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Eczema in Early Childhood, Sociodemographic Factors and Lifestyle Habits Are Associated with Food Allergy: A Nested Case-Control Study

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Key Words
Food allergy · Eczema · Demographic factors · Lifestyle

Abstract
Background: Studies suggest an increase in food allergy prevalence over the last decade, but the contributing factors remain unknown. The aim of this study was to evaluate the association between the most common food allergies and atopic history, sociodemographic characteristics and lifestyle habits. ***Methods:*** We conducted a case-control study nested within the SPAACE study (Surveying Prevalence of Food Allergy in All Canadian Environments) – a cross-Canada, random telephone survey. Cases consisted of individuals with probable food allergy (self-report of convincing symptoms and/or physician diagnosis) to milk, egg, peanut, tree nut, shellfish, fish, wheat, soy, or sesame. Controls consisted of nonallergic individuals, matched for age. Cases and controls were queried on personal and family history of atopy, sociodemographic characteristics and lifestyle habits. Multivariate logistic regression was used to evaluate the association between atopy, sociodemographic characteristics and lifestyle habits with probable food allergy. ***Results:*** Between September 2010 and September 2011, 480 cases and 4,950 controls completed the questionnaire. For all 9 allergens, factors associated with a higher risk of probable allergy were as follows: (1) personal history of eczema (in the first 2 years of life), asthma or hay fever (odds ratio, OR 2.3, 95% CI 1.6–3.5; OR 2.8, 95% CI 2.2–3.6, and OR 2.3, 95% CI 1.8–3.0, respectively), (2) maternal, paternal or sibling's food allergy (OR 3.7, 95% CI 2.5–5.6; OR 3.0, 95% CI 1.8–5.1, and OR 3.1, 95% CI 2.2–4.2), (3) high household income (top 20%; OR 1.5, 95% CI 1.2–2.0). Males and older individuals were less likely to have food allergy (OR 0.7, 95% CI 0.6–0.9, and OR 0.99, 95% CI 0.99–1.00). Eczema in the first 2 years of life was the strongest risk factor for egg, peanut, tree nut and fish allergy. ***Conclusions:*** This is the largest population-based nested case-control study exploring factors associated with food allergies. Our results reveal that, in addition to previously reported factors, eczema in the first 2 years of life is consistently associated with food allergies.

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Introduction

It is suggested that the prevalence of food allergy has increased worldwide in the last decade [1], and recent studies suggest this trend is continuing [1–3]. Although an interplay of genetic and environmental factors is likely to be responsible for this increase, the specific determinants remain largely speculative [1]. Until recently, delayed introduction of foods was thought to decrease sensitization and the risk for food allergy and, consequently, pregnant and lactating mothers and children younger than 3 years of age were advised to avoid peanut [4]. However, recent studies have challenged these conventional practices [1, 5]. Case-control and cohort studies have shown that the prevalence of milk allergy and peanut allergy, respectively, was lower with early exposure [1]. It is now proposed that low-dose cutaneous exposure to an allergen, potentially through a disrupted skin barrier in children with eczema, may promote allergic sensitization, whereas early oral consumption induces tolerance [1, 6]. However, the evidence is not yet sufficient to conclude that early feeding and an intact skin barrier prevent the development of food allergy [1].

To further illuminate the factors mediating the development of food allergy, we compared family and personal history of atopy, sociodemographic factors and lifestyle habits, as well as access to medical services (having a physician) in individuals with and without food allergy [7]. Our study is unique in that it specifically explores eczema stratified by age of onset (<2 years or ≥2 years) to better elucidate the role of an impaired skin barrier in the first years of life. If eczema in early childhood is identified as a risk factor for food allergy, it is potentially modifiable through the usage of barrier repair treatments, which restore epidermal function.

Methods

Study Sample

We conducted a case-control study nested within a nationwide population-based cross-sectional food allergy study performed between September 2010 and September 2011 [8]. In a previous population-based telephone survey performed between May 2008 and March 2009, Canadians of lower income and education and New Canadians were underrepresented [7, 9, 10]. Hence, to ensure these vulnerable populations were included in our subsequent 2010/2011 study, we used a targeted sampling strategy that included regions containing the highest proportions of those of lower income and education, immigrants, and those of self-reporting Aboriginal identity. Census tracts from all the census metropolitan areas in the 2006 Canadian census were obtained. Census tracts known to contain either a high proportion of households living under the low income cutoff [11], having migrated to Canada since 1996 and/or of Aboriginal identity were then identified and converted into postal codes using the 2006 Statistics Canada postal code conversion file. A random sample of household telephone numbers from these postal codes was provided by Info-Direct (a company that maintains the White Pages in Canada), and interviews were conducted using CATI (computer-assisted telephone interviewing) software [12]. To increase the response rate, as has been demonstrated in a previous study, an a priori incentive of CAD 5 was provided [11, 13]. A detailed description of the sampling strategy is published elsewhere [11].

Selection of Cases and Controls

The initial age-eligible household respondent was invited to participate and was asked whether any household member had an allergy to milk, egg, peanut, tree nut, fish, shellfish, wheat, soy, or sesame. If any household member reported an allergy, the self-reported allergy was validated by querying the potentially allergic individual (or an appropriate surrogate if the allergic individual was <18 years) on symptoms related to ingestion of the food and diagnosis of the allergy. Individuals were queried on the most severe reaction related to exposure to the food, characteristics of the reaction (if they experienced typical IgE-mediated symptoms such as oral pruritus, urticaria, angioedema, asthma, or throat closing), interval between exposure and symptom onset (≤2 h vs. >2 h) and if a physician made a diagnosis of food allergy. In addition, questions related to lactose intolerance (e.g. ability to tolerate certain quantities of milk or yogurt), inconsistent avoidance of the culprit food and the presence of celiac disease were included to avoid misclassification bias.

Cases included participants reporting a probable food allergy, i.e. self-report of a clinical history consistent with an IgE-mediated reaction to a food allergen and/or self-report of a physician diagnosis of a food allergy [7, 14]. Controls were selected from two sources of age-matched nonallergic participants, as follows: (1) nonallergic individuals living in the same household as the individual with food allergy and (2) randomly selected nonallergic individuals living within a household containing no individuals with food allergies. Cases and controls were matched for the following three age groups: <5 years, between 5 and 17 years and ≥18 years at the time of the questionnaire. We aimed to have a ratio of at least 1:4 between cases and controls for each of the three matched age groups [15].

Questionnaires

We designed a specific questionnaire based on studies published in the last decade [1], querying cases and controls on the presence of personal and family history of atopy, specific sociodemographic factors and lifestyle habits that may potentially contribute to the development of food allergy.

Atopic History

Participants reported on whether they or a first-degree relative had a physician diagnosis of eczema, asthma, food allergies, or hay fever and whether eczema (defined as chronic skin rashes, usually itchy and red that can be swollen) [16] was present in the first 2 years of life.

Sociodemographic Factors

Sociodemographic factors included age (child <18 years old), sex, household income (income <top 20% or ≥top 20% [7]), education (<postsecondary degree vs. ≥postsecondary degree; defined

for adults only), a three-level variable for immigrant status (New Canadian, immigrated ≥10 years ago, born in Canada), Aboriginal status (person identifying as First Nations, Inuit or Metis vs. not), sibship size, birth order, and geographic location (urban vs. rural defined as residing outside Canadian metropolitan areas or in Canadian metropolitan areas with a population ≤100,000).

Lifestyle Factors

Lifestyle factors included history of smoking in the household, mode of delivery (yes/no cesarean section), age of introduction for the 9 food allergens, frequency of consumption of these foods during pregnancy and lactation, consumption of raw/unpasteurized dairy products while pregnant, using vitamin D supplements during pregnancy, breast-feeding practices (exclusive breast-feeding vs. supplemental cow's milk formula vs. a combination), duration of breast-feeding, age at day care attendance, number of courses of antibiotics (>4 vs. ≤4 courses of antibiotics in the first year of life), number of respiratory (>10 vs. ≤10) and diarrheal illnesses (>3 vs. ≤3) in the first year of life, having an infection requiring admission to hospital in the first year of life, exposure to pets and to farm animals in the first year of life, and having a physician.

Given that recall bias is a major problem in case-control studies [15], we attempted to minimize it by developing two different versions of the questionnaire: one for those <5 years of age (including questions on mode of delivery, dietary habits during pregnancy, lactation and early infancy, day care attendance, use of antibiotics and infections in the first year of life, pet ownership, and living on a farm in infancy) and another for those ≥5 years of age (excluding questions related to early life dietary habits, use of antibiotics and infections).

The study was approved by the Institutional Review Board of the McGill University Health Center.

Statistical Analysis

Comparisons between univariate, intermediate and full logistic regression models were used to estimate the associations between the presence of probable food allergy and potential predictive factors as well as to investigate possible confounding factors. Potential predictive factors included all those atopic, sociodemographic and lifestyle habits itemized in the preceding section.

To ensure that potential overmatching did not bias our analysis (due to comparisons between cases and controls from the same household), we repeated the regressions using a more restricted sample, i.e. 1 randomly selected case from households with more than 1 allergic individual and 1 control per nonallergic household. Nonallergic controls from the same household as the case were excluded from this restricted sample analysis.

All statistical analysis was conducted using STATA® version 12 (StataCorp LP, College Station, Tex., USA).

Results

All 480 cases with probable food allergy and 4,950 controls completed the questionnaire. The ratio of cases to controls was 1:11 overall (1:16.6 for children <5 years, 1:5.9 for children between 5 and 17 years and 1:11.7 for adults). The median age for cases and controls was 38.0 years and 43.4 years, respectively. Cases (table 1) and controls were comparable regarding demographics (including age, sex, socioeconomic level, education level, and immigrant status) and lifestyle habits (table 2). However, cases were more likely to have a personal or family history of atopy.

Table 1. Characteristics of most severe reaction, physician diagnosis and use of confirmatory tests among cases

	Percent of all cases (n = 480)
Having a family physician	79.0 (75.0–82.6)
Report of physician diagnosis/convincing history	100
Report of physician diagnosis of a food allergy	70.4 (66.1–74.5)
Positive skin test	49.6 (45.0–54.2)
Positive blood test	22.7 (19.0–26.7)
Convincing history	83.1 (79.5–86.4)
Anaphylaxis	68.3 (64.0–72.5)

Values in parentheses are 95% CI.

The regression models for the factors associated with having an allergy to at least 1 of the 9 foods or to a specific food were compared for the entire sample and for the restricted sample (where only 1 case per household was included and controls from the same household as the case were excluded), and the results were similar. The results for the three age groups in the restricted or entire sample were also similar for all foods and for specific food allergies (tables 3–5). Hence, for the sake of clarity, in tables 4 and 5 (factors associated with specific food allergies), only the results for the entire sample for all age groups combined are presented.

Atopic History

Eczema in the first 2 years of life was associated with having at least 1 of the 9 food allergies (odds ratio, OR 2.3, 95% CI 1.6–3.5; table 3). Early-life eczema was also associated with individual food allergies, including egg (OR 8.9, 95% CI 5.4–14.7), peanut (OR 6.3, 95% CI 4.1–9.7), tree nut (OR 4.5, 95% CI 2.9–7.0), fish (OR 5.7, 95% CI 3.2–10.0), and wheat (OR 4.8, 95% CI 1.9–12.4; tables 4, 5). Eczema ever diagnosed was associated with shellfish (OR 2.6, 95% CI 1.9–3.7) and soy (OR 4.3, 95% CI 1.8–9.9).

Asthma was associated with having at least 1 food allergy (OR 2.8, 95% CI 2.2–3.6) as well as egg, peanut, tree nut, fish, shellfish, wheat, and sesame allergy. Hay fever was associated with milk, egg, peanut, tree nut, fish, shellfish, and soy allergy.

Table 2. Atopic, demographic and lifestyle factors in cases and controls

	Overall	Cases	Controls
Total sample, n	5,430	480	4,950
Adults, n	4,267	357	3,910
Children aged 5–17 years, n	583	89	494
Children <5 years, n	580	34	546
Mean age, years	42.9	38.0 (36.1–39.9)	43.4 (42.7–44.1)
Male	49.0	41.3 (36.8–45.8)	49.8 (48.4–51.2)
Postsecondary education	50.0	58.3 (53.0–63.4)	49.2 (47.6–50.8)
Immigrants	27.1	22.5 (18.8–26.5)	27.5 (26.3–28.8)
Immigrated ≤10 years ago	8.1	7.5 (5.3–10.3)	8.1 (7.4–8.9)
Aboriginals	10.8	11.9 (9.1–15.1)	10.7 (9.8–11.6)
High-income household (top 20%)	20.2	25.9 (21.5–30.6)	19.6 (18.3–20.9)
Personal history of eczema – ever diagnosed	14.3	38.3 (33.9–42.8)	12.0 (11.1–12.9)
Personal history of eczema – in first 2 years of life	7.2	25.9 (22.0–30.1)	5.4 (4.8–6.1)
Personal history of asthma	13.1	33.6 (29.4–38.1)	11.1 (10.2–12.0)
Personal history of hay fever	15.2	36.6 (32.2–41.1)	13.1 (12.2–14.1)
At least 1 atopic features in at least 1 family member other than the case or control	36.5	61.5 (56.9–65.8)	34.1 (32.7–35.4)
Infection/hospital before the age of 1 year	9.2	18.2 (7.0–35.5)	8.6 (6.4–11.3)
Had a pet before the age of 1 year	41.2	40.0 (35.6–44.5)	41.3 (39.9–42.7)
Lived on a farm before the age of 1 year	15.2	11.8 (9.0–15.0)	15.5 (14.5–16.6)
Born by cesarean section	10.1	13.0 (10.0–16.5)	9.9 (9.0–10.8)
Having older siblings	60.0	56.5 (51.9–61.0)	60.3 (58.9–61.7)
Having a family physician	78.6	79.0 (75.0–82.6)	78.5 (77.4–79.7)

Values are percentages unless otherwise indicated. Values in parentheses are 95% CI. Postsecondary education: among adults only. High-income household: in households reporting income only, representing 73% (n = 3,948) of the overall sample. Infection/hospital: among children <5 years only.

Table 3. Atopic and demographic factors associated with an allergy to at least 1 of the 9 foods

	All age groups	
	all cases and all controls	1 case or 1 control per household
Atopy		
Personal history of eczema – ever diagnosed	1.6 (1.1–2.3)	1.6 (1.1–2.3)
Personal history of eczema – in first 2 years of life	2.3 (1.6–3.5)	2.3 (1.5–3.6)
Personal history of asthma	2.8 (2.2–3.6)	2.7 (2.1–3.5)
Personal history of hay fever	2.3 (1.8–3.0)	2.4 (1.9–3.1)
Mother with at least 1 food allergy	3.7 (2.5–5.6)	3.4 (2.2–5.4)
Father with at least 1 food allergy	3.0 (1.8–5.1)	3.0 (1.7–5.4)
Sibling with at least 1 food allergy	3.1 (2.2–4.2)	3.6 (2.6–5.0)
Demographics		
Mean age, years	0.99 (0.99–1.0)	0.99 (0.99–1.0)
Male	0.7 (0.6–0.9)	0.7 (0.6–0.9)
High-income household (top 20%)	1.5 (1.2–2.0)	1.7 (1.3–2.2)

Values are percentages unless otherwise indicated. Values in parentheses are 95% CI.

Table 4. Atopic, demographic and lifestyle factors associated with milk, egg, peanut, tree nut, fish, and shellfish allergy

	Milk (n = 31)	Egg (n = 729)	Peanut (n = 124)	Tree-nut (n = 117)	Fish (n = 78)	Shellfish (n = 182)
Atopy						
Personal history of eczema – ever diagnosed						2.6 (1.9–3.7)
Personal history of eczema – in first 2 years of life		8.9 (5.4–14.7)	6.3 (4.1–9.7)	4.5 (2.9–7.0)	5.7 (3.2–10)	
Personal history of asthma		2.5 (1.5–4.3)	4.3 (2.8–6.7)	3.1 (2.0–4.9)	3.3 (1.9–5.5)	2.6 (1.8–3.7)
Personal history of hay fever	3.1 (1.3–7.0)	2.1 (1.2–3.7)	3.0 (1.9–4.8)	3.8 (2.4–5.9)	3.1 (1.8–5.4)	2.4 (1.7–3.5)
Mother with at least 1 food allergy			3.9 (1.9–8.1)	2.7 (1.2–5.8)		3.5 (1.9–6.4)
Father with at least 1 food allergy		6.4 (2.5–16.1)				
Sibling with a history of hay fever	2.6 (1.1–6.0)					
Sibling with at least 1 food allergy	3.3 (1.3–8.1)		2.7 (1.5–4.8)	2.8 (1.7–4.7)	4.6 (2.5–8.4)	3.8 (2.5–5.8)
Demographics						
Child <5 years						0.1 (0.0–0.5)
Mean age, years	0.98 (0.97–1.0)		0.97 (0.96–0.98)	0.98 (0.97–0.99)	0.99 (0.97–1.0)	
Male						0.7 (0.5–0.9)
High-income household (top 20%)			1.8 (1.1–2.9)			1.7 (1.2–2.5)
Postsecondary education				2.0 (1.3–3.1)		
Immigrant				0.5 (0.3–1.0)		
Minor who immigrated <10 years ago						2.7 (1.2–5.9)
Having older siblings	0.4 (0.2–1.0)					
Lifestyle habits						
Lived on a farm before the age of 1 year		0.2 (0.0–0.9)				
Introduction of food after the first year of life	9.4 (1.4–68.7)					
Having a family physician						0.7 (0.5–1.0)

Values are percentages unless otherwise indicated. Values in parentheses are 95% CI.

Table 5. Atopic and demographic features associated with wheat, soy and sesame allergies

	Wheat (n = 23)	Soy (n = 21)	Sesame (n = 14)
Atopy			
Personal history of eczema – ever diagnosed		4.3 (1.8–9.9)	
Personal history of eczema – in first 2 years of life	4.8 (1.9–12.4)		
Personal history of asthma	5.4 (2.1–13.7)		5.2 (1.8–15.1)
Personal history of hay fever		3.4 (1.4–8.1)	
Mother with at least 1 food allergy	11.7 (3.8–35.5)	7.4 (2.6–20.5)	
Father with asthma		5.8 (2.2–15.0)	
Father with hay fever			7.1 (2.2–22.9)
Father with at least 1 food allergy	12.9 (2.7–61.4)		
Sibling with hay fever	3.4 (1.3–9.0)		
Sibling with at least 1 food allergy			11.2 (3.7–33.5)
Demographics			
Male	0.2 (0.1–0.7)		

Values are percentages (with 95% CI).

Maternal food allergy was associated with peanut, tree nut, shellfish, wheat, and soy allergy, and paternal food allergy was associated with egg and wheat allergy. Having siblings with food allergies was associated with an increased risk for milk, peanut, tree nut, fish, shellfish, and sesame allergy.

In addition, early-life eczema was associated with both asthma (OR 3.5, 95% CI 2.8–4.5) and hay fever (OR 2.4, 95% CI 1.8–3.0). However, interactions of these with early-life eczema were not predictive of food allergy.

Sociodemographic Factors

Males were less likely to have any of the 9 probable food allergies (OR 0.7, 95% CI 0.6–0.9; table 3) as well as shellfish and wheat allergy. Older age was associated with a lower risk for food allergy for all foods combined (OR 0.99, 95% CI 0.99–1.00) per year (table 3) as well as for milk, peanut, tree nut, and fish allergy (table 4). When the age category was restricted to those <5 years versus those ≥5 years, young age was associated with a decreased risk for shellfish allergy.

High income (top 20%) was associated with higher risk (OR 1.5, 95% CI 1.2–2.0) for any food allergy and for peanut and shellfish allergy. Higher education (college and above) was associated with tree nut allergy.

Immigrants were less likely to have tree nut allergy (OR 0.5, 95% CI 0.3–1.0), but children who immigrated recently (<10 years ago) were more likely to have shellfish allergy (OR 2.7, 95% CI 1.2–5.9).

Lifestyle Habits

Those living on a farm in the first year of life had a lower risk for egg allergy. Having older siblings decreased the risk for milk allergy.

In those with milk allergy, late introduction of cow's milk formula (after the first year of life) was associated with higher odds for allergy (OR 9.4, 95% CI 1.4–68.7). However, due to the small sample size, the 95% CIs are relatively wide.

Having a family physician was not associated with any food allergy apart from shellfish allergy, where it was associated with a decreased risk. Large CIs preclude definitive conclusions regarding associations with other covariates.

Discussion

This is the first population-based nested case-control study to explore the association between food allergy and atopy, numerous sociodemographic factors and lifestyle habits. Although other studies showed an association between eczema and food allergy [17], ours is the first to examine the association between eczema early in life versus later in life and the development of food allergy. We have shown that eczema in the first 2 years of life is consistently associated with many food allergies, whereas eczema later in life is less associated.

In contrast to most of the other food allergies, we did not observe an association between shellfish allergy and eczema in the first 2 years of life. This is probably because shellfish is introduced after the age of 2 years in Canadian children [18]. In addition, we did not find an association between eczema in early childhood and milk allergy, probably because cow's milk is introduced in the first few weeks of life [19] before eczema is clinically present. This association with eczema in early life was also not observed for sesame and soy, possibly due to a small sample size.

Since the prevalence of eczema is increasing [20–22], and eczema is highly associated with food allergy [20–22], it may explain the increasing prevalence of food allergy. Understanding the role of the skin barrier is of particular interest as this represents a potentially modifiable risk factor. Thus, if food allergy results in some part from impairments in the skin barrier leading to abnormal exposure routes for food allergens, barrier repair treatment to restore epidermal integrity through the use of topical and/or systemic medications, combined with gradual oral introduction of potential allergens to promote the development of tolerance, will be a reasonable prevention strategy for food allergy.

It is postulated that factors related to the hygiene hypothesis may have contributed to the rise in the prevalence of eczema, although this was not substantiated [23]. It is also suggested that climate change and longer exposure to indoor air with lower humidity may contribute to the increase in the prevalence of eczema [23]. The link between eczema and food allergy is attributed to low-dose cutaneous exposure to an allergen that may promote allergic sensitization, whereas early oral consumption induces tolerance [1]. This is supported by animal models [24] and by reports suggesting that exposure in infancy to skin preparations, tabletops or hands containing food allergen increases the risk of food allergy in those with eczema (OR 2.4, 95% CI 1.9–3.0 [1, 25, 26] to OR 6.8, 95% CI 1.4–32.9) [27–29].

Various studies have established an association between eczema and food allergy, but none have assessed the presence of a critical age interval in which eczema increases the risk for the 9 food allergies [30]. It was dem-

onstrated that in infants with eczema who were never exposed to egg, the egg challenge was positive in almost 70% of cases [31] and that attempts at tolerance induction in the first 4 months of life often fail [32]. Indeed, in a cohort of 619 exclusively breast-fed infants, it was found that children with eczema were significantly more likely to be sensitized to foods (adjusted OR 6.18, 95% CI 2.94–12.98) and the likelihood of egg allergy was as high as 9.11 (95% CI 2.27–36.59) [33]. Establishing a causative link between early eczema and food allergy is crucial as it may contribute to the development of primary prevention strategies. In line with this hypothesis, recent studies suggest that controlling eczema might reduce the risk of food sensitization and, potentially, allergy [34, 35]. Indeed, recent studies suggest that food allergy may not be increasing in developed countries [36, 37] over the past decade, and it is possible that better treatment of eczema may explain this stabilization.

The sociodemographic associations demonstrated in our study have been previously reported by others, albeit with a smaller sample size and a more limited range of food allergens [1]. Worldwide, 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 [1]. Consistent with these findings, we found that the likelihood of food allergy in general decreased with increasing age. A lower risk for food allergy in males is consistent with other studies suggesting that anaphylaxis is more common in adult females, probably due 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 [1].

Similar to previous studies by our group and others, high income was associated with higher odds of food allergy [1, 9]. In line with previous findings by our group, high education was associated with tree nut allergy [9]. The observed reduced odds of tree nut allergy in immigrants might be due to genetic differences as well as environmental influences. It was reported that the risk for both asthma and eczema increase with the length of stay of immigrant children in North America [38, 39]. Indeed, although immigrants had lower odds for tree nut allergy, the odds for shellfish allergy was increased in children who had recently immigrated versus adult immigrants. This suggests a crucial role for environmental factors in the pathogenesis of allergic diseases in immigrant children due to changes in lifestyle [1]. It is also possible that children who immigrated and developed eczema prior to their introduction to shellfish were more likely to develop shellfish allergy [1].

Given that we have controlled for the presence of a treating physician, it is not likely that higher percentages of food allergies in the more educated, the Canadian born or those with a known atopic history are related to a higher level of diagnosis and better health care access. In fact, having a family doctor was associated with decreased rather than increased odds for shellfish allergy.

Having older siblings and living on a farm were associated with lower risk of milk and egg allergy, respectively. These findings are consistent with the hygiene hypothesis suggesting that smaller family size, decreased exposure to livestock, fewer infections during infancy, increased use of antibiotics and vaccinations, and improved sanitation might decrease microbial burden and lead predominantly to a type 2 T-helper cell response, which is responsible for triggering allergic disorders [1]. However, our results suggest that this simplified hypothesis is not the sole explanation for the increased prevalence of food allergies. Factors related to the hygiene hypothesis that were previously postulated to contribute to the development of food allergy, such as delivery through caesarean section, lower rate of infections in the first years of life, use of multiple courses of antibiotics, or number of respiratory or gastrointestinal infections, were not demonstrated in our study to be associated with food allergy.

Our study has some potential limitations. A major drawback of our study is the reliance on self-report for the diagnosis of probable food allergy. Hence, it is possible that the factors identified in the regression analysis are not valid predictors of a confirmed food allergy (based on the corroboration of history with confirmatory tests). However, given that previous studies by our group reveal that probable peanut allergy estimates in Canadian and Quebec children (Canada: 1.68%; Quebec: 1.69%) are consistent with confirmed peanut allergy estimates in Montreal schoolchildren (1.63%) [7, 36], we believe that the associations identified for probable allergy are also valid for confirmed allergy. There may be a differential recall bias by individuals with food allergy, such that they are more prone to remembering eczema in early life. However, had such a substantial recall bias existed we would expect to find such an association for all food allergies, while in fact this association was not observed for milk, shellfish, wheat, and sesame allergy. In addition, although we have presumably reduced recall bias by limiting questions related to pregnancy and infancy to those younger than 5 years, this has resulted in a small sample

size for examining most food allergy-related factors in infancy. Hence, although our results suggest that early introduction of cow's milk-based formula might reduce the risk of food allergy, as has been recently suggested [40], our small sample size precludes conclusive results.

In conclusion, our results reveal that atopy and, in particular, eczema in early childhood is strongly associated with the development of the 9 most common food allergies. Future cohort and randomized controlled trials exploring the effects of early feeding and eczema as well as genetic and other determinants will help disentangle the numerous factors mediating the development of food allergy.

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Disclosure Statement

Dr. Ben-Shoshan serves as a consultant for Novartis and Sanofi. The authors have no conflicts of interest to declare.

References

1 Ben-Shoshan M, Turnbull E, Clarke A: Food allergy: temporal trends and determinants. Curr Allergy Asthma Rep 2012;12:346–372.
2 Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JK, Fiocchi A, et al: A global survey of changing patterns of food allergy burden in children. World Allergy Organ J 2013;6:21.
3 Keet CA, Savage JH, Seopaul S, Peng RD, Wood RA, Matsui EC: Temporal trends and racial/ethnic disparity in self-reported pediatric food allergy in the United States. Ann Allergy Asthma Immunol 2014;112:222–229.
4 American Academy of Pediatrics; Committee on Nutrition: Hypoallergenic infant formulas. Pediatrics 2000;106(part 1):346–349.
5 Frazier AL, Camargo CA Jr, Malspeis S, Willett WC, Young MC: Prospective study of peripregnancy consumption of peanuts or tree nuts by mothers and the risk of peanut or tree nut allergy in their offspring. JAMA Pediatr 2014;168:156–162.
6 Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al: Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol 2008;122:984–991.
7 Ben Shoshan M, Harrington DW, Soller L, Fragapane J, Joseph L, St Pierre Y, et al: A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada. J Allergy Clin Immunol 2010;125:1327–1335.
8 Ben-Shoshan M, Knoll M, Soller L, Harrington DW, Fragapane J, Joseph L, et al: Prevalence of common food allergies in Canada: targeting specific demographic groups across Canada. J Allergy Clin Immunol 2012;129:AB235.
9 Ben-Shoshan M, Harrington DW, Soller L, Fragapane J, Joseph L, St Pierre Y, et al: Demographic predictors of peanut, tree nut, fish, shellfish, and sesame allergy in Canada. J Allergy (Cairo) 2012;2012:858306.
10 Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St Pierre Y, et al: Overall prevalence of self-reported food allergy in Canada. J Allergy Clin Immunol 2012;130:986–988.
11 Knoll M, Soller L, Ben-Shoshan M, Harrington D, Fragapane J, Joseph L, et al: The use of incentives in vulnerable populations for a telephone survey: a randomized controlled trial. BMC Res Notes 2012;5:572.
12 O'Brien EM, Black MC, Carley-Baxter LR, Simon TR: Sensitive topics, survey nonresponse, and considerations for interviewer training. Am J Prev Med 2006;31:419–426.
13 Singer E, Kulka R: Paying respondents for survey participation; in Committee on National Statistics, National Research Council (eds): Studies of Welfare Populations: Data Collection and Research Issues. Washington, National Academy Press, 2002, pp 105–128.
14 Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al: Second symposium on the definition and management of anaphylaxis: summary report – second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med 2006;47:373–380.
15 Gordis L: Epidemiology, ed 4. Philadelphia, Saunders, 2009.
16 Baek JO, Hong S, Son DK, Lee JR, Roh JY, Kwon HJ: Analysis of the prevalence of and risk factors for atopic dermatitis using an ISAAC questionnaire in 8,750 Korean children. Int Arch Allergy Immunol 2013;162:79–85.
17 Lack G: Epidemiologic risks for food allergy. J Allergy Clin Immunol 2008;121:1331–1336.
18 Hassaine A, Clarke A, Alizadehfar R, Joseph L, Shand G, Ben-Shoshan M: Initial allergic reactions to fish and shellfish in children: clinical characteristics and treatment. J Allergy Clin Immunol 2012;129:AB169.
19 Grimshaw KE, Maskell J, Oliver EM, Morris RC, Foote KD, Mills EN, et al: Introduction of complementary foods and the relationship to food allergy. Pediatrics 2013;132:e1529–e1538.
20 Hansen TE, Evjenth B, Holt J: Increasing prevalence of asthma, allergic rhinoconjunctivitis and eczema among schoolchildren: three surveys during the period 1985–2008. Acta Paediatr 2013;102:47–52.
21 Duggan EM, Sturley J, Fitzgerald AP, Perry IJ, Hourihane JO: The 2002–2007 trends of prevalence of asthma, allergic rhinitis and eczema in Irish schoolchildren. Pediatr Allergy Immunol 2012;23:464–471.
22 Kolokotroni O, Middleton N, Nicolaou N, Pipis S, Priftis KN, Milton DK, et al: Temporal changes in the prevalence of childhood asthma and allergies in urban and rural areas of Cyprus: results from two cross sectional studies. BMC Public Health 2011;11:858.
23 Weiland SK, Husing A, Strachan DP, Rzehak P, Pearce N: Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. Occup Environ Med 2004;61:609–615.
24 Wavrin S, Bernard H, Wal JM, Adel-Patient K: Cutaneous or respiratory exposures to peanut allergens in mice and their impacts on subsequent oral exposure. Int Arch Allergy Immunol 2014;164:189–199.
25 Ben-Shoshan M, Soller L, Harrungton D, Knoll M, La Vieille S, Fragapane J, et al: Environmental and sociodemographic factors associated with food allergy: a nested case-control study. J Allergy Clin Immunol 2014;133(suppl):AB205.
26 Bohme M, Lannero E, Wickman M, Nordvall SL, Wahlgren CF: Atopic dermatitis and concomitant disease patterns in children up to two years of age. Acta Derm Venereol 2002;82:98–103.
27 Lack G, Fox D, Northstone K, Golding J: Factors associated with the development of peanut allergy in childhood. N Engl J Med 2003;348:977–985.

28 Fox AT, Sasieni P, Du TG, Syed H, Lack G: Household peanut consumption as a risk factor for the development of peanut allergy. J Allergy Clin Immunol 2009;123:417–423.
29 Perry TT, Conover-Walker MK, Pomes A, Chapman MD, Wood RA: Distribution of peanut allergen in the environment. J Allergy Clin Immunol 2004;113:973–976.
30 Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ: Atopic dermatitis and the atopic march revisited. Allergy 2014;69:17–27.
31 Monti G, Muratore MC, Peltran A, Bonfante G, Silvestro L, Oggero R, et al: High incidence of adverse reactions to egg challenge on first known exposure in young atopic dermatitis children: predictive value of skin prick test and radioallergosorbent test to egg proteins. Clin Exp Allergy 2002;32:1515–1519.
32 Palmer DJ, Metcalfe J, Makrides M, Gold MS, Quinn P, West CE, et al: Early regular egg exposure in infants with eczema: a randomized controlled trial. J Allergy Clin Immunol 2013;132:387–392.
33 Flohr C, Perkin M, Logan K, Marrs T, Radulovic S, Campbell LE, et al: Atopic dermatitis and disease severity are the main risk factors for food sensitization in exclusively breastfed infants. J Invest Dermatol 2014;134:345–350.
34 Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al: Application of moisturizer to neonates prevents development of atopic dermatitis. J Allergy Clin Immunol 2014;134:824–830.
35 Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH, et al: Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. J Allergy Clin Immunol 2014;134:818–823.
36 Ben Shoshan M, Kagan RS, Alizadehfar R, Joseph L, Turnbull E, St Pierre Y, et al: Is the prevalence of peanut allergy increasing? A 5-year follow-up study in children in Montreal. J Allergy Clin Immunol 2009;123:783–788.
37 Venter C, Hasan AS, Grundy J, Pereira B, Bernie CC, Voigt K, et al: Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. Allergy 2010;65:103–108.
38 Silverberg JI, Simpson EL, Durkin HG, Joks R: Prevalence of allergic disease in foreign-born American children. JAMA Pediatr 2013;167:554–560.
39 Wang HY, Wong GW, Chen YZ, Ferguson AC, Greene JM, Ma Y, et al: Prevalence of asthma among Chinese adolescents living in Canada and in China. CMAJ 2008;179:1133–1142.
40 Katz Y, Rajuan N, Goldberg MR, Eisenberg E, Heyman E, Cohen A, et al: Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. J Allergy Clin Immunol 2010;126:77–82.