inhalant and food allergens by age 4, OR 0.68 (95 % CI, 0.53–0.82).	[103]
	Kemp AS	Cohort	In the entire cohort ($n=310$), there was no association between antenatal peanut ingestion and peanut sensitization ($P=0.17$). However, there was a strong association between antenatal peanut ingestion and decreased risk of rye sensitization and peanut sensitization in those ($n=201$) without a family history (FH) of asthma [Rye OR 0.30, (95 % CI 0.14–0.63) and peanut OR 0.18, 95 % CI, 0.04–0.78]. There was an increased risk of rye sensitization in those with a FH of asthma and antenatal peanut ingestion (Rye OR 2.69, 95 % CI 1.11–6.51 $P=0.03$).	[104]
	von Berg A	Randomized controlled cohort study	Use of partially or extensively hydrolyzed infant formulas did not have significant effect on food allergy development.	[105]
	Flinterman AE	Observational (no control)	Before the elimination period, all 11 children with atopic dermatitis were sensitized and had ingested CM without the development of acute reactions but during the elimination period, eight out of 11 children developed severe acute allergic reactions to CM after accidental ingestion and all 11 children experienced acute allergic reactions to CM during DBPCFC.	[106]
	Dean T	Cohort	Maternal consumption of peanut during pregnancy was not associated with peanut sensitization in the infant.	[107]
	Hourihane JO	Cohort	In the first school cohort (2003–2005) to have been conceived after government advice that atopic pregnant and breast-feeding mothers and their infants should avoid peanuts, 2.8 %; (95 % CIs, 1.8 %–3.8 %) had a positive peanut skin prick test result and 1.8 %; (95 % CIs, 1.1 %–2.7 %) were shown to have peanut allergy. This is the highest prevalence for peanut allergy recorded to date (but only 3.8 % of mothers followed the Government's advice by stopping the consumption of peanuts while pregnant).	[108]
	Lack G	Cohort	Peanut allergy was independently associated with intake of soy milk or soy formula (OR=2.6, 95 % CI, 1.3–5.2).	[109]
	Lack G	Cohort	Analysis of interview data showed a significant independent relation of peanut allergy with the use of skin preparations containing peanut oil (OR=6.8, 95 % CI, 1.4 to 32.9).	[109]

Table 3 (continued)

Factor	Study	Type of study	Effect	Reference number
Day care	Lowe AJ	RCT	There was no evidence that infants allocated to the pHWF (OR=1.21, 95 % CI, 0.81–1.80) or the soy formula (OR=1.26, 95 % CI, 0.84–1.88) were at a lower risk of allergic manifestations in infancy compared with conventional formula. There was also no evidence of reduced risk of SPT reactivity.	[110]
	DesRoches A	Case control	The reported consumption of peanut during pregnancy and breastfeeding was higher in the case group (those who developed peanut allergy and associated with an increased risk of peanut allergy in offspring [OR=4.22 (95 % CI, 1.57–11.30) and OR=2.28 (95 % CI, 1.31–3.97) for pregnancy and breastfeeding, respectively].	[114]
	Sicherer S	Case control	Multivariate analysis including clinical, laboratory, and demographic variables showed frequent peanut consumption during pregnancy {OR=2.9 (95 % CI, 1.7–4.9)} to be associated with peanut IgE $\geq$ 5 kU/L.	[115]
	Hagerthed-Engman L Gustafsson D	Cross-sectional Cohort	Self-reported allergic reactions to foods were more common in children attending day's care vs children at home (OR=1.27 (95 % CI, 1.07–1.52), Early day nursery (before the age of 18 months) was associated with food reactions (OR=2.21, 95 % CI, 1.30–3.74)	[116] [84]
Pets	Ege MJ	Cohort	In multivariable analysis for IgE to food allergens, consumption of boiled farm milk during pregnancy was positively associated with IgE to food allergens (OR=2.29 [95 % CI, 1.23–4.29] and particularly with IgE to cow's milk (3.64 (1.35–9.79),)	[117]
Food processing	Von HL	Cross sectional	Having pets, dogs in Finland (OR=0.57, 95 % CI, 0.35–0.95) and cats in Russia (OR=0.43, 95 % CI, 0.24–0.80), in early life was also inversely associated with atopy (defined as a positive skin prick tests against 14 common airborne and food allergens).	[118]
	Liu GM	Laboratory analysis	Extracts from raw shrimp bound higher IgE than extracts from boiled shrimp, but the purified boiled tropomyosin (the main shrimp allergen) demonstrates higher IgE binding vs raw shrimp.	[119]
	Chung SY	Laboratory analysis	After curing and roasting, mature peanuts exhibited approximately 20 % higher levels of advanced glycation end adducts and higher IgE binding vs immature peanuts.	[120]
	Samsen KT	Laboratory analysis	Thermal processing can lead to the formation of new antigenic structures.	[121]
Omega 3	Furuhjelm C	Randomized controlled trial	Daily maternal supplementation with either 1.6 g eicosapentaenoic acid and 1.1 g docosahexaenoic acid or placebo was given from the 25th gestational week to average 3–4 months of breastfeeding. The period prevalence of food allergy was lower in the omega-3 group (1/52, 2 %) compared to the placebo group (10/65, 15 %, $p<0.05$).	[122]
Vitamin D	Almqvist C	Randomized controlled trial	Randomized controlled trial conducted in children with a family history of asthma. Plasma levels of omega-3 or omega-6 fatty acids were not associated with wheezing, eczema, or atopy at age 5 years ($p=0.11$ – 0.96).	[123]
	Liu X	Cohort	A significant interaction between IL4 gene polymorphism (rs2243250) and vitamin D deficiency (p(interaction)=0.003, p(FDR)=0.10) was found: Vitamin D deficiency increased the risk of food sensitivity among children carrying CC/CT genotypes (OR=1.79, 95 % CI, 1.15–2.77).	[44]
	Milner JD	Cohort	Early vitamin D use (within the first 6 months of life) was associated with a higher risk for food allergies in the exclusively formula-fed population [OR=1.63 (95 % CI, 1.21–2.20)]. Vitamin use at 3 years of age was associated with increased risk for food allergies but not asthma in both breastfed [OR=1.62(95 % CI, 1.19–2.21)] and exclusively formula-fed infants [OR=1.39 (95 % CI, 1.03–1.88)].	[124]
	Nwaru BI	Cohort	Maternal intake of vitamin D (OR=0.56, 95 % CI, 0.35–0.91) was inversely associated with sensitization to food allergens.	[125]
	Marmstö K	Cohort	Children who reported that they started taking multivitamins before or at age 4 had a decreased risk of sensitization to food allergens (OR=0.61, 95 % CI, 0.39–0.97)	[126]
	Sharief S	Cross sectional	After multivariate adjustment, 25(OH)D levels of less than 15 ng/mL were associated with peanut (OR=2.39, 95 % CI, 1.29–4.45)	[127]

Table 3 (continued)

Factor	Study	Type of study	Effect	Reference number
Breastfeeding	Rudders SA	Ecologic study	In a multivariable model, the Northeast of US had a higher odds ratio (OR) than the South (1.13, 95 % CI, 1.01–1.27; $P=0.04$) regarding emergency department (ED) visits for acute allergic reactions. The association was stronger when restricting the analysis to visits for food-related allergic reactions (OR=1.33, 95 % CI, 1.14–1.56; $P<0.001$).	[128]
	Camargo CA	Ecologic study	Strong north–south gradient for the prescription of EpiPens in the United States, with the highest rates found in New England. [adjusted β for New England vs the rest of the US, 4.07 (95 % CI, 2.77–5.36)]	[129]
	Mullins RJ	Ecologic study	Using multivariate analysis, EpiPen prescription rates were higher in southern latitudes (less sunlight) compared with northern regions [β , -19.22 (95 % CI, -26.71 to -11.73)].	[130]
	Mullins RJ	Ecologic study	Southern latitudes were associated with higher hypoallergenic formula prescription rates [β , -147.98 (95 % CI, -281.83 to -14.14)].	[131]
	Kull I	Cohort	Children supplemented with vitamins A and D in water-soluble form during the first year of life had an almost 2-fold increased risk of food hypersensitivity (adjusted OR=1.89, 95 % CI, 1.33–2.65) at age 4 years compared with those receiving vitamins in peanut oil.	[132]
	Gustafsson D	Cohort	No increased risk of allergic symptoms even in those breast fed for <3 months.	[84]
	Sánchez-Valverde F	Cohort	Use of supplementary artificial formula while breast feeding was associated with higher risk for IgE-mediated CMA (OR=2.86, 95 % CI: 1.33–6.13).	[88]
	Venter C	Cohort	Exclusive breast feeding for less than 2 months compared to more prolonged breastfeeding was associated with higher odds for IgE-mediated CMA. (<2 months, OR=4.14, 95 % CI, 2.17–7.89).	[133]
	Matheson MC	Cohort (Tasmanian)	The rate of food allergy (based on parent report, confirmatory tests and physician diagnosis) and sensitization to foods were significantly lower in those weaned before 16 wk for sensitization at 1 yr ($p=0.03$, OR=0.26, 95 % CI, 0.05, 0.94), allergy by 1 yr ($p=0.02$, OR=0.41, 95 % CI 0.18–0.89), sensitization at 3 yr ($p=0.01$, OR=0.33, 95 % CI, 0.11, 0.86) and allergy by 3 yr ($p=0.02$, OR=0.51, 95 % CI, 0.28–0.92).	[134]
	Kusunoki T	Cross sectional	Exclusive BF in the first 3 months of life had a reduced risk of self-reported food allergy at age 7 years but an increased risk of food allergy (OR=1.26, 95 % CI, 1.1–1.5) at 44 years.	[135]
	Han Y	Cross sectional	After adjustment for sex, age, birth order, family history, eczema or wheezing within 6 months after birth, there was no association between complete artificial feeding, mixed and complete BF and self-reported food allergy at school age.	[136]
	Rennick GJ	Cross sectional	The total IgE level ($p=0.004$) and egg specific IgE level ($p=0.002$) were significantly higher in the BF group than in the FF group. The percentage of sensitization to egg ($p=0.001$) was also significantly higher in the BF group when compared with the FF group, as was the egg allergy rate (defined according to 95 %-predictive IgE levels ($p=0.004$)).	[137]
	Savilahti EM	Cross sectional	In predominantly breast fed infants with moderate to severe atopic dermatitis, 53 infants (90 %) had a positive SPT to one or more of the five common food allergens (egg white, cow's milk, peanuts, wheat or soy) and 80 % were positive to egg white. The authors concluded that the positive skin prick tests to foods, particularly to egg white, are very common in this selected population of breast-fed infants. Infants with IgE-mediated cow's milk allergy had lower β -lactoglobulin and α -casein specific IgG1, IgG4 and IgG levels ($p<0.05$) than infants with non-IgE-mediated cow's milk allergy or control subjects. Within the group of infants with cow's milk allergy, exposure to cow's milk during the first few days after birth led to higher β -lactoglobulin and α -casein specific IgG4 levels ($p<0.005$) compared to infants fed with either breast milk or extensively hydrolyzed formula.	[138]

OR, odds ratio; RR, Relative Risk; CI, confidence interval; EBV, Epstein Barr virus; Hp, *Helicobacter pylori*; CMA, Cow's Milk Allergy; RSV, respiratory syncytial virus; CMPI, Cow's Milk Protein Intolerance; pHWF, Partially hydrolyzed whey formula; BF, breastfeeding

studies have failed to find such an effect [85, 93]. Further, given that studies reporting an association are not randomized, it is hard to determine if these findings are not a result of an a priori selection bias that would lead those with a higher risk for food allergy to choose a certain mode of delivery. In a systematic review, it was concluded that there is evidence that the risk of developing IgE-mediated sensitization to food allergens is increased among children delivered by caesarean section [61]. Studies using objectively diagnosed food allergy as the outcome are needed to verify whether this equates to an increase in confirmed food allergy. In a meta-analysis done between 1966 to 2007, it was concluded that the association between C-section and food allergy/food atopy could be difficult to interpret due to publication bias [62].

Food Consumption (Quantity and Timing and Route of Exposure). It is proposed that allergic sensitization to food can occur through low-dose cutaneous sensitization, while early consumption of food protein induces oral tolerance [59]. It is also suggested that certain types of foods in the diet may increase food sensitization [94]. Small amounts of food on tabletops, hands, and dust may penetrate the skin barrier and be taken up by Langerhan's cells. This leads to Th2 responses and IgE production by B cells. Thus, the timing and balance of cutaneous and oral exposure determine whether a child will have allergy or tolerance [59]. While previous American Academy of Pediatrics recommendations and case control studies [95] suggested that early food exposure leads to food allergy, more recent cohort [96–110], and cross sectional studies [111, 112] and a randomized controlled trial [comparing extensively hydrolyzed versus conventional milk formula] [101] suggested that late introduction of potential food allergens or cutaneous exposure [109] might be associated with allergy, while early oral exposure might contribute to tolerance. In a study on 11 atopic children who tolerated cow's milk with no acute reactions, an elimination diet resulted in the development of an IgE-mediated allergy to milk in all (confirmed with a DBPCFC) [106]. Further, the only studies supporting the premise that late introduction might be beneficial [113] are based on the development of food sensitivity rather than confirmed food allergy or parental recall [114, 115]. The UK group led by Gideon Lack is one of the main pioneers in this area. Following their observational studies, they have embarked on the first randomized controlled study, the LEAP (Learning Early About Prevention) Study (www.leapstudy.co.uk) that is attempting to address this issue. Given that “complete” allergen avoidance is impossible and that current evidence does not justify allergen avoidance for allergy prevention, the debate has shifted on whether to deviate further from the current consensus of “equipoise” and move to a position of “deliberate exposure” [63].

Day Care Attendance. Attendance at a day-care centre involves a high exposure to infections and also antibiotic treatments. Two cohort studies reported higher risk for food allergy in children attending daycare although potential factors responsible for this observation have not yet been elucidated [84, 116].

Pets and Farming Environment. It has been hypothesized that high microbial exposure on a farm (including nonviable microbial components, such as lipopolysaccharide, peptidoglycan, and bacterial DNA that is recognized by the innate immune system), either through contact with farm animals or via consumption of unpasteurized milk, promotes the development of the non-allergic phenotype by effects on the development of T-helper and T-regulatory cells [84]. In contrast, in affluent Western societies characterized by living in apartments and houses, exposure to such microorganisms was reduced substantially and hence atopy might have increased. Although two studies have reported an inverse association between having pets and living on a farm and food sensitization [117, 118], no study has explored the potential effect on clinically confirmed food allergy.

Food Processing. Food processing (e.g. heating or vinegar addition) may either decrease [119] or increase [120, 121] food allergenicity.

Omega 3 Fatty Acids (FA). Over the last 50 years, the consumption of saturated fat and n-6 FA has been substantially increased, while the consumption of n-3 FA derived from plant and marine food has declined, resulting in increased ratios of n-6/n-3 FA in many countries. Epidemiological studies suggest that the increased intake of n-6 FA in the Western diet might be one triggering factor for the increased prevalence of atopic diseases, including allergic sensitization to food antigens [122]. However, two randomized controlled trials exploring this issue have provided inconsistent results [122, 123].

Vitamin D. There is growing interest in the potential role of sunlight/vitamin D status on allergic conditions. Studies have reported a link between food sensitization and vitamin D levels [44, 124–132]. However, while some cohort [125, 126], cross-sectional [127], and ecological studies [128–131] have suggested a protective effect of vitamin D on the development of food allergy; others failed to substantiate this association and some even suggested an inverse effect, i.e. high levels of vitamin D are associated with increased food allergy risk [124, 132].

Breastfeeding. Breastfeeding has been explored in numerous studies as a means of protection against the development of allergic diseases. With the exception of one study

[88], all studies so far have failed to find any protective effect of breastfeeding on the development of food allergy [84, 133–138]. It is also suggested that the food allergy-promoting effects of breastfeeding reported by some studies [133, 134, 137] are most likely because of reverse causation, and there are neither promoting nor preventive effects of breastfeeding on food allergy. Infants at the highest risk of allergic diseases (because of a family history of allergic diseases or presence of early signs of allergy, such as infantile eczema and wheeze) might be breastfed for longer periods in the hope that breastfeeding might reduce the risk of long-term allergic diseases [135].

Demographic Factors

Very few studies have evaluated demographic predictors of food allergy (Table 4). Among those that do examine potential predictors, the following factors have been associated with food allergy:

Age. World-wide, food allergy is more prevalent in children, potentially due to the high rate of resolution with age of milk and egg allergy and/or due to a possible cohort effect with higher levels of peanut allergy in more recent cohorts [13, 139–155]. In a recent US study, estimates of food allergy, based on IgE levels [139], revealed that the prevalence of clinical food allergy differed significantly and declined with age, being highest at 1–5 years (4.2 %) and lowest in adults ≥ 60 years (1.3 %). The estimates for specific foods also varied by age. The prevalence of clinical food allergy to milk, egg, and peanut were each approximately 1.8 % at 1–5 years and clinical peanut allergy was most prevalent (2.7 %) at 6–19 years; clinical shrimp allergy was most prevalent (1.2 %) at 20–59 years [139]. These findings are consistent with other studies suggesting that milk, egg, peanut, tree nut, and sesame allergy are more common in children [13, 142, 143, 146, 147, 150, 151, 154, 155], while shellfish allergy (and in other studies, also fish allergy) is more common in adults [13, 140, 146, 150, 151]. However, in Asia, shellfish allergy is reported to be the leading cause of allergy in children as well [141].

Gender. In adults, anaphylaxis is more common in females [156]. However, in studies estimating anaphylaxis incidence in children, males predominate [156, 157]. The higher frequency of anaphylaxis in adult females could be related to higher estrogen levels that may lead to enhanced mast cell activation and allergic sensitization and/or progesterone inhibiting histamine release, but potentiating IgE induction [158]. Studies have suggested that this trend is true also for food allergy, i.e. in children, food allergy is more common

in males, while in adults, females predominate [13, 18, 139, 142, 144, 146–148, 150, 159–165].

Race/Ethnicity. It is reported that non-Hispanic black race/ethnicity have increased odds for food allergy after adjusting for socioeconomic status and education (Table 4) [139, 144, 151, 164, 166]. In a prospective UK study that involved 76 children with IgE-mediated food allergy presenting consecutively to a pediatric allergy clinic, it was found that ethnic minorities were over-represented in terms of the number of children with food allergy (when compared to the general pediatric clinics serving the same population) and the number of food allergies per child; they also presented at an earlier age with food allergy, and possibly had a greater variety of food allergies compared with Caucasians. However, the authors did not control for potential cultural differences in dietary habits and life style that could affect the development of food allergy [167]. There are a few studies, based on epinephrine auto-injector dispensing rates [168] or parental self-report [169], which suggested that whites have a higher prevalence of food allergy. However, this may be attributed to minority children being under-diagnosed or undertreated for allergic disorders requiring injectable epinephrine rather than having a lower prevalence of food allergy.

Socioeconomic Factors. Most studies suggest an increased rate of food allergy in higher socioeconomic populations [18, 87, 130, 144, 170].

Although the recent National Health and Nutrition Examination Survey study (NHANES) and a Swedish study reported higher levels of food sensitization and likely clinical food allergy in individuals living in poverty compared to those in higher income households [139, 171], the 95 % CI for the effect reported in these studies crosses 1 (Table 4). Further, food allergy estimates in these studies were based primarily on IgE levels and the conclusions might have differed had food allergy reflected clinical allergy.

Education. Of six studies discussing a potential relation between education and food allergy, five suggested that a higher education level is associated with a higher prevalence of food allergy [146, 160, 164, 169, 172]. In the NHANES study, food sensitization was reported to be higher in households with less educated participants, but the 95 % CI (Table 4) reported crosses 1 and hence there was no conclusive effect of education on the prevalence of food allergy [139]. Additional studies are required to better define the association between level of education and food allergy.

Maternal Age. Two studies reported higher odds for food allergy with increased maternal age [87, 173], potentially due to higher genetic predisposition for developing food allergy in children with older mothers [173].

Table 4 Demographic factors associated with food allergies

Factor	Study	Study design	Comments	Reference number
Age	Sicherer SH	Cross sectional	Self-report peanut allergy 1.4 % for children and 0.6 % for adults.	[13]
	Liu AH	Cross sectional	Overall clinical food allergy prevalence differed significantly and declined with age, being highest in 1–5 year old children (4.2 %) and lowest in adults 60+ years old (1.3 %). The OR for possible/likely food allergy was 2.04 (1.42–2.93) in those 1–5 years old vs older participants.	[139]
	Sicherer SH	Cross sectional	Seafood allergy was more common in adults compared with children (2.8 % vs 0.6 %; $p < 0.001$).	[140]
	Leung TF	Cross sectional	The six leading causes of adverse food reactions in Chinese children in Hong Kong were shellfish (15.8 %), egg (9.1 %), peanut (8.1 %), beef (6.4 %), cow's milk (5.7 %), and tree nuts (5.0 %).	[141]
	Rudders SA	Cross sectional	Peanuts and milk were more common food triggers in infants, whereas adolescents more frequently reported reactions to tree nuts, and fruits/vegetables.	[142]
	Chen J	Cross sectional	The overall prevalence of challenge-proven food allergy in 0 to 1 year old children in Chongqing, China, was 3.8 % (95 % CI, 2.5–5.9 %) with 2.5 % egg allergic and 1.3 % cow's milk allergic.	[143]
	Gupta RS	Cross sectional	Food allergies were more common in those 3–5yo versus 0–2yo [OR = 1.5, 95 % CI, (1.3–1.8)] and odds of severe food allergy progressively increased with age, peaking at more than twofold higher odds of severe reaction history among children aged 14 to 17 years versus those aged 0 to 2 years.	[144]
	Ostblom E	Birth cohort	The mean number of foods reported to cause symptoms showed a significant increase at 1, 2, 4 and 8 years of age: 1.4 (1.3–1.5), 1.6 (1.5–1.7), 2.1 (1.9–2.2) and 2.3 (2.1–2.5), respectively, and 27 % (22–32 %), 38 % (34–45 %), 51 % (45–56 %) and 51 % (46–56 %) were reported to react to at least two foods at the corresponding ages.	[145]
	Ben-Shoshan M	Cross sectional	Peanut, tree nut, and sesame allergy were more common in children (OR=2.24 (95 % CI, 1.40–3.59), 1.73 (95 % CI, 1.11–2.68), and 5.63 (95 % CI, 1.39–22.87), respectively) while fish and shellfish allergy were less common in children (OR 0.17 (95 % CI, 0.04, 0.72) and 0.29 (95 % CI, 0.14–0.61)).	[146]
	Ferrari GG	Cross sectional	Among children referred for allergy assessment, in those less than 3 years of age, egg and wheat were the major food allergens (37.9 %, 31 % and 10.3 % respectively) but after 3 years peanut, egg and fish were the most common (21.4 %, 14.3 % and 10.2 % respectively).	[147]
	Namork E	Cross sectional (the Norwegian food registry)	Two age groups, small children and young adults are over-represented in the reported adverse reactions to foods.	[148]
	De Knop KJ	Cross sectional	The majority of hazelnut allergic preschool and school children in a birch-endemic region show systemic reactions on consumption of processed hazelnut, mostly being sensitized to the hazelnut legumin-like allergen C or a 9 (65 % and 50 % of these groups respectively versus 17 % of adults with systemic reactions to hazelnuts) but unrelated to birch pollen allergy. In contrast, adults generally suffer from an OAS apparently as a result of cross-reactivity between C or a 1.04 from hazelnut and Bet v 1 from birch pollen.	[149]
	Jones RB	Cross sectional (regional allergy clinic)	Amongst the 410 with food allergy, those allergic to seafood were older (39 Vs 30; $t = -4.4$; $p < 0.001$), those allergic to nuts were much younger (26 Vs 38; $t = 8.7$; $p < 0.001$), those to allergic to egg were younger (25 Vs 32; $t = 2.7$; $p = 0.008$), but there was no age difference for fruit, dairy, or grain. The children under 16 were much more likely to have nut allergy (45 % Vs 21 %, $\chi^2 = 28$, $p < 0.001$) than adults.	[150]
	Ross MP	Cross sectional (a nationwide probability sample from hospital ED based on the National Electronic Injury Surveillance System)	Events in children ≤ 12 months most often involved miscellaneous items, eggs, and fruit, whereas events in children age 13 months to 5 years most often involved peanuts, tree nuts, and fruit. Children age 6 to 18 years had a food reactivity profile similar to adults, with shellfish and combination foods implicated most often.	[151]
	Wang LJ	Cross sectional (children with atopic dermatitis)	Age correlated negatively with food allergens and positively with aeroallergens after adjusting for sex ($P < 0.04$).	[152]

Table 4 (continued)

Factor	Study	Study design	Comments	Reference number
Gender	Steinke M	Cross sectional	Parentally perceived food allergy was most common in 2 to 3 years old (7.2 %).	[153]
	Melioli G	Cohort	Food-related components (in particular those of milk and egg) were the most frequently recognized in the earliest ages (infancy), whereas specific IgE to plant allergens appeared invariably later. IgE against cross-reacting allergens was virtually absent in the first years and tended to appear only after the age of 6.	[154]
	Dean T	Nested cohort of children	The prevalences of sensitization to food allergens were 2.8 %, 3.9 %, and 3.7 % at 1, 2, and 3 years of age. Among those with a positive SPT at 1 year, 29 % tested positive to additional allergens at 2 years ($P=0.0054$). Sensitization to milk or egg at 1 year was a predictor for increased sensitization to peanut at 3 years ($OR=34.8$; $P<0.0001$).	[155]
	Sicherer SH	Cross sectional	A male predominance of peanut-TN allergy was reported in children younger than 18 years (1.7 % vs 0.7 %, $P=0.02$), and a female predominance was reported among adults (1.7 % vs 0.9 %, $P=0.0008$).	[13]
	Kotz D	Cross sectional	In those under 18 years of age, the crude lifetime prevalence rate was higher in males than females. For peanut allergy: In the age group 0 to 19 years, the crude lifetime prevalence rate in males was 1.77/1000; (95 % CI, 1.63, 1.91) vs 1.39/1000; (95 % CI, 1.27–1.52) in females. In the age group 20 years and older, the crude lifetime prevalence rate was lower in men vs women [0.13/1000(95 % CI, 0.11–0.15) vs 0.19/1000(95 % CI, 0.17–0.22) respectively].	[18]
	Liu AH	Cross sectional	Food sensitization and estimated clinical food allergies for the entire population were more prevalent in males than females, to peanut, shrimp, and milk, but not egg. The prevalence of detectable food sensitization, possible and likely food allergy to peanut in males was 10.0 %, 2.4 %, and 0.6 %, respectively, compared with 5.2 %, 1.4 %, and 0.1 % in females. The OR for possible/likely food allergy in males vs females was 1.87 (1.32–2.66).	[139]
	Rudders SA	Cross sectional	Patients were predominantly male in younger age groups; however, females represented approximately half (52 %) of the adolescents.	[142]
	Gupta RS	Cross sectional	No gender difference in children reporting food allergies	[144]
	Ben-Shoshan M	Cross sectional	Tree nut and shellfish allergy were less common in males [$OR=0.55$ (95 % CI, 0.36–0.83) and OR 0.63 (95 % CI, 0.43–0.91)].	[146]
	Ferrari GG	Cross sectional	There were significantly more boys ($n=101$) than girls ($n=50$) in the study population.	[147]
Race/ethnicity	Namork E	Cross sectional	The overall gender distribution was 40:60 males-females.	[148]
	Jones RB	Cross sectional	The only difference in the genders was for fruit allergy: females were more likely to have fruit allergy (20 Vs 11 %; $\chi^2=5.5$; $p=0.019$).	[150]
	Pyrhonen K	Cross sectional (nationwide population registry in children 0–4yo)	Food allergy was more common in boys vs girls ($RR=1.44$, 95 % CI 1.2–1.8).	[159]
	Soost S	Cross sectional (randomly sampled survey in adults)	Based on weighted data, the point prevalence of adverse reactions to food resulted in 3.3 % [95 % CI (2.4–4.5 %)] for women and 1.8 % [95 % CI (1.2–2.7 %)] for men after DBPCFC. However, among individuals with symptoms of food allergy, men have a higher prevalence of food-specific IgE-sensitization and of raised total IgE than women. Females were twice as likely to be sensitized to eggplant as males.	[160]
	Harish Babu BN	Cross sectional	Among all patients with diagnosed mustard allergy, the male:female ratio was 10:19.	[161]
	Caballero T	Cross sectional	Food hypersensitivity was reported more often by female (66.3 %) than by male (47.9 %) students ($P=0.003$).	[162]
	Matila L	Cross sectional	Characteristics associated with a higher percentage of probable food-allergy according to maternal self report were male gender, relative to female gender.	[163]
	Luccioli S	Cohort (through first year of life)	Females were more frequently affected (60.6 %) by adverse reactions to food.	[164]
	Zuberbier T	Cross sectional (adults)		[165]
	Liu AH	Cross sectional	OR for non-Hispanic black vs non-Hispanic whites was 3.06 (2.14–4.36).	[139]
Race/ethnicity	Gupta RS	Cross sectional	In children self-reported food allergies were more common in Black non-Hispanic ($OR=1.8$ (1.6–2.1) and in Asians non-Hispanic (1.4 (1.2–1.7)) vs whites non-Hispanic.	(144)

Table 4 (continued)

Factor	Study	Study design	Comments	Reference number
	Ross MP	Cross sectional	The majority of reported events occurred in white persons (58 %).	[151]
	Luccioli S	Cohort (through first year of life)	Characteristics associated with a significantly higher percentage of probable food-allergy according to maternal self report were black race (12.5), relative to white (5.5 % and Hispanic race (5.1 %).	[164]
	Kumar R	Birth cohort	In multivariate models, both self-reported black race [OR=2.34 (95 % CI, 1.24-4.44)] and African ancestry (in 10 % increments; OR=1.07 [95 % CI, 1.02-1.14]) were associated with food sensitization. Self-reported black race (OR=3.76 [95 % CI: 1.09-12.97]) and African ancestry [OR=1.19 (95 % CI, 1.07-1.32)] were associated with a high number (≥ 3) of food sensitizations. African ancestry was associated with increased odds of peanut sIgE levels of ≥ 5 kU/L [OR=1.25 (95 % CI, 1.01-1.52)]. Similar ancestry associations were seen for egg sIgE levels of ≥ 2 kU/L (OR=1.13 (95 % CI: 1.01-1.27)).	[166]
	Dias RP	Cohort (a population-based cohort of 6,100 white and 2,600 South Asian)	Among wheezers, food as a trigger for wheezing was reported more commonly by parents of South Asian children (OR=3.84 (2.6-5.67) and 9.06 (4.52-18.18) for age groups 1-4 years and 6-9 years respectively). The average number of food allergens per child in the non-Caucasian group was 2.05 vs 1.22 in the Caucasian group, mean difference 0.83, which is significant ($t=4.15$, d.f. = 74, $p<0.01$).	[167]
	Hannaway PJ	Cross sectional (School nurses in 44 schools recorded the characteristics of students dispensed injectable epinephrine in the 2003-2004)	Whites were more likely to have been dispensed injectable epinephrine than nonwhites (OR=4.76; $p<0.001$). Whites were nearly 5 times more likely to be dispensed injectable epinephrine for peanut or tree nut allergy than nonwhites (OR=4.5; $p<0.001$).	[168]
	Victorino CC	Cross sectional (self report for children)	Race was not associated with self-reported food allergy.	[169]
Socioeconomic status	Kotz D	Cross sectional	Highest prevalence of peanut allergy found in the most affluent group.	[18]
	Metsälä J	Nested case control	Low maternal socioeconomic status (OR=0.65, 95 % CI, 0.59-0.71) was associated with decreased risk of CMA.	[87]
	Mullins RJ	Ecologic	Annual IHF sales rates were higher in those with the greatest compared with the least socio-economic advantage (47,830 vs. 21,384 tins/100,000 population; $P<0.001$). EpiPen sales trends were also higher in those with the greatest socio-economic advantage in all age groups, most marked in those aged 0-4 (1713 vs. 669/100,000; $p=0.002$) and 5-14 years (1628 vs. 600/100,000; $p=0.001$).	[130]
	Liu AH	Cross sectional	Highest prevalence found in the least affluent group. OR=0.94 (95 % CI, 0.65-1.34) for food allergy in those more affluent vs those less affluent.	[139]
	Gupta RS	Cross sectional	The odds for food allergies were lower in those with lower income [$<50,000$ vs $>50,000$; OR=0.5 (95%CI, 0.4, 0.7)]	[144]
	Victorino CC	Cross sectional	Self reported food allergy in children was not associated with household income.	[169]
	Sheikh A	Cohort	Analysis of 2,323 patients with primary diagnosis of anaphylaxis among all emergency admissions for anaphylaxis to English hospitals between 1991 and 1995. The rate ratio for anaphylaxis among non-deprived vs deprived was 1.32 (95 % CI 1.19-1.46).	[170]
	Almqvist C	Birth cohort	The risk of sensitization to food allergens decreased with increasing socioeconomic status; OR=0.65 (95%CI<0.41-1.02) in the highest socioeconomic group (Ptrend=0.03).	[171]
Education	Liu AH	Cross sectional	The prevalence of food sensitization tended to be higher in households with less educated participants, but these differences were not statistically significant. OR=1.03 (95 % CI, 0.79-1.34).	[139]
	Ben-Shoshan M	Cross sectional	Tree nut allergy was common in postsecondary graduates OR=1.9 (95%CI, 1.18, 3.04).	[146]
	Soost S	Cross sectional	Higher education (13 years vs 9 years of school) was associated with increased odds for self-reported dysaesthesia of the tongue (OR=1.92 (95 % CI, 1.19-2.85)).	[160]

Table 4 (continued)

Factor	Study	Study design	Comments	Reference number
	Victorino CC	Cross sectional (data from the 2003 US National Survey of Children's Health involving 102,353 children aged 0 to 17 years). Cohort	Children in families who had someone with greater than a high school education were <i>more</i> likely to have had food allergies as told by a health care professional in the past 12 months (OR = 1.27 (95%CI, 1.07–1.52)).	[169]
	Luccioli S	Cohort	Characteristics associated with a higher percentage of probable food-allergy according to maternal self report were mothers with a college degree, relative to lower education.	[164]
	Pawlinska-Chmara R	Cross sectional	Higher maternal/paternal education associated with higher prevalence of allergy. $\chi^2=19.34$, $df=2$, $P=0.0001$ and $\chi^2=16.76$, $df=2$, $P=0.0002$ respectively.	[172]
Maternal age at delivery	Metslä J	Nested case-control study	High maternal age (> or =35 years; OR=1.23, 95 % CI: 1.11–1.36) were associated with increased risk of diagnosed CMA.	[87]
	Dioun AF	Case control	Maternal age 30 and over increased the risk of having a child with a food allergy (covariate adjusted odds ratio of 3.70, 95 % confidence interval 1.67–8.20, $p=0.001$)	[173]
Household size and birth order	Metslä J	Nested case-control study	High number of previous deliveries (> or =5; OR=0.71, 95 % CI: 0.59–0.86) was associated with decreased risk of diagnosed CMA.	[87]
	Ege MJ	Cohort	In multivariable analysis for IgE to food allergens, there was inverse association of the number of previous pregnancies with IgE to food allergens (OR=0.87 [95 % CI, 0.76–1.00]).	[117]
	Dioun AF	Case control	Being first born increased the risk of having a food allergy (covariate adjusted odds ratio of 2.22, 95 % CI: 1.06–4.66, $p=0.035$).	[173]
	Al-Hammadi S	Cross sectional	In households with at least 5 children, the odds for physician diagnosed food allergies were higher (OR=0.41, 95 % CI, 0.19–0.89).	[174]
Immigrants	Leung TF	Cross sectional	When compared with children born and raised in Hong Kong, children born in mainland China ($n=253$) had less parent-reported AFR (4.0 % vs. 6.7 %; $p=0.016$).	[141]
	Ben-Shoshan	Cross sectional	Shellfish allergy was less prevalent in immigrants compared to individuals born in Canada (OR 0.49 (95 % CI, 0.26–0.95)).	[146]
	Cataldo F	Cross sectional (hospital records)	Despite differences in their origin, the clinical features of immigrant children were similar to the ones of Italian patients and among each ethnic group.	[175]
	Keet CA	Cross sectional (Nation Health and Examination Survey 2005–2006)	US-born children and adolescents had higher odds of sensitization to any food (OR=2.05; 95%CI, 1.49–2.83; $p<0.001$). Among the foreign-born group, those who arrived before 2 years of age had higher odds of food sensitization than those who arrived later (OR=2.68; 95 % CI, 1.19–6.08; $p=0.02$). Within the US-born group, in contrast, children of immigrants were at the highest risk (OR=1.53; 95 % CI, 1.05–2.24; $p=0.02$).	[176]
	Shek LP	Cross sectional	Respondents born in Western countries were at higher risk of peanut (adjusted odds ratios [95 % CIs]: 4–6 years, 3.47 [1.35–8.93]; 14–16 years, 5.56 [1.74–17.76]) and tree nut allergy (adjusted odds ratios [95 % CIs]: 4–6 years, 10.40 [1.61–67.36]; 14–16 years, 3.53 [1.00–12.43]) compared with those born in Asia.	[177]
Obesity	Visness CM	Cross sectional (National Health and Nutrition Examination Survey data from 2005–2006)	aOR for food sensitization was increased in the obese children compared with that seen in those of normal weight [OR = 1.59 (95 % CI, 1.28–1.98)]. (Obesity was defined as the 95th percentile or greater of body mass index for age).	[178]
	Irei AV	Cross sectional	Vietnamese children at >85th percentile group showed a significantly higher risk of allergy (OR=2.34, 95 % CI 1.06–5.17; $p=0.035$). This association was not observed when children with atopic dermatitis or food allergy (Determined according to the question: “Have you ever had a rash in the skin and sickness within an hour of eating some food?” and “Were these symptoms repeated each time the same food was eaten?”) were excluded.	[179]

Table 4 (continued)

Factor	Study	Study design	Comments	Reference number
Family/ individual history of diabetes	Irei AV	Cross sectional	Food allergy was not related to obesity in this study population.	[180]
	Luccioli S	Cohort	Characteristics associated with increased incidence of probable food allergy included family histories of type 1 diabetes and gestational diabetes.	[164]
	Kumar R	Cohort	Dichotomized analyses for probable-food-allergy group versus all other infants (combining other-food-related problem and no food-related problem) revealed a statistically significant association ($p<0.05$) with gestational diabetes.	[181]
	Caffarelli C	Case control	There was no association between skin-prick test results to inhalants and food allergens and DM1.	[182]
	Camargo CA	Ecologic study	Strong north-south gradient for the prescription of EpiPens in the United States, with the highest rates found in New England [adjusted β for New England vs the rest of the US, 4.07 (95 % CI, 2.77–5.36)].	[129]
	Mullins RJ	Ecologic study	Southern latitudes were associated with higher hypoallergenic formulae prescription rates [beta, −147.98; 95 % CI, −281.83 to −14.14; $p=0.03$].	[130]
	Mullins RJ	Ecologic study	Using multivariate analysis, EpiPen prescription rates were higher in southern latitudes (less sunlight compared with northern regions (β , −19.22; 95 % CI, −26.71 to −11.73; $p<0.001$)).	[131]
	Liu AH	Cross sectional	In the US, the estimated prevalence of clinical food allergy was 2.5 % (peanut, 1.3 %; milk, 0.4 %; egg, 0.2 %; shrimp, 1.0 %; not mutually exclusive).	[139]
	Gupta RS	Cross sectional	The prevalence of food allergies was higher in Northeast, South and West US compared to Midwest US (OR=1.3 (1.2–1.5), 1.5 (1.3–1.7) and 1.3 (1.1–1.5) respectively).	[144]
	Ben-Shoshan M	Cross sectional	Shellfish allergy was more common in urban settings (OR=1.55 (95 % CI, 1.04–2.31)).	[146]
Geography	Jones RB	Cross sectional	Food allergies (particularly nut allergies) clustered in the South Hams.	[150]
	Steinke M	Cross sectional	Parentally perceived food allergy prevalence ranged between 1.7 % (Austria) to 11.7 % (Finland).	[153]
	Gupta R S	Cross sectional	In the US, prevalence according to allergen among food-allergic children was highest for peanut (25.2 % [95 % CI: 23.3–27.1]), followed by milk (21.1 % [95 % CI, 19.4–22.8]) and shellfish (17.2 % [95 % CI, 15.6–18.9]).	[144]
	Shek LP	Cross sectional	Shellfish allergy was more common in the local Singapore (4–6 years, 1.19 %, 14–16 years, 5.23 % and Philippine (14–16 years, 5.12 %) school children compared with expatriate children (4–6 years, 0.55 %, 14–16 years, 0.96 %, $P<0.001$). When data were pooled, respondents born in Western countries were at higher risk of peanut [OR=3.47 (95%CI,1.35–8.93); 4–6 years; OR=5.56 (95 %CI, 1.74–17.76) 14–16 years, and tree nut allergy (OR=10.4 (95%CI, 1.61–67.36) 4–6 years; OR=3.53 (1.00–12.43) 14–16 years, compared with those born in Asia].	[177]
	Vereda A	Cross sectional	American patients frequently had IgE antibodies to rAra h 1 to 3 (56.7 %–90.0 %) and often presented with severe symptoms. Spanish patients recognized these 3 recombinant peanut allergens less frequently (16.0 %–42.0 %), were more often sensitized to the lipid transfer protein rAra h 9 (60.0 %), and typically had peanut allergy after becoming allergic to other plant-derived foods. Swedish patients detected rAra h 1 to 3 more frequently than Spanish patients (37.1 %–74.3 %) and had the highest sensitization rate to the Bet v 1 homologue rAra h 8 (65.7 %), as well as to rBet v 1 (82.9 %). Spanish and Swedish patients became allergic to peanut at 2 years or later, whereas the American children became allergic around 1 year of age.	[184]
	Thong BY	Cross sectional	In Singapore, the most common causative foods were seafood crustaceans, (25, 33.8 %), molluscs (14, 18.9 %) and bird's nest (seven, 9.5 %).	[185]
	Dalal I	Cross sectional	In Israel, the most common food allergens in children were egg (0.5 %), cow's milk (0.3 %), and sesame (0.18 %).	[186]
	Marrugo J	Cross sectional	Fruit/vegetables (41.8 %), seafood (26.6 %), and meats (20.8 %), were the most reported allergens in Colombia.	[187]
	Hooper R	Cross sectional	The prevalence of skin test sensitization to foods was higher in urban than in rural children (37.3 vs 22.4 % in those with concomitant exercise induced bronchospasm). There was strong evidence of an effect of the urban vs rural types of diet (fried potatoes, carrots, tinned fruit salad, chicken, sausages, yoghurt, packet custard and jelly vs pumpkin leaves, young pumpkin, cabbage and wild leaves and berries).	[188]
Atopy	Lack G	Cohort	Peanut allergy was independently associated with rash over joints and skin creases (odds ratio, 2.6; 95 percent confidence interval, 1.4–5.0), and oozing, crusted rash (odds ratio, 5.2; 95 %, 2.7–10.2).	[109]

Table 4 (continued)

Factor	Study	Study design	Comments	Reference number
Liu AH	Cross sectional		Study participants with doctor-diagnosed asthma (vs no asthma) exhibited increased risk of all measures of food sensitization. Moreover, in those with LFA, the adjusted odds ratio for current asthma (3.8, 1.5–10.7) and an emergency department visit for asthma in the past year (6.9, 2.4–19.7) were both notably increased.	[139]
Gustafsson D	Cohort		Among children who presented with severe eczema initially (score 6–8 at the first visit), 69 % had a positive IgE test on at least one occasion (for either hen's egg, cow's milk, soya bean, cod, wheat or peanut), as opposed to 53 % who presented with mild eczema initially (RR=1.30, 95%CI, 0.93–1.81). All but a few became sensitized before the age of 3 years. All but a few became sensitized before the age of 3 years.	[84]
Leung TF	Cross sectional		On logistic regression, parent-reported adverse food reactions (AFR) associated with AFR history in father ($p=0.001$), mother ($p<0.001$), siblings ($p=0.020$), and paternal history of rhinitis ($p=0.044$).	[141]
Ostblom E	Cohort		Food hypersensitivity at young ages increased the risk for persistent asthma, eczema and allergic rhinitis at 8 years of age (aOR : 6.9 (4.1–11), 13 [8, 22] and 2.3 (1.1–5.1) respectively.	[145]
Harish-Babu BN	Cross sectional		Sensitization to eggplant by SPT was more in atopic (16.7 %) compared with non-atopic subjects (3.8 %).	[161]
Mattila L	Cross sectional		Food hypersensitivity was most frequent among subjects with AD, among those with current AD in 73.2 %, with past AD in 66.3 %, and with ARC or asthma in 63.8 %; 44.8 % of subjects without any atopic disease reported FH.	[163]
Thong BY	Cross sectional		More than half of the patients diagnosed with food allergy had concomitant allergic rhinitis, asthma and/or eczema.	[185]
Marrugo J	Cross sectional		Self-reported food allergy was most frequent in subjects reporting atopic diseases (62.9 % vs. 29.6 %, χ^2 test, $p<0.001$).	[187]
Hill DJ	Cohort (children with eczema)		There was a statistically significant association between the early age of onset of eczema and the 95 %-positive predictive levels of food specific IgE (w2 85.6, Po0.0001 for any high food specific IgE and age of onset of eczema). Of the children with 95 % positive predictive levels of specific IgE, 99 % were to egg, 25 % to cow's milk and 11.5 % to peanut.	[190]
Kim JS	Cross sectional		Atopic sensitization was common in this rural farming Chinese population, particularly to shellfish, peanut, dust mite, and cockroach. The prevalence of allergic disease, in contrast, was quite low.	[52]
Hon KL	Cross sectional		Patients with severe AD (objective SCORAD>40) were more likely to be positive for at least one of the food items (Yates corrected $p=0.024$ for ≥ 1 food-specific IgE in severe vs. moderate AD, OR 3.42 and (95 % CI, 1.15–10.32); and for at least seven of the food items ($p=0.001$ for ≥ 7 food-specific IgE vs. nil with OR 11.67 and (95 % CI, 2.29–67.77), respectively. The Spearman coefficients between the number of positive food-specific IgE and total SCORAD, objective SCORAD, area of AD involvement, Children's Dermatology Life Quality Index (CDLQI), total IgE levels, and eosinophil counts were 0.42 ($p<0.001$), 0.45 ($p<0.001$), 0.50 ($p<0.001$), 0.17 ($p=0.116$), 0.80 ($p<0.001$), and 0.22 ($p=0.043$), respectively.	[194]
Gelincik A	Cross sectional		The most significant factor influencing food allergy/nonallergic food hypersensitivity was familial atopy (OR=4.3; 95 % CI, 3.67–4.99), and the most related atopic disease was itching dermatitis/turcica	[12]
Boussault P	Cross sectional		Oat sensitization in AD children seen for allergy testing is higher than expected (Oat APT and SPT were positive in 14.6 % and 19.2 % of cases, respectively.	[195]
Ritci G	Cohort		Hen's egg sensitization was significantly related to the appearance of asthma (Fisher's exact test $P<0.007$) and RC (Fisher's exact test $P<0.05$).	[196]
Hill DJ	Cohort		Using age-specific 95 %-predictive cutoff values, CAP-FEIA identified 34 of 41 infants (83 %; 95 % CI=68 % to 93 %) with IgE-food sensitivity (cow's milk, 23 %; egg, 80 %). Forty-six (90 %) infants had IgE-food sensitivity to at least 1 food item by either SPT or CAP-FEIA.	[197]
Estrada-Reyes E	Case control		There were more children with positive skin tests for food hypersensitivity among cases with atopic dermatitis than controls, OR=4.2 (95 % CI, 1.3–13.4).	[198]
Garcia C	Cross sectional		Food sensitization (positive prick test and/or specific IgE > 0.35 kU/l) was seen in 27 out of the 44 (61 %) patients with atopic dermatitis studied.	[199]
Hill DJ	Cohort		As atopic dermatitis severity increased so did the prevalence of IgE-mediated food allergy, defined when the SPT diameter for a specific food was greater than or equal to twice the histamine reference (Gp 0, 40/346 vs. Gp 1, 6/36 vs. Gp 2, 8/35 vs. Gp 3, 12/35 vs. Gp 4, 24/35; $\chi^2(2)=76$; $p<10(-6)$).	[200]

Table 4 (continued)

Factor	Study	Study design	Comments	Reference number
	Penin M	Case control	Children with food hypersensitivity vs children without it, can develop asthma (17.6 % vs 3.4 %) and other allergies (29.4 % vs 5.1 %) as inhalant allergy more frequently and their relatives have more allergic diseases (62 % vs 32 %).	[201]
	Annesi-Maesano I	Cross sectional	In those with food allergy the OR for asthma were 1.88 (1.28, 2.76).	[202]
	Monti, G	Cohort	In infants with atopic dermatitis who were never exposed to egg, the egg challenge was positive in 72/107 children (67.3 %).	[203]
	Böhme M	Cohort	Associations between atopic dermatitis and adverse reactions to foods (RR 3.20, CI 2.83–3.62).	[204]
	Al-Hammadi S	Cross sectional	The best predictors for childhood food allergy were a personal history of asthma ($p<0.001$), a personal history of atopic dermatitis ($p<0.001$), a paternal history of atopic dermatitis ($p<0.005$) and a paternal history of allergic rhino-conjunctivitis ($p<0.012$).	[205]
	Santadusit S	Cross sectional	Significant risk factors for developing adverse food reactions among Thai children, were personal allergic history, OR=4.89, (95 % CI, 2.2–10.75) and family history of allergy, OR=2.87, (95 % CI, 1.42–5.89).	[209]
	Schnabel E	Cohort	Children with atopic heredity had a higher risk for a doctor-diagnosed food allergy at the age of 2 years, OR=1.8 (95 % CI, 1.1–3.0), but not at 6 years OR=1.0 (95 % CI, 0.6–1.8).	[210]

OR, odds ratio; RR, Relative Risk; CI, confidence interval; Yo, years old; OAS, oral allergy syndrome; TN, tree nut; DBPCFC, double blind placebo controlled food challenge; CMA, Cow's milk allergy; IHF, infant hypoallergenic formulae; DMI, type 1 diabetes mellitus; AFR, adverse food reaction; AD, atopic dermatitis; ARC, allergic rhinoconjunctivitis; APT, atopic patch test; FH, Food hypersensitivity; RC, rhinoconjunctivitis

Household Size and Birth Order. Only a few studies have examined the association between household size and food allergy; all reported that food allergy prevalence decreased with increased household size [87, 117, 173, 174]. It has been suggested that the protective association of multiple pregnancies and older siblings is due to increased exposure to infections in early childhood from close contact with siblings. Alternatively, these associations may have their origin in the prenatal period and may be due to hormonal and immunologic conditions that differ in the uterus between first and subsequent pregnancies [87].

Immigrants. Very few studies have explored the relationship between being an immigrant and the presence of food allergy. Although one European study did not find any difference in allergy status between immigrants and non immigrants [175], in general, studies suggest an increased prevalence of allergic diseases (mainly asthma) that correlates with the length of stay in Westernized countries regardless of age at arrival, sex or atopic status [141, 146, 176, 177]. In a study estimating food allergy prevalence in Hong Kong and Singapore, it was shown that individuals born in Western countries, compared to those born in Asia, have a higher risk of peanut and tree nut allergy although the risk for shellfish allergy was unrelated to the place of birth [177].

Obesity. Obesity might be a contributor to the increased prevalence of allergic disease in children, particularly food allergy. Systemic inflammation (due to proinflammatory cytokines that are over expressed in obesity) might play a role in the development of allergic disease [178]. However, three studies assessing a potential association revealed inconsistent findings [178–180].

Family/Individual History of Diabetes. Autoimmune disorders are considered to be associated with a Th1 immune response while allergic diseases with a Th2 response. A few studies aimed to determine whether there is an inverse relationship between allergic diseases and type 1 diabetes mellitus in mothers [164, 181] or children [182]. However, the results are inconsistent [164, 181, 182].

Geography. Recent studies, based on epinephrine auto-injector distribution data, suggested higher rates of anaphylaxis in northern versus southern areas [129–131]. It has been speculated that this north–south gradient might be due to differences in vitamin D status [129]. However, given that the majority of these studies are ecological studies, they are all susceptible to ecological fallacy in that relationships observed for groups may not necessarily hold for individuals [183]. In a cross-sectional phone survey involving households with children, Gupta et al. found that age and geographic region were significantly associated with having

a food allergy. However, no plausible explanation for this geographic difference was suggested [144]. In addition, studies suggested that food allergy may differ not only according to north–south gradients but also in different countries located in similar latitudes [153, 177, 184–188]. and in rural versus urban [146, 150] environments. These differences may be due to differences in life style including different dietary habits.

Atopy. Atopy, defined as the presence of high levels of any allergen specific-IgE [189, 190], is common in subjects with food allergy [191, 199]. The extracellular cytokine milieu associated with atopic diseases may contribute to the increased risk of an allergic reaction [52, 84, 161, 163, 192]. Although some studies suggested that atopy does not confer an additional risk of anaphylaxis [193], the majority of studies reported a strong association between food sensitization [12, 190, 194–200] or allergy [109, 141, 145, 185, 187, 201–205] and atopy [206, 207]. In the NHANES study, it was reported that the presence of doctor-diagnosed asthma increased the risk of food sensitization. Moreover, in those with a likely food allergy, the adjusted odds ratio for current asthma (3.80, 95 % CI, 1.50–10.70) and an emergency department visit for asthma in the past year (6.90, 95 % CI, 2.40–19.70) were both notably increased [139]. Similarly, studies conducted in Europe [208] and Asia [209] suggested that atopy increases the risk of food allergy. In addition, a history of atopy in family members is also a known risk factor for the development of food allergy [210].

Conclusions and Future Directions

This review reveals that while food allergy prevalence might have stabilized in certain countries, it continues to increase in others. Food allergy is associated with timing and route of exposure to potential food allergens and it appears that certain food allergies are more common in children. In children, males are more likely to have a food allergy, while in adults, food allergy is more common in females. However, the association between food allergy and environmental factors such as season, drugs, microbial exposure, pets, omega-3 fatty acids and vitamin D as well as demographic factors such as race/ethnicity, socioeconomic status, education, immigration status and geographic location is not well established.

Given the relatively rapid increase in food allergy prevalence, it is likely that this results from the interplay of several, rather than a single, environmental factor(s). One of the most appealing and widely known explanations is the hygiene hypothesis. The 'hygiene hypothesis', as originally formulated by Strachan, proposes that a cause of the recent

rapid rise in atopic disorders could be a lower incidence of infection in early childhood, transmitted by unhygienic contact with older siblings [211].

This hypothesis is supported by studies in animal models suggesting that certain bacterial components may repress the development of allergic reactions potentially through the induction of Tregs [212]. Hence, lifestyle changes accruing in the last decades including smaller family size, decreased exposure to pets and livestock, fewer infections during infancy, increased use of antibiotics and vaccinations, and improved sanitation may have contributed to the development of food allergy [213]. However, this hypothesis has been criticized given the lack of correlation between the increase in allergic disorders and the decrease in infection with pathogenic organisms. The suggestion that childhood infections would protect against allergic disease led to unfortunate speculations that vaccinations would increase the risk for allergies. Numerous epidemiological studies have revealed that vaccinations against infectious agents neither significantly increase nor reduce the likelihood of immunologically mediated diseases [214]. More recent studies suggested that protection against allergy is mediated by broad exposure to a wealth of commensal, non-pathogenic microorganisms early in life, rather than by infections.

Hence, it has been suggested that the hygiene hypothesis should be updated to include dietary factors and the interaction of these factors with the microbiota and that a better term would be the "microbial exposure" hypothesis or "microbial deprivation" hypothesis [215].

Future studies examining the relative role of potential environmental and demographic determinants as well as their interaction with the individual's genetic background are required. It is hoped that enhanced understanding of the pathogenesis of food allergy will contribute to the development of more effective preventive and management strategies.

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