Severe Food Allergies in Canada and Potential Demographic Predictors.

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Table of Contents

Abstract

Recent studies suggest an increased prevalence of food-induced allergy; peanut, tree nut, seafood and sesame cause most of the severe clinical manifestations of food allergy, i.e. anaphylaxis and death. However, estimates of severe food allergies vary considerably between studies and no population-based studies assessing the prevalence and potential demographic predictors of these allergies had been conducted in Canada. We aimed to determine the prevalence of peanut, tree nut, fish, shellfish, and sesame allergy in Canada and identify potential demographic predictors of these allergies. Using comparable methodology to Sicherer et al in the US (*JACI 2003;112:1203 & JACI 2004;114:159*), we performed a cross-Canada, random telephone survey. Food allergy was defined as either perceived (based on self-report), probable (based on convincing history or self-report of physician diagnosis), or confirmed (based on history and evidence of confirmatory tests). Data on demographic characteristics of participating households were collected and multivariate logistic regressions were used to assess potential determinants of probable allergies. Of 10,596 households surveyed in 2008 –2009, 3666 responded (34.6% participation rate), of which 3613 completed the entire interview, representing 9667 individuals. The prevalence of perceived peanut allergy was 1.00% (95% CI, 0.81%, 1.22%); tree nut, 1.22% (95% CI, 1.01%, 1.46%); fish, 0.51% (95% CI, 0.38%, 0.67%); shellfish, 1.60% (95% CI, 1.36%, 1.87%); and sesame, 0.10% (95% CI, 0.05%, 0.19%). The prevalence of probable allergy was 0.93% (95% CI, 0.75%, 1.14%); 1.14% (95% CI, 0.94%, 1.37%); 0.48% (95% CI, 0.35%, 0.63%); 1.42% (95% CI, 1.19%, 1.67%); and 0.09% (95% CI, 0.04%, 0.18%), respectively. Peanut, tree nut and sesame allergy were more common in children [odds ratio (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)]. Tree nut and shellfish allergy were less common in males [OR 0.55 (95% CI, 0.36, 0.83) and 0.63 (95% CI, 0.43, 0.91)]. Shellfish allergy was more common in urban settings [OR 1.55 (95% CI, 1.04, 2.31)]. There was a trend for most food allergies to be more prevalent in the more educated [tree nut OR 1.90 (95% CI, 1.18, 3.04)] and less prevalent in immigrants [shellfish OR 0.49 (95% CI, 0.26, 0.95)], but

wide CIs preclude definitive conclusions for most foods. Our results indicate disparities between perceived and confirmed food allergy and that age and sex, place of residence, socioeconomic status and birth-place may influence the development of food allergy.

Résumé

Les résultats d'études récentes suggèrent une prévalence accrue d'allergies d'origine alimentaire notamment aux arachides, aux noix provenant d'arbres, aux fruits de mer et au sésame, ces dernières causant les manifestations cliniques les plus graves, c.-à-d. l'anaphylaxie et la mort. Cependant, les estimations d'allergies alimentaires graves varient énormément d'une étude à l'autre. Par ailleurs, aucune étude de cohorte visant à évaluer la prévalence des facteurs prédictifs démographiques en cause dans ces allergies n'a été menée au Canada. Notre objectif est d'établir la prévalence des allergies aux arachides, aux noix provenant d'arbres, au poisson, aux mollusques et crustacés et au sésame au Canada et d'identifier les facteurs prédictifs démographiques qui y sont associés. À l'aide d'une méthodologie similaire à celle de Sicherer et coll. aux É.-U. (*JACI 2003;112:1203 et JACI 2004;114:159*), nous avons mené une enquête téléphonique aléatoire à travers le Canada. L'allergie alimentaire a été définie comme étant perçue (basée sur l'auto déclaration), possible (basée sur des antécédents convaincants ou l'auto déclaration du diagnostic du médecin) ou confirmée (basée sur les antécédents et sur la présence de tests de confirmation). Nous avons collecté auprès des ménages participants, des données sur les caractéristiques démographiques et des modèles de régression logistique multiple ont été utilisés pour évaluer les facteurs de risque potentiels associés aux allergies. Des 10 596 ménages sollicités en 2008 et 2009, 3666 ont répondu (taux de participation de 34,6 %). De ce nombre, 3613 ont complété l'entrevue, ce qui représente 9667 personnes. La prévalence de l'allergie aux arachides perçue était de 1,00 % (IC 95 %, 0,81 %, 1,22 %); celle de l'allergie aux noix provenant d'arbres de 1,22 % (IC 95 %, 1,01 %, 1,46 %); celle de l'allergie au poisson 0,51 % (IC 95 %, 0,38 %, 0,67 %); celle de l'allergie aux mollusques et crustacés de 1,60 % (IC 95 %, 1,36 %, 1,87 %); et celle de l'allergie au sésame de 0,10 % (IC 95 %, 0,05 %, 0,19 %). La prévalence d'une allergie possible était de 0,93 % (IC 95 %, 0,75 %, 1,14 %); 1,14 % (IC 95 %, 0,94 %, 1,37 %); 0,48 % (IC 95 %, 0,35 %, 0,63 %); 1,42 % (IC 95 %, 1,19 %, 1,67 %); et 0,09 % (IC 95 %, 0,04 %, 0,18 %) respectivement. Les

allergies aux arachides, aux noix provenant d'arbres et au sésame étaient plus répandues chez les enfants [rapports de cote (RC) 2,24 (IC 95 %, 1,40, 3,59), 1,73 (IC 95 %, 1,11, 2,68) et 5,63 (IC 95 %, 1,39, 22,87) respectivement] alors que les allergies au poisson et aux mollusques et crustacés étaient moins courantes chez les enfants [RC 0,17 (IC 95 %, 0,04, 0,72) et 0,29 (IC 95 %, 0,14, 0,61)]. Les allergies aux noix provenant d'arbres et aux mollusques et crustacés étaient moins répandues chez les hommes [RC 0,55 (IC 95 %, 0,36, 0,83) et 0,63 (IC 95 %, 0,43, 0,91)]. L'allergie aux mollusques et crustacés était plus courante en milieu urbain [RC 1,55 (IC 95 %, 1,04, 2,31)]. On a observé une tendance voulant que pour la plupart des allergies alimentaires, la prévalence soit plus importante auprès des populations bénéficiant d'un niveau de scolarité plus élevé [noix provenant d'arbres RC 1,90 (IC 95 %, 1,18, 3,04)] et moins importante chez les immigrants [mollusques et crustacés RC 0,49 (IC 95 %, 0,26, 0,95)]. Par contre, pour la plupart des aliments, la présence de larges IC ne permet pas de tirer des conclusions définitives. Nos résultats indiquent une disparité entre l'allergie alimentaire perçue et confirmée ainsi que le fait que l'âge et le sexe, le lieu de résidence, le statut socioéconomique et le lieu de naissance pourraient être en cause dans le développement d'une allergie alimentaire.

Preface

This thesis discusses the prevalence of peanut, tree nut, fish, shellfish and sesame allergy in Canada as well as potential demographic predictors. First, an introduction highlighting the importance of severe food allergies is given (chapter 1). To determine the prevalence of severe food allergies and understand the disparities in the published prevalence estimates, it is crucial to understand how the presence of food allergy is established through recognition of clinical symptoms and positive confirmatory tests. Hence, chapter 2.1, 2.2 and 2.3 provide a detailed overview of the classifications, clinical presentation and confirmatory tests used to diagnose severe food allergies. A review of our current knowledge regarding the prevalence of severe food allergies follows (chapter 2.4). Similarly, to assess the contribution of potential predictors to the development of food allergies, one needs to be able to recognize potential genetic and environmental factors; therefore, the current knowledge regarding genetic and environmental factors

associated with food allergies is presented in chapters 2.5, 2.5.1 and 2.5.2. An outline of the primary and secondary objectives of the thesis follows (chapter 3). Next, the study methodology (including study design, questionnaire and statistical analyses (chapter 4) and the results (chapter 5), summarized in two manuscripts, are presented. Finally, chapters 6 and 7 discuss the results (presented through 2 manuscripts) and concluding remarks are provided.

The following thesis has been prepared according the guidelines for a "Manuscript-Based Thesis".

Contribution of Authors

Moshe Ben-Shoshan MD - Study design (study design, adaptation of questionnaire and generation of new sections), **data collection** (specifically, reviewing participant responses for inconsistencies and re-contacting patients to clarify), **data analysis and interpretation** and **preparation of the manuscript**

Daniel Harrington BSc, MSc - Study design (under mentorship of Dr Elliott, assisted with study design and generation of additional sections in the questionnaire), **data collection** (conduct of interviews with participants), **data analysis and interpretation** and **preparation of critical revision of the manuscript**

Lianne Soller BSc - Data collection (supervised telephone interviews), **data analysis, interpretation** and **preparation of critical revision of the manuscript**

Joseph Fragapane BSc, MEng - Data collection (programming of CATI software), **analysis** and **interpretation** and **preparation of critical revision of the manuscript**

Lawrence Joseph PhD- Study design, data analysis and interpretation and **preparation of critical revision of the manuscript**

Yvan St. Pierre, MSc - Data analysis and interpretation and **preparation of critical revision of the manuscript**

Samuel B. Godefroy ,PhD - Study design (adaptation of questionnaire) and **preparation of critical revision of the manuscript**

Susan J. Elliott, PhD - Study design (adaptation of questionnaire and generation of risk perception questionnaire), **analysis and interpretation** and **preparation of critical revision of the manuscript**

Ann Clarke MD, MSc - Study design (led the study conception and design and participated in adaptation of questionnaire, generation of new questions and recruitment), **data collection** (queries), **analysis and interpretation** and **preparation of critical revision of the manuscript**

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Abbreviations:

SPT, skin prick test

FC, food challenge

Hx, History

CI, Confidence intervals

IQR, Interquartile range

OR, Odds Ratio

1.0 Introduction

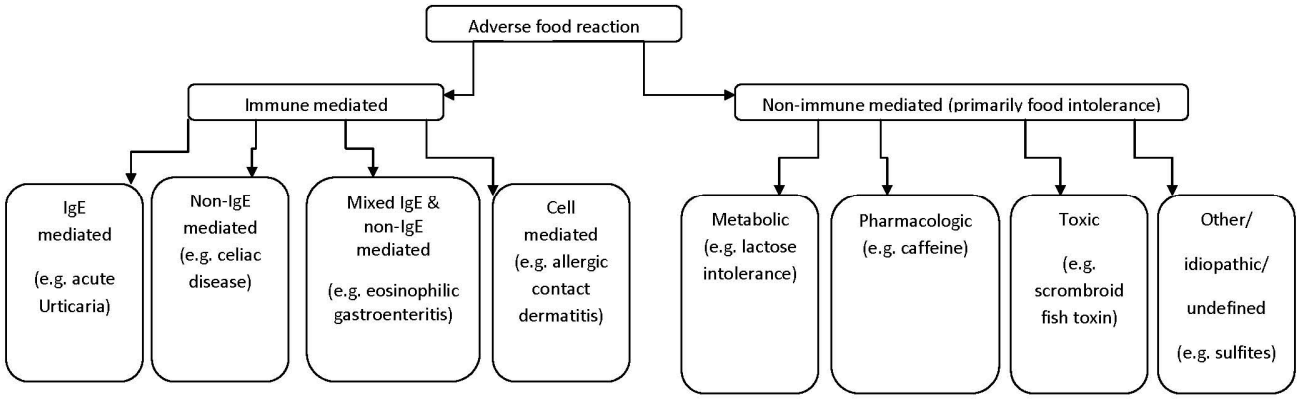
Anaphylaxis is a severe, life-threatening generalized hypersensitivity reaction [1;2] triggered mainly by food allergens and it accounts for 100–125 deaths/year in the US.[3-5] Recent studies suggest that the overall incidence rate of anaphylaxis is 49.8 per 100,000 person-years, which is higher than previously reported and that foods, mainly peanuts and nuts, continue to be major inciting agents (33.2% of reactions).[6] While peanuts and tree nuts account for more than 90% of the fatalities in North America,[5] fish, shellfish and sesame account for the majority of severe reactions in Asia,[7;8] parts of Europe [9] and the middle-east.[10] 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.[11] Food allergy in infancy increases the risk of not only other allergic diseases ('atopic march'), but also allergy to other foods ('food allergen march').[12] The fact that individuals with food allergies face food and social restrictions due to the potentially life-threatening nature of their disease inevitably impacts upon their quality of life.[13;14] Thus, correctly identifying patients with these severe food allergies, following them and managing their food allergy appropriately is crucial. This thesis will focus on peanut, tree nut, fish, shellfish and sesame allergies, their diagnosis, prevalence, and pathogenesis and potential demographic predictors of these food allergies in Canadians.

2. Literature Review

2.1 Classification

Adverse reactions to foods include non-immune and immune mediated reactions. Non-immune reactions are also referred to as food intolerances (including pharmacologic, enzymatic/metabolic, toxic and undefined reactions). Immune mediated hypersensitivity reactions are also referred to as food allergy. Food allergies can be IgE mediated, non-IgE mediated, mixed IgE and non-IgE mediated and cell mediated (Figure 1). [15;16] This thesis will focus only on IgE mediated food allergies.

Figure 1: Classification of adverse food reactions.



2.2 Clinical presentation

IgE mediated food allergy usually occurs within seconds to 2 hours after exposure. Several systems may be affected resulting in a range of clinical symptoms. Cutaneous symptoms include pruritus, urticaria and angioedema. Gastrointestinal symptoms include vomiting, diarrhea and abdominal cramps. Respiratory symptoms include breathing difficulties, wheezing, stridor and cyanosis and cardiovascular symptoms include hypotension, syncope and shock. [17-19]Anaphylaxis is the most severe clinical manifestation of an IgE mediated food allergy. Anaphylaxis symptoms primarily involve several organ systems including: the skin, causing mainly urticaria (80-90% of episodes), respiratory tract (70% of episodes), gastrointestinal tract (30-45% of episodes), cardiovascular (10-45% of episodes) and central nervous system (10-15% of episodes).[20;21] Symptoms may occur in a substantial part of the population in response to small amounts of the culprit food (e.g. 100mcg of peanut), making accurate declaration of the potential allergen content in prepackaged and prepared foods an absolute necessity. This is even more important in those with a history of severe reactions as they tend to react to lower doses than patients with mild symptoms.[22]

2.3 Establishing the diagnosis of food allergy

The diagnosis of food reactions can be challenging for both the patient and the clinician and requires corroboration of clinical history with appropriate confirmatory tests.

Confirmatory tests include skin prick tests (SPT), specific IgE levels and food challenges.[23-25]

A clinical history of a food allergy has only a 50% positive predictive value for clinical allergy.[26] In those with no previous peanut exposure or an uncertain clinical history, a single diagnostic test, such as a SPT or peanut-specific IgE level, may not be sufficient to establish the diagnosis.[27] Pucar et al have shown that only 31.3% of children who had no known peanut exposure and a positive SPT[28] were truly allergic to peanut. Furthermore, although the double-blinded placebo-controlled food challenge (DBPCFC) still represents the 'gold standard' for diagnosing food allergy, even it may sometimes be misleading. [29]

A SPT is usually performed by placing a drop of allergen extract on the skin and pricking it with a needle; histamine phosphate in 50% glycerin served as the positive control and 50% glycerosaline as the negative control. A SPT is defined as positive if the greatest diameter of the wheal was at least 3 mm larger than the negative control (saline) within 12 to 15 minutes of placement.[30] Sporik et al had reported that it was possible to identify a skin wheal diameter cut-off of 8 mm; at this level and above, negative reactions did not occur for peanut, although he also reported that positive reactions could occur with a skin wheal diameter of 0 mm.[31] Others have suggested a higher threshold of 13mm for SPT in peanut naïve children.[32] No similar SPT thresholds are currently reported for tree nut, fish, shellfish or sesame.

The serum level of food -specific IgE is usually measured by the CAP system Fluoroenzyme Immunoassay (Phadia AB Diagnostics, Uppsala, Sweden).[33;34] Current thresholds associated with 95% positive predictive values are based on studies conducted in the US, where recent prevalence estimates for peanut, tree nut and fish allergy were comparable to our current Canadian estimates. [35;36]

Diagnosis of food allergy based solely on SPT and/or IgE may be largely misleading.[37;38] In a recent population based study in Australia among 2848 infants (73% participation rate), the prevalence of any sensitization (based on positive SPTs) to peanut was 8.9% (95% CI, 7.9-10.0) and sesame, 2.5% (95% CI, 2.0-3.1). In contrast, the prevalence of challenge-proven peanut allergy was 3.0% (95% CI, 2.4-3.8) and sesame allergy, 0.8% (95% CI, 0.5-1.1).[39] Similarly, in a study conducted recently in Ghana, no

association was found between reported adverse reactions to food and SPT or specific IgE.[40]

The most reliable method to diagnose food allergy is the oral food challenge in which a potential food allergen is administered in gradually increasing doses under medical supervision. There are three types of oral food challenge: double-blind; placebo controlled (DBPC); single-blind; and open (in which the patient can recognize the target food without blinding).[41;42]The DBPCFC is recognized as the gold standard for the diagnosis of food allergy,[28;41;43] but it requires specialized facilities and trained personal, is costly and time consuming, and may trigger severe reactions.[41;43] The type of the challenge is determined by the clinical history, patient's age, and the likelihood of encountering subjective reactions. Open challenges are easier to perform and are considered safe and effective.[44] There is no international standardization for food challenges. In one approach, the total dose is 10g for dry foods, 20g for meat/fish and 100ml for wet food (e.g. apple sauce). The initial dose is usually 1% of the total dose with incremental doses given at intervals of 15 minutes. It has been suggested that once an amount of 8–10 g of dried food is tolerated during a DBPCFC, food hypersensitivity can be ruled out, but should be confirmed by a negative open challenge (i.e. no reaction to an open challenge).[41;45]

Diagnosis of food allergy in this research was based on a combination of history suggestive of allergy (as described in section 2.2 and 5.2) and confirmatory tests.

2.4 Prevalence (table 1).

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.[34;46-48] However, these initial estimates are based on studies conducted 3 decades ago[48;49] in relatively small communities[48;50] and do not represent a nation-wide sample. Further, the diagnostic algorithm did not consistently include confirmatory tests for IgE mediated reactions such as SPT and specific IgE levels and instead used elimination diets (i.e. exclusion diets to specific foods) that have inherent difficulties (mainly regarding choosing the elimination diet and the patient's compliance).[51] 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. More recent estimates of food allergy range between 3% to 35% for any food in the entire population.[52-54] The variability in estimated food allergy prevalence may be due to different methodologies used to estimate the presence of food allergies or different study populations. The least rigorous estimates are based on mere reports of food sensitization, while more rigorous studies are based on self-report of food allergy symptoms and corroboratory, confirmatory tests. The most rigorous estimates rely solely on DBPCFC, but these are usually restricted to a relatively small selective sample of patients.[19;53] In addition, it is clear that some of the disparities between prevalence estimates cannot be eliminated through the use of identical methodologies, potentially due to differences between populations studied as well as temporal changes in food allergy prevalence.[55;56]

Based on self-report, the prevalence of food allergy is 9.1% among adults in the US, with 5.3% of all respondents reporting a doctor-diagnosed food allergy[57] and the prevalence of self reported food allergy in children 0 to 17 years of age in the US is almost 4%.[58] Most of the studies based on self report of perceived food allergy seem to have overestimated the prevalence of food allergy compared with studies that include objective diagnostic tools.[52] In a meta-analysis published by Rona et al [52] in 2007, it was indicated that only a few reports included a DBPCFC for the diagnosis of food allergy and that these have provided estimates that differ substantially from those based on parental perception or self-report. A random sample survey of adults in the Netherlands had shown that although more than 10% of the population (12.4%) reported food allergy/ intolerance to specific food(s), when a DBPCF was performed, the prevalence of food allergy/ intolerance in the Dutch adult population was estimated to be as low as 2.4%.[59] This is in line with two recent studies. The first study conducted in Norway reveals that only a third of those reported by the parents as having milk allergy had a true milk allergy based on history and confirmatory tests. [60] In the second study conducted in Brazil, only 50% of those reporting symptoms attributed to milk allergy had a positive food challenge.[61] Similarly, in a recent random telephone survey conducted in Turkey in which individuals reporting food allergies were invited for a personal clinical investigation that included a DBPCFC, it was found that the lifetime prevalence of self-reported food allergy is 9.5% (95% CI, 8.94, 10.00%), decreasing to 0.3% (95% CI, 0.17,

0.36%) after the incorporation of clinical investigations, and to as low as 0.1% (95% CI, 0.05, 0.18%) based on DBPCFC only.[62]

Further, most of the studies suggesting increased prevalence of food allergies during the last decade are based on self-report. Studies in the US comparing the prevalence of self reported food allergies across 5 to 10 year periods, replicating the same methodologies, suggest that the prevalence of food allergy in general and peanut allergy in particular had increased significantly during the last decade. [36;58;63;64] These findings are in line with the National Health and Nutrition Examination Survey (NHANES) 2005-2006 estimates on a representative sample of the US population in which prevalence estimates were based on previously reported food specific IgE levels associated with a 95% positive predictive value for clinical allergy .[35] In the NHANES survey, food-specific serum IgE were measured to peanut, cow's milk, egg white and shrimp. Food-specific IgE and age-based criteria were used to define likely food allergy, possible food allergy, and unlikely food allergy and to develop estimates of clinical food allergy.[65] However, given that it was shown that clinical history is superior to specific IgE levels alone (or SPTs alone) in predicting food allergy, establishing the diagnosis of food allergy by using IgE levels alone may be insufficient.[66] Accordingly, studies conducted by our group and others combining clinical history with positive confirmatory tests suggest that the prevalence might have stabilized in recent years although it is still higher than previous reports.[67;68] However, studies conducted over longer periods of time in other countries establish a true increase in the prevalence of food allergies. 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. The results revealed that although the rate of parent-reported food allergy increased from 13.7% (1999 study) to 16.7% (2009 study), (95% CI for the difference crossing 0), positive SPT response was significantly higher in 2009 (18.0%) than in 1999 (9.9%) and the prevalence of confirmed food allergy (based on food challenge) increased markedly from 3.5% (1999 study) to 7.7% (2009 study).[69] In conclusion, based on current evidence, it is likely that to better estimate the prevalence of food allergies in population based studies, it is important to collect data not only on self reported food allergies, but also on

confirmatory tests and to incorporate both to generate an appropriate diagnostic algorithm.

2.4.1 Peanut allergy

Of the major peanut allergens, Ara h 1, [70] Ara h 2 [71] and Ara h 3,[72] Ara h 2 is considered the most clinically important peanut allergen that is recognized most frequently by IgE and basophils in individuals with peanut allergy.[73;74]

Peanut allergy is usually manifested in the first 2 years of life and about 75% of reactions occur with the first known peanut exposure.[75] Although less common, late onset peanut allergy occurring at a median age of 25 years has also been described.[76] Symptoms experienced during subsequent adverse peanut reactions may not be consistent with symptoms reported during initial reactions although the majority of those with subsequent reactions will experience potentially life-threatening symptoms.[77]

Although peanut allergy is similar to other allergies in that proper diagnosis requires corroboration of clinical history with confirmatory tests, we have recently shown that almost 20% of those who were never exposed to peanut or had an uncertain history were incorrectly diagnosed by a physician with peanut allergy without fulfilling even the least stringent diagnostic criteria.[23] This may lead to mislabeling of individuals with peanut allergy with subsequent dietary restrictions and reduced quality of life.[14;78] Other factors that place food-allergic patients in general and peanut allergic patients in particular at greater risk for a fatal anaphylactic episode include severe asthma, lower levels of angiotensin-converting enzyme concentrations and severe eczema.[79-81] Peanut allergy also serves as an early marker for asthma morbidity[82].

The prevalence of peanut allergy ranges from 0% to 2%.[52]Although studies suggest increased peanut allergy prevalence, we have recently reported a prevalence of 1.62% among Montreal school children that has stabilized during the last 5 years which is in line with other recent studies.[68;83] It is reported that 15% of children not having a reaction to peanuts in the past 2 years outgrow their peanut allergy.[84]

2.4.2 Tree nut allergy

Reactions to tree nuts may be either IgE mediated systemic reactions or manifestations of the pollen-food allergy syndrome [also known as oral allergy syndrome (OAS)]; the OAS refers to reactions confined to the oral mucosa (mainly itching of the oral cavity and/or lips and sometimes angioedema of the oral mucosa, tongue, palate or throat) in pollen-allergic patients with IgE cross reacting with heat labile allergens (found in raw fruits/vegetables and nuts) which can rarely progress to severe systemic reactions.[85;86] OAS is described in 47–70% of pollen-allergic individuals with fruit and vegetable ingestion.[87-89] However, to date no studies have evaluated the prevalence of potential OAS among those reporting tree nut allergy.

Severe manifestations of food induced allergic reactions are reported to be more common after ingestion of tree nuts compared with peanuts. [80] There is a 2.5% rate of co-allergy to peanut and tree nuts[64] which rises to 34% in atopic children.[90;91] Given that sensitization and allergy to multiple nuts increase with age (19% at 2 years to 86% at 5-14 years of multi-nut sensitization and 2% at 2 years to 47% at 14 years of multi-nut allergy), it was suggested by some that children with nut allergy should avoid all nut types from the onset.[92]

Peanut and tree nut allergy account for most severe food related allergic reactions in English speaking countries.[79;93;94] The highest prevalence estimate for perceived reactions to a specific tree nut was reported in Swedish adolescents: 4.1% to almond. The prevalence of perceived reactions to any nuts ranged from 0% to 7.3% (these include also peanut).[95]Tree nut allergy, like peanut and sesame allergy, is usually life-long and it was estimated that 9% of those not experiencing a reaction to tree nut in the past year will outgrow their allergy.[96]

Given the high likelihood that those with tree nut allergy will experience a severe allergic reaction, it is crucial to study both the prevalence and potential predictors of tree nut allergy in Canadians.

2.4.3 Seafood allergy

Seafood refers to both fish and shellfish; shellfish can be subdivided into crustaceans (mainly shrimps and crabs) and mollusks (e.g. oysters, clams, scallops).[97-102] There is

substantial cross reactivity within the fish family (up to 50%) and within the shellfish family (up to 75%) due to the presence of common major allergens.[103-106]

The prevalence of seafood allergy is higher in regions where seafood consumption is higher, e.g. Asia [7;107;108] and Spain,[9] and recent studies suggest increased consumption of seafood in the US and higher rates of seafood-induced anaphylaxis[109;110]. The clinical expression of seafood allergy includes immediate IgE mediated reactions after ingestion, contact or inhalation as well as late IgG, cellular or mixed immune mediated reactions.[97;102;111-116] A single study following a cohort of children with asthma reported that 17.2% not experiencing a reaction to fish in the past 2 years will outgrow their fish allergy,[117] although there are currently no estimates of the rate of shellfish allergy resolution.

It is important to differentiate between seafood allergy and seafood poisoning (scombroid poisoning and ciguatera fish poisoning) or an immune mediated reaction to parasites infesting fish.[118-124]Although seafood allergy is a major food allergy especially in adults, currently there are no data on the prevalence or potential predictors of seafood allergy in Canadians.

2.4.4 Sesame allergy

Several seed storage and oil body proteins in sesame seed have been identified as allergens.[125-127] Allergic individuals can experience anaphylactic shock to only a few milliliters of sesame oil containing sesame allergens known as oleosins.[128] Other oils shown to contain oleosins[129] such as peanut or soybean oil do not consistently provoke such severe reactions. Challenges with refined peanut and soy oils are regularly negative in adults, [130;131] but some studies suggest that in children, these may induce a reaction.[128] It is also noteworthy that falsely negative prick tests could be due to the lack of oleosins in presently available extracts, or to epitopes buried in the inner molecule.[127]

Sesame allergy may present as either immediate hypersensitivity, often expressed as systemic anaphylaxis, to sesame proteins with some cross-reactivity with other foods, or as delayed hypersensitivity to compounds in sesame oil leading to a contact allergic dermatitis.[132]

Sesame allergy is reported to cause severe reactions especially in Asia, the Middle East and parts of Europe where sesame consumption is relatively high.[132-134] The estimated prevalence of sesame allergy ranges between 0 and 0.79%.[54;133;135;136] The prevalence of sesame allergy in the US and Israel is similar and much lower than in the UK, potentially due to the fact that allergy is related not only to prevalence of consumption but also to age of introduction.[10;55;137] Thirty percent of those not experiencing a reaction to sesame in the past 2.8 years might outgrow their allergy.[132;138] Although it is suggested that sesame allergy is increasing,[139] no estimates of the prevalence of sesame allergy in Canadians have been reported.

Table 1. Studies on peanut, tree nut, shellfish, fish and sesame allergy prevalence

	Study	Country	Publication year	Food allergy prevalence	Data collection method	Comments	Reference number
Peanut	Emmett	UK	1999	0.48%	Self report	Peanut allergy prevalence in children (0-14 years) was higher compared to adults(15-44) (0.61%, 95%CI, 0.41%,0.82% vs 0.53%, 95%CI,0.41%,0.66% respectively) Peanut allergy commoner in those reporting other atopies	(140)
	Tariq	UK	1996	0.5%	Self report, SPT	Cohort of children (age 4 years) born on the Isle of Wight in 1989	(141)
	Grundy	UK	2002	1.4%	Self report, SPT, FC	Cohort of children (age 3-4 years) born on the Isle of Wight in between 1994 and 1996	(142)
	Venter	UK	2010	1.2%	Self report, SPT, FC	Cohort of children (age 3 years) born on the Isle of Wight between 2001 and 2002	(68)
	Du Toit	UK	2008	1.85%	Self report, SPT, IgE , FC	Jewish children 4-18 years old	(135)
	Du Toit	Israel	2008	0.17%	Self report, SPT, IgE, FC	Jewish children 4-18 years old	(135)
	Dalal	Israel	2002	0.04%	Self report, SPT	Infants (0-2 years)	(133)
	Sicherer	US	1999	0.4%	Self report	Children (less than 18 years old) based on a random digital phone survey of US population	(143)
	Sicherer	US	2003	0.8%	Self report	Children (less than 18 years old) based on a random digital phone survey of US population	(144)
	Sicherer	US	2010	1.40%	Self report	Children (less than 18 years old) based on a random digital phone survey of US population	(55)
	Liu	US	2010	1.3%	IgE	1.8% for those 1-5 years old , 2.7% for those 6-19 years old and 0.29% for those 60 and older	(65)
	Kagan	Canada	2003	1.50%	Self report, SPT, IgE	Montreal school children 5-9 years old	(145)
	Ben-Shoshan	Canada	2009	1.62%	Self report, SPT and IgE	Montreal school children 5-9 years old	(83)
	Osborne	Australia	2011	3.0%	Self report, SPT, specific IgE IgE,FC	1 year old infants	(39)
	Kotz	2011	UK	0.05%	All	GP-recorded diagnosis of peanut allergy The highest rates were found in boys 5 to 9 years old (0.251%) and girls (0.207%)	(146)
	Shek	2010	Singapore	0.47%,	Self report	Children 14-16 years old and 0.64 % in those 4-6 years old	(147)

						But up to 1.29% in Singapore expatriates 4-6 years old (1.12% in expatriates 14-16 years old)	
	Shek	2010	Philippines	0.43%	Self report	Children 14-16 years old	(147)
Tree nut	Sicherer	US	1999	0.20%	Self report	Children less than 18 years old	(143)
	Sicherer	US	2003	0.50%	Self report	Children less than 18 years old (0.66% for all and 0.74% in adults)	(144)
	Sicherer	US	2010	1.10%	Self report	children less than 18 years old	(55)
	Dalal	Israel	2002	0.02%	Self report, SPT	Infants 0-2 years old	(133)
	Du Toit	UK	2008	1.95%	Self report, SPT, IgE, FC	Jewish children 4-18 years old	(135)
	Du Toit	Israel	2008	0.13%	Self report, SPT, IgE, FC	Jewish children 4-18 years old	(135)
	Shek	2010	Singapore	0.30%	Self report	Children 14-16 years old (0.28% in those 4-6 years old) But up to 1.29% in Singapore expatriates 4-6 years old (1.12% in expatriates 14-16 years old)	(147)
	Shek	2010	Philippines	0.33%	Self report	Children 14-16 years old	(147)
Fish	Sicherer	US	2004	0.39	Self report	All	(63)
Shellfish	Sicherer	US	2004	2.03%	Self report	All. For children : 0.52% vs 2.54% for adults	(148)
	Liu	US	2010	1.0%	IgE	Prevalence of 1.1% for children 5-16 years old with no substantial change with age	(65)
	Osborne	Australia	2011	0.4%	SPT	Sensitization to shellfish in a random sample of 1 year old infants	(39)
	Shek	2010	Singapore	5.23%	Self report	Children 14-16 years old (1.19% in those 4-6 years old Vs 0.96% in expatriate children 14-16 years old (0.55% in expatriates 4-6 years old)	(147)
	Shek	2010	Philippines	5.12%	Self report	Children 14-16 years old	(147)
Sesame	Dalal	Israel	2002	0.18%	Self report, SPT	Infants 0-2 years	(133)
	Du Toit	UK	2008	0.79%	Self report, SPT, IgE, FC	Jewish children 4-18 years old	(135)
	Du Toit	Israel	2008	0.13%	Self report, SPT, IgE, FC	Jewish children 4-18 years old	(135)
	Osborne	Australia	2011	3.0%	Self report, SPT , IgE, FC	Infants 1 year old	(39)

SPT, Skin Prick Test; FC, Food Challenge; GP, General Practitioner

2.5 Pathogenesis

Regardless of the process leading to sensitization to food allergens, all IgE mediated food allergies share the same common final pathway. Food allergens are presented by antigen presenting cells that interact with Th2 cells that promote the transformation of B cells to IgE producing cells. Allergic reactions occur as a result of an interaction between allergen and mast cells via the antibody immunoglobulin E (IgE).[17;149] This interaction results in the release of preformed mediators from mast cells such as histamine, heparin, tryptase, chymase, carboxypeptidase A3, TNFα (Tumor Necrosis Factor alpha) and cathepsin G and newly formed mediators such as PAF (Platelet Activating Factor), PGD_2 (Prostaglandin D2), leukotriene C_4, cytokines such as IL (Interleukin)-5, IL-6, IL-8, IL-13, TNFα, and GM-CSF (Granulocyte Macrophage Colony Stimulating Factor) and chemokines such as MIP (Macrophage Inflammatory Protein)-1α, MIP-1β, and MCP (Monocyte Chemoattractant Protein)-1 [150] and possibility also activated kallikrein.[2;151]

Tolerance is defined when a person is believed to be able to consume the food safely.[152] Food antigens delivered through the oral route usually induce a tolerogenic or regulatory immune response. To initiate allergic sensitization, food allergens need to breach the normal gut barriers, induce signals by dendritic cells and other cells for Th2 differentiation and overcome tolerance mechanisms. [153;154]

2. 5.1 Factors associated with the development of food allergies.

It is suggested that processes inducing tolerance versus allergy are affected by genetic and environmental factors and potentially by gene-environment interactions although currently very few studies have established the potential contribution of these factors.

a. Genetic effects (table 2)

Animal models have clearly shown that there is a genetic selection for susceptibility/resistance to oral tolerance.[155] 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 study on 581 nuclear families (2,004 subjects) in Chicago, IL, 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)=2.6, 95% CI, 1.2,5.6]. 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 tested in this sample (sesame, peanut, wheat, milk, egg white, soy, walnut, shrimp and cod fish).[156] 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.[157]These results are in line with other studies in the US [158]and Europe[159] suggesting 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[160;161] and Serine Pprotease Inhibitor Karzal type 5 (SPINK5) [162;163]] and genes involved in innate [including Nucleotide-binding domain and Leucine-rich Repeat-containing family Pyrin domain containing 3 (NLRP3) [164] and CD14 [165]] and adaptive immunity [e.g. The Signal Transducers and Aactivators of Transcription 6 (STAT-6) [166;167], Forkhead bOX P3 (FOXP3) gene, [168], IL-10[169-171] and IL-13[172]].

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 even independently of the presence of atopic dermatitis (OR: 1.9; 95% CI, 1.4,2.6).	(161)
	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).	(163)
Innate immunity genes	NLRP3: SNPs (rs4612666 and rs10754558)	NLRP3 controls the activity of inflammasomes. NLRP3 SNPs (rs4612666 and rs10754558) were significantly associated with susceptibility to food-induced anaphylaxis (P = .00086 and P = .00068, respectively).	(164).
	CD-14	CD14 gene codes a lipopolysaccharides 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).	(165)
Adaptive immunity	STAT6	Key transcription factor involved in both IL-4- and IL-13-mediated biological responses. Dinucleotide repeat polymorphism of the STAT6 exon 1 (13/15-GT 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).	(166;167)
	FOXP3	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.	(168)
	IL10	IL-10 A-1082G gene polymorphism is associated with food allergy susceptibility (OR: 2.5 ;95% CI, 1.0, 6.4 vs atopic control subjects).	(171)
	IL13	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).	(172)

SPINK5,Serine Protease Inhibitor Karzal type 5 ;NLRP3, NLR(Nucleotide-binding domain and Leucine-rich Repeat-containing) family Pyrin domain containing 3; SNP, Single-Nucleotide Polymorphism ; STAT-6, Signal Transducers and Activators of Transcription 6;FOXP3, Forkhead bOX P3 IL,Interleukin;.

b. Environmental effects (table 3).

Season: It is suggested that food allergy is more common in those born in the fall or winter potentially due to reduced UV-B exposure and subsequent lower levels of vitamin D generation during a vulnerable period of immune development. It was reported that children younger than 5 years born in the fall or winter had a 53% higher odds of food allergy compared with controls.[173] 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 allergies,[173;174] or adjuvant effects of winter time infection on the development of food allergies.[173;175]

Drugs: It is 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.[176] In an observational cohort study of 152 adult patients from a gastroenterological outpatient clinic with negative case histories for atopy or allergy who were medicated with H2-receptor blockers or proton pump inhibitors for 3 months, 10% of the patients showed a boost of preexisting 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 10.5 (95%CI, 1.44,76.48). The authors also found that 5 months after stopping treatment, food-specific IgE could still be measured in 6% of the patients.[176]

Microbial exposure: Several hypothesis suggest a crucial role of the microbacterial environment in the pathogenesis of Th2 responses (the hygiene hypothesis) emphasizing the route of antigen exposure as the crucial factor in the development of allergic reactions.[177]

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

(1) Bacteria can enhance the integrity of the intestinal barrier.[178;179]

(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.[180] In contrast, pathogen-associated molecular patterns rich environment induces high-level

PRRs activation that results in allergen presentation with IL-12 secretion, leading to Th1/T reg responses to allergen, without allergic sensitization.[180;181]

These hypothesis 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 allergies.[182] However, the bibliographical 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.[182]

Food consumption (quantity and timing): It is proposed that allergic sensitization to food can occur through low-dose cutaneous sensitization while early consumption of food protein induces oral tolerance.[137;174;183]

Low-dose exposure to environmental foods (on tabletops, hands, and dust) penetrates the skin barrier and is 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.[174] In contrast to previous American Academy of Pediatrics recommendations and case control studies[184;185] suggesting that early food exposure leads to food allergy, more recent cross sectional [135;186;187] and cohort studies [188;189] suggest that late introduction of potential food allergens is associated with allergy while early oral exposure is associated with tolerance. 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'.[190]

Food processing: Food processing (e.g. heating or vinegar addition) may affect food allegencity either by decreasing [191;191-193] or increasing allergencity.[194-196]

Vitamin D: There is growing interest in the potential role of sunlight/vitamin D status on allergic conditions. However, while some ecological studies suggest a protective effect of vitamin D on the development of food allergies, [197-199] others fail to

substantiate this association; some even suggest an inverse effect, i.e. high levels of vitamin D are associated with increased food allergy risk.[200]

c. Atopy:

Atopy, defined as the presence of either atopic dermatitis, allergic rhinitis, asthma, or food allergy [201] is common in subjects who experience anaphylaxis, regardless of its origin.[202] The extracellular cytokine milieu associated with atopic diseases may contribute to the increased risk of an anaphylactic reaction.[203;204] Although some studies suggest that atopy does not confer an additional risk of anaphylaxis, the majority of studies report a strong association between food allergy and atopy.[205;206] 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 (3.8; 95% CI,1.5,10.7) and an emergency department visit for asthma in the past year (6.9; 95% CI, 2.4,19.7) were both notably increased.[65] Similarly, studies conducted in Europe[140] and Asia[207] suggest 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 allergies. [208]

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 with controls.	(173)
Drugs	Palli-Scholl	Case control	The relative risk to develop food-specific IgE after anti-acid therapy was 10.5 (95% CI,1.44,76.48).	(176)
Microbial exposure	Gourbeyre	Review of case control and cohort studies	No clear conclusion regarding probiotic beneficial effects on the prevention or treatment of allergy .	(182)
Food consumption (quantity and timing)	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 (≥7 months: adjusted OR: 3.8; 95% CI, 1.18,12.28)	(187)
	Du Toit	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 ($P < .0001$). By 9 months of age, 69% of Israelis were eating peanut compared with only 10% of UK infants.	(135)
	Katz	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 < .001) vs those introduced to cow milk protein before 15 days.	(189)
	Joseph	Cohort	Early feeding reduced the risk of peanut sensitization among children with a parental history [adjusted OR, 0.2 (95% CI, 0.1,0.7); P = .007]. The relationship also became significant for egg when a cutoff for IgE of ≥0.70 IU/mL was used [adjustedOR, 0.5 (95% CI, 0.3,0.9)].	(188)
	Koplin	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)].	(186)
	Des Roches	Case control	The reported consumption of peanuts 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].	(185)
	Sicherer	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 ≥5 kUA/L.	(209)

Food processing	Chung	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.	(210)
	Yadzir	Laboratory analysis	Extracts from raw shrimp bound higher IgE than extracts from boiled shrimp, but the purified boiled tropomysoin (the main shrimp allergen) demonstrates higher IgE binding vs raw shrimp.	(211)
	Samson	Laboratory analysis	Thermal processing can lead to the formation of new antigenic structures.	(196)
Vitamin D	Milner	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)].	(200)
	Cramago	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)]	(197)
	Mulins et al	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 , −11.73)].	(198)
	Mulins et al	Ecologic study	Southern latitudes were associated with higher hypoallergenic formulae prescription rates [beta, -147.98(95% CI,-281.83 , -14.14)].	(199)

OR, odds ratio;RR, Relative Risk; CI,confidence interval ;CMA, Cow's Milk Allergy

d. Demographic factors (table 4).

Very few studies report on demographic predictors of food allergies and none have been conducted in Canada. Among those that do examine potential predictors, the following factors have been associated with food allergy:

Age: World-wide, food allergies are 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 allergies in more recent cohorts. In a recent US study, estimates of food allergy, based on IgE levels,[65] 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. These findings suggesting that peanut, tree nut and sesame allergy are more common in children, while shellfish allergy (and in other studies, also fish allergy) is more common in adults are in line with other US studies.[55;65;148] However, in Asia, shellfish allergy is reported to be the leading cause in children as well (table 4).[212] Further, while in the US, peanut and milk allergies are most common in children and tree nut and fruit/vegetable allergies are most common in adolescents,[213] studies in Asia suggest peanut is a rare cause in infants.[214]

Gender: In adults, anaphylaxis is more common in females.[6;215;216]However, in studies estimating anaphylaxis incidence in children, males predominate.[65;217] Studies suggest that this trend is true also for food allergies, i.e. in children; food allergies are more common in males, while in adults, females predominate.[146;213] This could be related to higher estrogen levels in women that are suggested to lead to enhanced mast cell activation and allergic sensitization and/ or due to progesterone inhibiting histamine release, but potentiating IgE induction.[216;218]

Race/ ethnicity: It is reported that non-Hispanic black race/ethnicity have increased odds for food allergy once socioeconomic status and education are controlled (table 4).[65]

In a prospective UK study that involved 76 children with IgE mediated food allergy presenting consecutively to a Paediatric Allergy Clinic, it was found that ethnic minorities are over-represented in terms of the number of children with food allergy (when compared to the General Paediatric Clinics serving the same population) and number of food allergies per child; they also present at an earlier age with food allergy, and possibly have a greater variety of food allergies compared with Caucasians (table 4). However, the authors did not control for potential cultural differences in dietary habits and life style that could affect the development of food allergies.[219]

Socioeconomic factors: Studies suggest an increased number of food allergies in higher socioeconomic populations [146;215;220] and with smaller sibship size.[221]

Although the recent NHANES study indicates higher levels of food sensitization and likely clinical food allergies in individuals living in poverty compared to those with higher income households,[65] the 95% CI for the effect reported in this study crosses 1 (table 4). Further, food allergy estimates in this study were based primarily on IgE levels and the conclusions might have differed had food allergy reflected clinical allergy.

Education: Some studies suggest that higher education level is associated with a lower prevalence of food allergies while other studies suggest the opposite, .i.e. high education level is associated with higher prevalence of food allergies .In the NHANES study, given the 95%CI (table 4) for education cross 1, there was no conclusive effect of education on the prevalence of food allergy although the authors suggest that food sensitization is higher in households with less educated participants.[65]Other studies report that in the highly educated, allergy is more common (table 4) although the latter used any self reported allergy (including asthma and allergic contact dermatitis) as the outcome of interest and did not define specifically the association with food allergies.[222] Hence, further studies are required to better define the association between level of education and food allergy.

Immigrants: Very few studies explore the relationship between being an immigrant and the presence of food allergies. In general, studies suggest an increased prevalence of allergic diseases (mainly asthma) that correlate with the length of stay in Westernized countries regardless of age at arrival, sex or atopic status.[223;224] In a study estimating food allergies 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.[147]

Geography: Recent studies suggest higher rates of anaphylaxis in northern versus southern areas. These are based on epinephrine auto-injector distribution data [199] or diagnostic billing codes. [225] It has been suggested that this north-south gradient might be due to differences in vitamin D status.[198] 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.[226]In addition, studies suggest a lower prevalence of allergic diseases in general (according to self-report) in rural versus urban environments,[227;228] although no studies have assessed that association for specific food allergies. In addition, studies suggest that food allergy may differ not only according to north-south gradients but also in different countries located in similar latitudes. These differences may be due to differences in life style including different dietary habits. Thus, while in the US, allergies to milk, egg, and peanut are more common in children,[55;65;148] in Asia, shellfish allergy is reported to be the leading cause of food allergies [212] and peanut is a rare cause in infants .[214] The crucial role of life style is reflected by the change in allergy prevalence in general and food allergy in particular in Asian immigrants that is commensurate with the length of stay in westernized countries. [147;223;224]

Based on the review above 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 allergies are more common in females. However, the association between food allergy and race/ethnicity, socioeconomic status, education, immigration status and geographic location is not well established.

Table 4.Demographic factors associated with food allergies

Factor	Study	Study design	Comments	Reference number
Age	Sicherer	Cross sectional	Self-report peanut allergy 1.4% for children and 0.6% for adults.	(55)
	Liu	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.	(65)
	Leung	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%).	(212)
	Rudder	Cross sectional	Peanuts and milk were more common food triggers in infants, whereas adolescents more frequently reported reactions to tree nuts, and fruits/vegetables	(213)
	Chen	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.	(214)
Gender	Rudder	Cross sectional	Patients were predominantly male in younger age groups; however, females represented approximately half (52%) of the adolescents.	(213)
	Kotz	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).	(146)
	Liu		Food sensitization and estimated clinical food allergy 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).	(65)

Race Ethnicity	Liu	Cross sectional	OR for non-Hispanic black vs non-Hispanic whites was: 3.06 (2.14, 4.36).	(65)
	Dias	Prospective	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).	(219)
Socioeconomic status	Sheikh	Cohort	Analysis of 2323 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).	(215)
	Kotz	Cross sectional	Highest prevalence of peanut allergy found in the most affluent group.	(146)
	Liu	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.	(65)
Education	Liu	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).	(65)
	Pawlinska-Chmara	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.	(227)
Immigrants	Shek	Cross sectional	The prevalence of peanut allergy in those born in Singapore aged 14-16 years old was 0.47% and 0.64 % in those 4-6 years old ,but up to 1.29% (4-6 years old) and 1.12% (14-16 years old) in Singapore expatriates.	(147)
Geography	Cramago	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)]	(197)
	Mulins	Ecologic study	Using multivariate analysis , EpiPen prescription rates were higher in southern latitudes (less sunlightcompared with northern regions (β, −19.22; 95% CI, −26.71 to −11.73; *P* < .001).	(198)
	Mulins	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].	(199)

3. Study objectives

3.1 Overall objectives

Given the apparent, yet unexplained, increase in food allergy[55;142;229] and the knowledge gaps regarding the societal burden and potential predictors of food allergies, we aim to determine the prevalence of peanut, tree nut, fish, shellfish, and sesame allergy in Canada and identify potential demographic predictors of these allergies. Our study addresses the following primary and secondary research questions:

3.2 Primary objective

What is the prevalence of peanut, tree nut, shellfish, fish and sesame allergy in Canada and how are these allergic individuals diagnosed and treated?

3.3 Secondary objectives

1. What are the demographic predictors of food allergies?
2. What subgroups or populations of Canadians are more likely to have food allergies?

4. Study methodology

4. 1 Study design

To address our research questions, we conducted a nationwide cross-sectional telephone interview of households. Our survey was a modified version of a validated telephone survey shared with us by Dr. Scott Sicherer of Mount Sinai Hospital in New York City who has conducted general population surveys on food allergy prevalence in the US .[64;148;230] The territories were excluded as we anticipated that there are likely to be considerable cultural differences between individuals living in these regions and those in the rest of Canada. Households were selected through a random selection of telephone numbers from the electronic white pages (done by Info-Direct) given that sampling from the white pages is more efficient and much less costly than random digit dialing; although the directory database excludes unlisted numbers, random digit dialing generates many non-functional, business, and fax numbers. This process should ensure age and gender representativeness in a general population sample. Persons living within households

without telephones (2% of the Canadian population) were excluded as well as those having cellular telephone service only (less than 5% of the population) [231] as public access to these numbers is currently not permissible in Canada because cell users incur charges for incoming calls.[232] Full methodological details on sampling frame and survey are provided in the manuscripts. However, additional methodological details which were felt to be too lengthy to be included in the manuscript are provided here.

4.2 Sample size calculations

Given that we have estimated the prevalence of peanut allergy in Montreal [83;145]and data already exist on the prevalence of tree nut, shellfish, and fish allergy in the United States,[55;64;148;230] it is most accurate to base our sample size calculation on these data. These data indicate that the prevalence of peanut allergy is 2.0 % (95% CI, 1.4%, 2.7%), the prevalence of tree nut allergy is 0.5%, the prevalence of shellfish allergy is 2.0% (95% CI, 1.8%, 2.3%), and the prevalence of fish allergy is 0.4% (95% CI, 0.3%, 0.5%). Hence, assuming the prevalence of these allergies in the general Canadian population is similar to these estimates, a sample of approximately 9000 individuals (or 3000 households assuming there are 3 persons per household) will enable us to estimate the prevalence of peanut allergy to within ± 0.30%, nut allergy to within ± 0.15%, shellfish allergy to within ± 0.30%, and fish allergy to within ± 0.175 % using 95% CIs.

4.3 Statistical Analysis

The point estimate and associated variance for the overall prevalence of specific food allergies will be calculated using standard formulae [233] and 95% CIs constructed. The point estimate will initially be based on the observed fraction of allergic participants of the total number of participants who completed the questionnaire. Given that the observations within a cluster (i.e. household) may not be treated as independent, but the clusters themselves are independent, we will compute a robust variance estimator to account for clustering within households while accounting for the contribution of each individual cluster.[234;235] In this thesis, all statistical analysis was performed using STATA Version 9.

4.4 Ethics approval

All appropriate ethics reviews and approvals were obtained before beginning this study.

The study was approved by the Institutional Review Boards of the McGill University Health Centre and McMaster University on February 2008. Additionally, a letter of support for this project was obtained from Dr Scott Sicherer of the Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine, New York.

5. Study results

5.1 Preface

The results of this thesis are presented in two manuscripts (Sections 5.2 and 5.3). The manuscripts include:

Ben-Shoshan M, Harrington DW, Soller L, Fragapane J, Joseph L, St Pierre Y, Godefroy SB, Elliott SJ, Clarke AE. **A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada**. (J Allergy Clin Immunol. 2010 Jun;125(6):1327-35. Epub 2010 May 7.)

Ben-Shoshan M, Harrington DW, Soller L, Fragapane J, Joseph L, St Pierre Y, Godefroy SB, Elliott SJ, Clarke AE. **Demographic Predictors of Peanut, Tree Nut, Fish, Shellfish and Sesame Allergy in Canada.** Submitted to *Journal of Allergy.*

The first manuscript (Section 5.2) addresses the primary objectives and provides estimates of perceived, probable and confirmed peanut, tree nut, fish, shellfish and sesame allergy. The second manuscript assesses potential demographic predictors of food allergy, thus addressing the secondary objectives.

5.2 Manuscript 1 : A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada

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Word Count: 3,363

Abstract:

Background: Recent studies suggest an increased prevalence of food-induced allergy and an increased incidence of food-related anaphylaxis. However, prevalence estimates of food allergies vary considerably between studies.

Objectives: To determine the prevalence of peanut, tree nut, fish, shellfish, and sesame allergy in Canada.

Methods: Using comparable methodology to Sicherer et al in the US (*JACI 2003;112:1203 & JACI 2004;114:159*), we performed a cross-Canada, random telephone survey. Food allergy was defined as either perceived (based on self-report), probable (based on convincing history or self-report of physician diagnosis), or confirmed (based on history and evidence of confirmatory tests).

Results: Of 10,596 households surveyed in 2008 –2009, 3666 responded (34.6% participation rate), of which 3613 completed the entire interview, representing 9667 individuals. The prevalence of perceived peanut allergy was 1.00% (95% CI, 0.80%, 1.20%); tree nut, 1.22% (95% CI, 1.00%, 1.44%); fish, 0.51% (95% CI, 0.37%, 0.65%); shellfish, 1.60% (95% CI, 1.35%, 1.86%); and sesame, 0.10% (95% CI, 0.04%, 0.17%). The prevalence of probable allergy was 0.93% (95% CI, 0.74%, 1.12%); 1.14% (95% CI, 0.92%, 1.35%); 0.48% (95% CI, 0.34%, 0.61%); 1.42% (95% CI, 1.18%, 1.66%); and 0.09% (95% CI, 0.03%, 0.15) respectively. Due to the infrequency of confirmatory tests and the difficulty in obtaining results if performed, the prevalence of confirmed allergy was much lower.

Conclusions: This is the first nationwide Canadian study to determine the prevalence of severe food allergies. Our results indicate disparities between perceived and confirmed food allergy that might contribute to the wide range of published prevalence estimates.

Clinical Implications: Guidelines regarding increased use of confirmatory tests in general and food challenges in particular should be disseminated and might contribute to a more accurate diagnosis in those reporting food allergies.

Capsule Summary: This is a nationwide Canadian study on the prevalence of severe food allergies. Our results indicate disparities between perceived and confirmed food allergy that might contribute to the wide range of published prevalence estimates.

Key words: food allergy; peanut allergy; tree nut allergy; fish allergy; shellfish allergy; sesame allergy; perceived food allergy; probable food allergy; confirmed food allergy.

Abbreviations:

SPT, skin prick test

FC, food challenge

Hx, History

CI, Confidence intervals

IQR, Interquartile range

Introduction

Food allergy affects up to 2.5% of the adult population and 6–8% of children less than 3 years of age, and is associated with significant morbidity and mortality.[49;236] The incidence rate of anaphylaxis is increasing and recent US reports suggest that it may be as high as 49.8 per 100,000 person-years.[237-242] Foods are primary inciting allergens for anaphylaxis[229;242-245] and hospitalizations due to food-induced anaphylaxis are reported to have increased by 350% during the last decade.[229;246]

Peanut and tree nut account for the majority of severe reactions,[229;244;247] but fish, shellfish and sesame are also reported to cause severe reactions especially in Asia and parts of Europe.[133;212;245;248-251] However, there is considerable heterogeneity in the prevalence estimates of these severe food allergies, possibly due to differences in study design, methodology or study populations. The prevalence estimates of food allergies range between 0-2% for peanut,[53;83;143] 0-7.3% for tree nut,[54;143;252;253] 0-2% for fish,[53;148;254] 0-10% for shellfish,[53;148;253;255;256] and 0-0.79% for sesame.[54;133;135;136] There

have been a few population-based studies estimating the prevalence of peanut, tree nut, fish, and shellfish allergies in the US,[143;148] but no such studies have been conducted in Canada. Recently, our research team reported that the prevalence of peanut allergy in Montreal school children had stabilized between 2002 and 2007, although it exceeded [1.63% (95% confidence interval (CI), 1.30%, 2.02%)] estimates from most other countries, except the UK.[83]

The SCAAALAR study (**S**urveying **C**anadians to **A**ssess the Prevalence of Common Food **A**llergies and **A**ttitudes towards Food **LA**belling and **R**isk), launched in 2008, was designed to estimate the prevalence of food allergies responsible for the majority of severe/fatal anaphylactic reactions (peanut, tree nut, fish, shellfish, and sesame) in Canada.

Methods

Selection of study population

Households were chosen by purchasing, from Info-Direct, a random selection of telephone numbers and their accompanying addresses from the electronic white pages. (Info-Direct maintains an electronic listing of all Canadian household telephone numbers listed in the white pages and updates these records monthly). Households were limited to the ten Canadian provinces; the territories were excluded because it was thought that there would be considerable cultural difference between individuals living in these regions and the rest of Canada. Interviews were conducted from May 2008 to March 2009.

Survey methodology

The telephone surveys were conducted by teams of similarly trained interviewers, based at either McGill (Montreal, Quebec) or McMaster (Hamilton, Ontario) Universities, using Computer Assisted Telephone Interview (CATI) software (WinCati 4.2, Copyright 1986-2004 Sawtooth Technologies Inc, Northbrook, Illinois). Respondents were eligible to participate if they were 18 years or older, were living in the household, and appeared to have no language-mental-hearing barriers. The initial age-eligible household respondent was invited to participate and asked whether any household member had an allergy to peanut, tree nut, shellfish, fish, 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 not eligible or was unavailable at the time of the interview) on symptoms related to ingestion of the food and diagnosis and management of the allergy. If no food allergy was reported in the household, demographic data were obtained. In addition, data on attitudes towards food labeling for allergens and the societal risk associated with food allergy were also collected (results of the latter will be described in subsequent manuscripts).

To optimize response rates and minimize bias, a maximum of 10 attempts were made to contact households during different days and times between the hours of 9:30 AM to 9:00 PM (local time) Monday through Friday and 10:30 AM to 5:00 PM (local time) on Saturdays and Sundays. In addition, households were advised that we were conducting a survey on food allergies a few weeks in advance by a mailed information letter.[257]

The study was approved by the Institutional Review Boards of the McGill University Health Centre and McMaster University.

Questionnaire

We used a standardized questionnaire developed previously by Sicherer et al to determine the general population prevalence of peanut, tree nut, fish and shellfish allergy[143;148] in the US, and modified it to incorporate questions regarding sesame allergy. In addition, in cases in which respondents reported that the allergy was diagnosed by a physician, we requested permission to obtain confirmatory information from the physician. To increase response rate among physicians, up to 3 letters were sent requesting medical information regarding the use of confirmatory tests to diagnose the food allergy.

The participant questionnaire included questions on specific types of tree nut (e.g., hazelnut, pecan, and pistachio), fish (e.g., tuna, cod, and salmon), and shellfish including crustaceans (e.g., shrimp and lobster) and mollusks (e.g., clams and squid). Individuals were queried on the history of the most severe allergic reaction, (i.e., if they experienced typical IgE mediated symptoms such as pruritus, urticaria, flushing, rhinoconjunctivitis, angioedema, throat tightness, gastrointestinal complaints, breathing difficulties, wheeze, cyanosis or circulatory collapse), interval between exposure and symptom onset, if medical care was sought, if epinephrine was administered, if diagnosed by a physician,

and if confirmatory tests (i.e., skin prick tests (SPT), measurement of serum allergen-specific IgE, and/or food challenge) were performed. Demographic data were collected including number, ages, and gender of household members, education level of household respondent, whether the household respondent was born in Canada and country of origin of respondent if not born in Canada as well as number of years living in Canada, and household income level. The questionnaire was translated into French and back-translated to English.

Definitions of food allergy

We developed 3 definitions of food allergy.

1. Perceived food allergy

This includes all cases of self-reported food allergy, regardless of history or presence of supporting confirmatory tests.

2. Probable food allergy

This refers to those self-reporting food allergy who have a convincing history of food allergy or who report a physician confirmed food allergy.

A convincing clinical history of an IgE mediated reaction to a specific food was defined as a minimum of 2 mild signs/symptoms or 1 moderate or 1 severe sign/symptom that was likely IgE mediated and occurred within 120 minutes after ingestion or contact (or inhalation in the case of fish and shellfish). Reactions were considered mild if they involved pruritus, urticaria, flushing, or rhinoconjunctivitis; moderate if they involved angioedema, throat tightness, gastrointestinal complaints, or breathing difficulties (other than wheeze); and severe if they involved wheeze, cyanosis, or circulatory collapse.[83;258-260]

3. Confirmed food allergy

Participants were considered to have a confirmed allergy only if one of the following was fulfilled:

1) They had a convincing clinical history of an IgE mediated reaction attributed to food and their physician provided confirmation of EITHER a positive SPT defined as a wheal diameter at least 3 mm larger than that elicited by the negative control within 10 to 15 minutes of placement[261] OR a serum food-specific IgE > 0.35 kU/L OR a positive food challenge;

2) They were never exposed to the food or had an uncertain clinical history (i.e., any history other than convincing) of an IgE mediated reaction and their physician provided confirmation of EITHER a positive SPT AND a food-specific IgE above previously published thresholds (i.e., >15 kU/L for peanut and tree nut and > 20 kU/L for fish[262]) OR a positive SPT AND a positive food challenge OR a positive food challenge alone. It should be noted, however, that for peanut allergy, a SPT > 8 mm in those ≥ 2 years and a SPT > 4 mm in those < 2 years were considered sufficient diagnostic criteria in those never exposed or with an uncertain history. It has been reported that these thresholds are highly predictive of peanut allergy.[263;264] It should be noted that although these thresholds are widely used among allergists in different countries including Canada [265] they are nonetheless not universally accepted [266] and there are physicians who would use a higher threshold of 13 mm. [267]

Statistical analysis

Preliminary point estimates and 95% CIs for the overall prevalence of perceived and probable food allergy were calculated, accounting for the fact that households were the primary sampling units in this survey data, rather than individuals.[233]

Given that sufficient confirmatory test data were not available for all participants, a third estimate was computed, based on the data provided, as a tentative lower bound for the prevalence of confirmed food allergy in all participants.[268;269] However, with no results of food challenges having been obtained, a proportion of true negatives among self-reported cases could not be established. Hence, the lower end of a one-sided binomial 97.5% CI for the proportion of confirmed cases was first calculated, with a value that decreases as the number of confirmed observations gets smaller. As an example, if for a given allergy, 15 of 15 cases providing test results were confirmed, the lower end of the interval would be 78%, whereas it would only be 48% if only 5 of 5 cases were confirmed. This percentage was then multiplied by the proportion of all responders who reported a comparable history to that of confirmed cases. Pursuing the same example, if 15 cases were confirmed among patients with a convincing history, and 5 among those with an uncertain history, the prevalence estimate for confirmed allergy would be the sum of 78% of the proportion of convincing histories plus 48% of that of

uncertain histories. Relevant 95% CIs were also adjusted to account for the multilevel aspect of this data.

Results

Participation rate

Of 10,596 households contacted, 3666 responded (34.6% participation rate), of which 3613 completed the entire interview, representing 9667 individuals.

Compared to the general Canadian population, immigrants within the last 10 years as well as those with lower household income are underrepresented in our study population (Table 1).

Prevalence estimates

The prevalence of perceived peanut allergy was 1.00 % (95% CI, 0.80%, 1.20%); tree nut, 1.22% (95% CI, 1.00%, 1.44%); fish, 0.51% (95% CI, 0.37%, 0.65%); shellfish, 1.60% (95% CI, 1.35%, 1.86%); and sesame, 0.10% (95% CI, 0.04%, 0.17%) (Figure 1A-E, Table 2).

The prevalence of probable peanut allergy was 0.93% (95% CI, 0.74%, 1.12%); tree nut, 1.14% (95% CI, 0.92%, 1.35%); fish, 0.48% (95% CI, 0.34%, 0.61%); shellfish, 1.42% (95% CI, 1.18%, 1.66%); and sesame, 0.09% (95% CI, 0.03%, 0.15%) (Figure 1A-E, Table 2).

Although most participants self-reporting food allergy had testing performed (Table 3), only 56.7%, 55.9%, 51.0%, 34.2% and 70.0% of those self-reporting peanut, tree nut, fish, shellfish and sesame allergy allowed us to contact their physician to obtain confirmatory tests results. In over 50% of cases, these physicians failed to provide results and in only 21.6%, 10.2%, 6.1%, 4.5% and 40.0% of those self-reporting food allergy were these results sufficient to establish the diagnosis (Table 3). None of the patients reported a food challenge. Confirmatory tests for peanut, tree nut, and shellfish were performed less often in adults (Table 3). Based on the results obtained, the prevalence of confirmed peanut allergy was 0.61% (95% CI, 0.47%, 0.74%) and the prevalence of confirmed tree nut, fish, shellfish and sesame allergy was 0.68% (95% CI, 0.54, 0.83); 0.10% (95% CI, 0.07%, 0.14%); 0.73% (95% CI, 0.59%, 0.86%); and 0.03% (95% CI, 0.01%, 0.06%), respectively (Figure 1A -E , Table 2).

Characteristics of reactions

Initial allergic reactions in children with probable peanut, tree nut and sesame allergy occurred at a median age of 2 years [Interquartile Range (IQR), 1, 4], 7 years (IQR, 2, 12) and 2 years (IQR, 1, 4), respectively (Table 4). Initial reactions in participants 18 years and older with probable peanut, tree nut and sesame allergy occurred at a median age of 11 years (IQR, 2, 30), 20 years (IQR, 10, 40) and 10 years (IQR, 2, 15), respectively. Initial reactions to fish and shellfish occurred in children at a median age of 4 years (IQR, 2.5, 5) and 6.5 years (IQR, 4, 9) and in adults, at a median age of 12 years (IQR, 5, 25) and 25 years (IQR, 17, 37) (Table 4).

Recurrent reactions were common and occurred in 73.7%, 77.4%, 88.9%, 74.6% and 87.5% of those with peanut, tree nut, fish, shellfish and sesame allergy, respectively (Table 4). Among those with moderate or severe reactions (defined above) to peanut, tree nut, fish, shellfish and sesame, only 36.1%, 38.7%, 21.1%, 14.6% and 37.5% reported receiving epinephrine treatment, respectively (Table 4).

The most prevalent tree nut, fish and shellfish associated with allergic reactions were reported to be hazelnut, cod/salmon and shrimp, respectively. These were also the most common foods associated with moderate/severe reactions.

Discussion

We have conducted the first nationwide study on food allergy prevalence that attempts to confirm participant self-report of allergy by obtaining physician records of diagnostic testing. However, retrieving such information proved to be challenging as all participants did not undergo such testing and of those who did, many participants or physicians refused to provide results. Hence, our prevalence estimates of confirmed allergy are very conservative and we have therefore also provided estimates for perceived and probable allergy which likely better approximate true prevalence. The difference between perceived and confirmed estimates certainly contributes to the wide range of published values for food allergy prevalence.[53]

Although we tried to increase the participation rate through the use of an introductory letter and by calling on different days and different times of the day, it is still relatively low. This is consistent with recently reported trends of low participation rates in telephone surveys, especially among persons with lower education.[270;271] This low participation rate is in line also with the most recent food allergy telephone survey

conducted by Sicherer et al in 2008 (42% participation rate) [36] Additionally, although digital telephone surveys using White Pages sampling are suitable to collect information for prevalence on most common self-reported health conditions in the population including minorities,[272-274] they may result in selection bias due to exclusion of unlisted numbers,[272] persons who are primary or exclusive cell-phone users, ethnic minorities, immigrants,[275] and lower socioeconomic groups.[276] Accordingly, these latter 2 groups are relatively underrepresented in our study. Further, our low response rate may have led to a higher participation rate among those with food allergies. However, We believe that our estimates for the prevalence of perceived and probable food allergy are valid given that these estimates for peanut allergy in Canadian and Quebec children (Canada: perceived 1.77% and probable 1.68%; Quebec: 1.69% and 1.69%, respectively) are consistent with our estimates for confirmed peanut allergy in Montreal school children (1.63%) where the participation rate was 64.2%.[83]

Our results demonstrate that there is substantial misconception on behalf of both health care providers and patients regarding the diagnosis and management of food allergy. In our study, physicians under-utilized the confirmatory tests required to establish or refute the diagnosis of food allergy, supporting our recent observation on the underuse of confirmatory tests in children never exposed to peanut or with an uncertain history.[265] Under-use of confirmatory tests was most frequent in adults reporting shellfish allergy and cannot be entirely attributed to recall bias, given that shellfish allergy usually develops in adulthood.[254] Inadequate use of confirmatory tests can have substantial consequences, with some being mislabelled as allergic and burdened with a lifetime of unnecessary dietary vigilance, whereas others may be falsely re-assured that they are not at risk for fatal anaphylaxis. Furthermore, most of our food allergic participants had experienced at least one repeat reaction and few reactions were managed appropriately with epinephrine.

It is possible that some participants deemed to have a convincing history for tree nut or fish allergy did not actually experience an IgE mediated reaction with the potential to develop into anaphylaxis. Tree nut allergy was the most prevalent food allergy reported in our study and our estimates exceed most others.[148;277] It is possible that the 4.5% of participants with probable tree nut allergy who reported symptoms limited to

itching/swelling of the mouth immediately after oral contact with a specific nut have a pollen-food allergy syndrome,[278-282] and are less likely to experience severe anaphylactic reactions. It is also possible that patients reporting fish allergy may have had scombroid fish poisoning due to bacterial contamination of fish and production of histamine[283] or an IgE mediated reaction to Anisakis simplex associated with consumption of raw fish.[284;285] However, given that all participants reporting fish allergy had either multiple reactions or a positive SPT to fish, the diagnosis of scombroid fish poisoning or Anisakis allergy is unlikely.

It is possible that a small percentage of children who did not experience a recent reaction had actually developed tolerance. Although we only had data on the date of the most severe reaction and not the most recent, if we assume that the most severe reaction is actually the most recent, 15% of children not having a reaction to peanut in the past 2 years,[286] 9% not experiencing a reaction to tree nut in the past year,[287] 17.2% not experiencing a reaction to fish in the past 2 years[288] and 30% not experiencing a reaction to sesame in the past 2.3 years[138;139] might have outgrown their allergy. Thus, our probable prevalence estimates in participants with peanut, tree nut, fish and sesame allergy would decrease to 0.88% (95% CI, 0.71%, 1.09%), 1.11% (95% CI, 0.91%, 1.34%), 0.47% (95% CI, 0.34%, 0.63%) and 0.09% (95% CI, 0.04%, 0.17%), respectively. This clearly represents a lower bound as some of the participants might have experienced a more recent, but less severe reaction. Given that there are no reports on the rate of resolution of shellfish allergy, we were unable to conduct a similar sensitivity analysis.

Our estimates of the median age of the initial reaction to peanut, tree nut and sesame in children are similar to published estimates[139;289;290] but for adults, the median age exceeds that reported in most other studies. This is likely due to recall bias, i.e., adults have difficulty recalling the date of a personal remote reaction and likely report the date of a more recent one, whereas parents usually recall the date of their child's initial reaction.[291;292] The median age of the initial reaction to fish and shellfish in both children and adults is comparable to other reports possibly because the onset of these allergies is usually at an older age.[148;293] In addition, the age of the initial introduction of

a food (for which we did not collect data) may have influenced the age of the initial reaction.[135]

Our definitions for food allergy differed slightly from those used previously by Sicherer et al in the US.[143;260] However, to compare our results to US estimates, we have used comparable definitions. Our 2009 nationwide estimates for the perceived prevalence of peanut allergy exceeded those published by Sicherer et al in 2002 by 0.27% (95% CI, 0.02%, 0.52%) for all participants and by 0.88% (95% CI, 0.24%, 1.52%) for children. Canadian estimates for the perceived prevalence of tree nut allergy were higher by 0.44% (95% CI, 0.18%, 0.71%) for all participants and by 1.15% (95% CI, 0.55%, 1.76%) for children. Canadian estimates for the prevalence of peanut and tree nut combined, based on a convincing history, exceeded US estimates by 0.31% (95% CI, 0.02%, 0.60%). In contrast, our 2009 estimates for the probable prevalence of shellfish allergy were lower than US 2002 estimates by 0.69% (95% CI, 0.37%,1.01%) for all and by 0.96% (95% CI, 0.56%,1.37%) for adults. The difference between Canadian and US estimates for fish allergy was not significant [0.07% (95% CI, -0.10% to 0.23%)].[148]

The observed difference in prevalence estimates between Canada and the US might be due to several factors. Our study was conducted 7 years later than Sicherer's and therefore temporal trends may contribute to an increase in true prevalence as well as enhanced awareness and an attendant increase in perceived prevalence. Several studies suggest an increase in the prevalence of peanut allergy during the last decade [142;143] that has recently stabilized.[83;294] The difference may also be due to inherent differences in the 2 countries. Despite assumed similarities in Canadian and US dietary habits, studies report differences in life styles, food availability and nutrition fortification between the countries which might affect the emergence of food allergies.[295-298] Finally, some of the observed differences may be attributed to the lower response rate in our study (i.e., 35% versus 67.3% in the US seafood study and 52% in the US peanut and tree nut study) that may have led to overrepresentation of those with food allergies.

Given that there are no US estimates for sesame allergy, we were able to compare our estimates only to previously published UK and Israeli estimates.[135] The prevalence of sesame allergy in Canada and Israel is similar and much lower than in the UK. This contrasts sharply with the prevalence of peanut allergy which is similar in Canada and the

UK [1.85% (95% CI, 1.45%, 2.32%)] and much higher than in Israel [0.17% (95% CI, 0.07%, 0.34%)].[135]

In conclusion, our results reveal significant disparities between perceived and confirmed food allergies. Guidelines regarding increased use of confirmatory tests in general and food challenges in particular should be disseminated and might contribute to a more accurate diagnosis in those never exposed or with an uncertain history. Research should be expanded to include vulnerable populations such as those of lower socioeconomic status and immigrants and the role of environmental factors in the pathogenesis of food allergies should be explored.

Acknowledgements: We thank Dr Scott H Sicherer from the Elliot and Rosyln Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine, New York for sharing with us the food allergy telephone questionnaire.

Table 1: Demographic Characteristics

	SCAAALAR Population	Canadian Population
College/university/professional degree or diploma	60.5%	32.9% (as of 2001)
High school diploma	90.7%	68.7% (as of 2001)
Born in Canada	85.6%	80.6% (as of 2006)
Immigrated to Canada in the last 10 years	1.9%	6.3% (as of 2006)
Married/co-habitation	70.3%	72.5% (as of 2006)
Dwelling owned	82.1%	68.0% (as of 2006)
Median annual household income	$70,000	$63,600 (as of 2006)
Household income under low-income cut-off*†	8.9%	14.5% (as of 2006)
Rural (based on postal code) location	15.5%	13.7% (as of 2001)
Rural ‡	39.0%	32.4% (as of 2007)
Residing in Atlantic Canada	5.4%	6.9% (as of 2006)
Quebec	39.5%	23.4%
Ontario	32.6%	38.9%
Prairies	12.2%	17.5%
British Columbia	10.3%	13.2%

*Among respondents who provided income-related information, representing 61% of our household sample.

†Low Income Cut-offs, defined as income levels at which families or unattached individuals spend at least 70% of before tax income on food, shelter and clothing and is determined according to family size and geographic location.

‡Residing outside Canadian metropolitan areas or in Canadian metropolitan areas with a population ≤100,000

Table 2: Prevalence Estimates for Perceived, Probable, and Confirmed Food Allergy

	Peanut	Tree nut	Fish	Shellfish	Sesame
Children, % (95% CI)					
Perceived	1.77%(1.26-2.42)	1.73%(1.23-2.37)	0.18%(0.05-0.47)	0.55%(0.28-0.95)	0.23%(0.07-0.53)
Probable	1.68%(1.19-2.31)	1.59%(1.11-2.21)	0.18%(0.05-0.47)	0.50%(0.25-0.89)	0.23%(0.07-0.53)
Confirmed	1.03%(0.72-1.46)	0.69%(0.44-1.02)	-	0.06%(0.02-0.11)	0.03%(0.01-0.07)
Adults,% (95% CI)					
Perceived	0.78%(0.59-1.00)	1.07%(0.85-1.33)	0.60%(0.44-0.81)	1.91%(1.62-2.25)	0.07%(0.02-0.16)
Probable	0.71%(0.53-0.93)	1.00%(0.79-1.26)	0.56%(0.41-0.76)	1.69%(1.41-2.01)	0.05%(0.01-0.14)
Confirmed	0.26%(0.19-0.36)	0.35%(0.27-0.45)	0.12%(0.08-0.17)	0.71%(0.59-0.85)	0.01%(0.00-0.02)
Entire study population,% (95% CI)					
Perceived	1.00%(0.81-1.22)	1.22%(1.01-1.46)	0.51%(0.38-0.67)	1.60%(1.36-1.87)	0.10%(0.05-0.19)
Probable	0.93%(0.75-1.14)	1.14%(0.94-1.37)	0.48%(0.35-0.63)	1.42%(1.19-1.67)	0.09%(0.04-0.18)
Confirmed	0.61%(0.48-0.76)	0.68%(0.55-0.84)	0.10%(0.07-0.14)	0.73%(0.60-0.87)	0.03%(0.01-0.06)

Table 3: Number and Percentage of Participants with Reported and Sufficient Confirmatory Tests*

	Peanut	Tree nut	Fish	Shellfish	Sesame
Children, N (%*)					
Self-report of tests†	35(89.7%)	33(86.8%)	3(75.0%)	11(91.7%)	4 (80.0%)
Consent to contact MD	30(76.9%)	30(78.9%)	2(50.0%)	9(75.0%)	3 (60.0%)
Results provided by MD	16(41.0%)	16(42.1%)	1(25.0%)	5(41.7%)	2(40.0%)
Results sufficient to confirm allergy	16(41.0%)	8(21.1%)	0(0.0%)	2(16.7%)	2(40.0%)
Adults, N (%*)					
Self-report of tests†	42(72.4%)	56(70.0%)	34(75.6%)	69(48.3%)	5 (100.0%)
Consent to contact MD	25(43.1%)	36(45.0%)	23(51.1%)	44(30.8%)	4 (80.0%)
Results provided by MD	8(13.8%)	9(11.3%)	6(13.3%)	8(5.6%)	2 (40.0%)
Results sufficient to confirm allergy	5(8.6%)	4(5.0%)	3(6.7%)	5(3.5%)	2 (40.0%)
Entire study population N (%*)					
Self-report of tests†	77(79.4%)	89(75.4%)	37(75.5%)	80(51.6%)	9 (90.0%)
Consent to contact MD	55(56.7%)	66(55.9%)	25(51.0%)	53(34.2%)	7 (70.0%)
Results provided by MD	24(24.7%)	25(21.2%)	7(14.3%)	13(8.4%)	4(40.0%)
Results sufficient to confirm allergy	21(21.6%)	12(10.2%)	3 (6.1%)	7 (4.5%)	4 (40.0%)
Difference in reported tests percentages in children versus adults (%)	17.3(2.4, 32.3)	16.8(2.1, 31.6)	-0.6(-44.8,43.7)	43.4(25.8,61.1)	-20(-55.1, 15.1)

*Among those reporting food allergy

† Including those who did not know if tests were done

Table 4. Characteristics of Reactions

	Peanuts	Tree nut	Fish	Shellfish	Sesame
Children					
Initial reaction median age: years(IQR)*	2(1,4)	7(2,12)	4(2.5,5)	6.5(4,9)	2(1,4)
Participants with probable allergy reporting at least 1 allergic reaction(N)	30	26	4	10	5
% with recurrent reactions*	56.7	58.3	50.0	44.4	80.0
% with moderate/severe reaction*	90.0	88.5	100.0	90.0	100.0
% treated with epinephrine†	29.6	34.8	25.0	33.3	20.0
Adults					
Initial reaction median age: years(IQR)*	11(2,30)	20(10,40)	12(5,25)	25(17,37)	10(2,15)
Participants with probable allergy reporting at least 1 allergic reaction (N)	49	73	37	122	4
% with recurrent reactions*	84.8	84.1	93.8	77.0	100.0
% with moderate/severe reaction*	91.8	95.9	91.9	93.4	75.0
% treated with epinephrine†	40.0	40.0	20.6	13.2	66.7
Entire study population					
Initial reaction median age : years(IQR)*	4(2,16)	15.5(6,30)	8(5,25)	25(14,35)	3(1.5,12.5)
Participants with probable allergy reporting at least 1 allergic reaction(N)	79	99	41	132	9
% with recurrent reactions*	73.7	77.4	88.9	74.6	87.5
% with moderate/severe reaction*	91.1	93.9	92.7	93.2	88.9
% treated with epinephrine†	36.1	38.7	21.1	14.6	37.5

*Among participants with probable food allergy reporting at least 1 allergic reaction
† Among participants with moderate/severe reactions as defined in the text
IQR, Interquartile range

Figure 1A: Algorithm for the diagnosis of confirmed peanut allergy. Where are the figures?

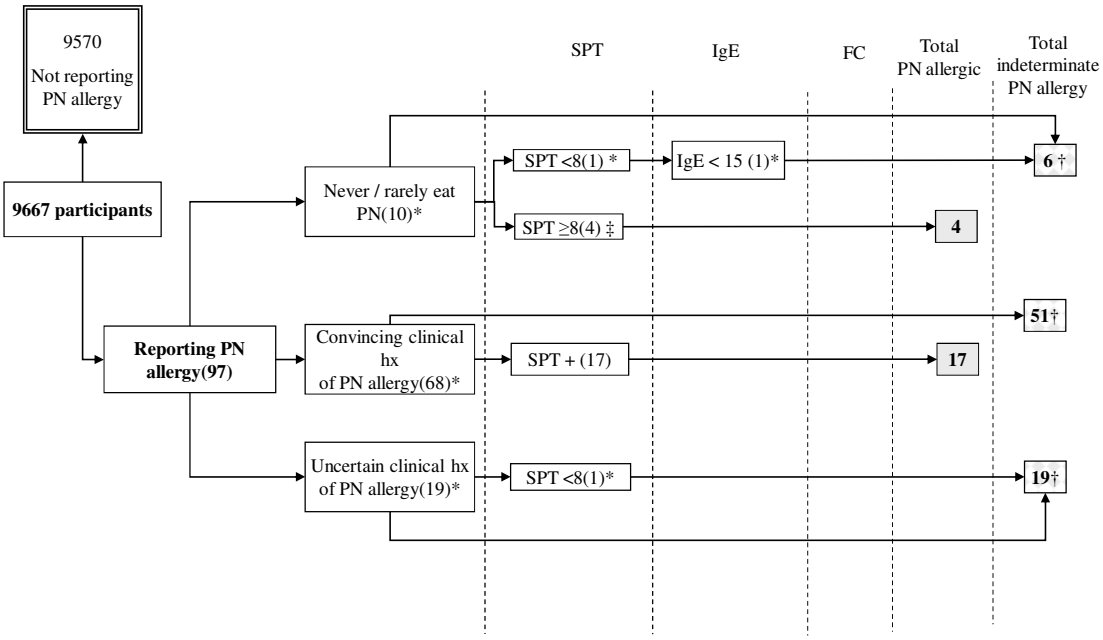

Figure Legend:

PN, peanut

Hx , history

SPT , prick skin test

FC, food challenge

* The number of participants eligible for SPTs, measurement of PN-specific IgE levels, or FCs exceeds the number of available tests results because participants did not have the tests done, participants refused to release medical information from treating physician or because physicians did not provide tests results.

†Data provided not sufficient to establish the diagnosis of allergy.

‡For those below 2 years, the cutoff will be 4 instead of 8 mm.

Figure 1B: Food Allergy Algorithm - Tree Nut

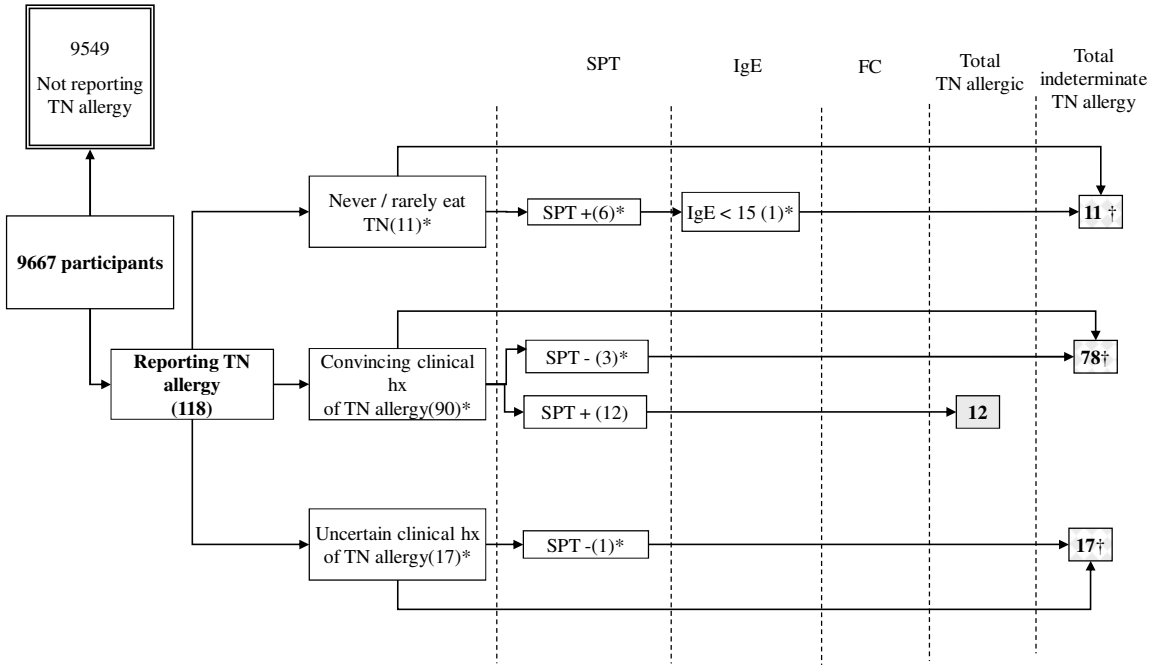

Figure Legend: Algorithm for the diagnosis of confirmed tree nut allergy.

TN, Tree Nut

Hx, history

SPT, prick skin test

FC, food challenge

*The number of participants eligible for SPTs, measurement of TN-specific IgE levels, or FCs exceeds the number of available tests results because participants did not have the tests done, participants refused to release medical information from treating physician or because physicians did not provide tests results..

†Data provided not sufficient to establish the diagnosis of allergy.

Figure 1C: Algorithm for the diagnosis of confirmed fish allergy.

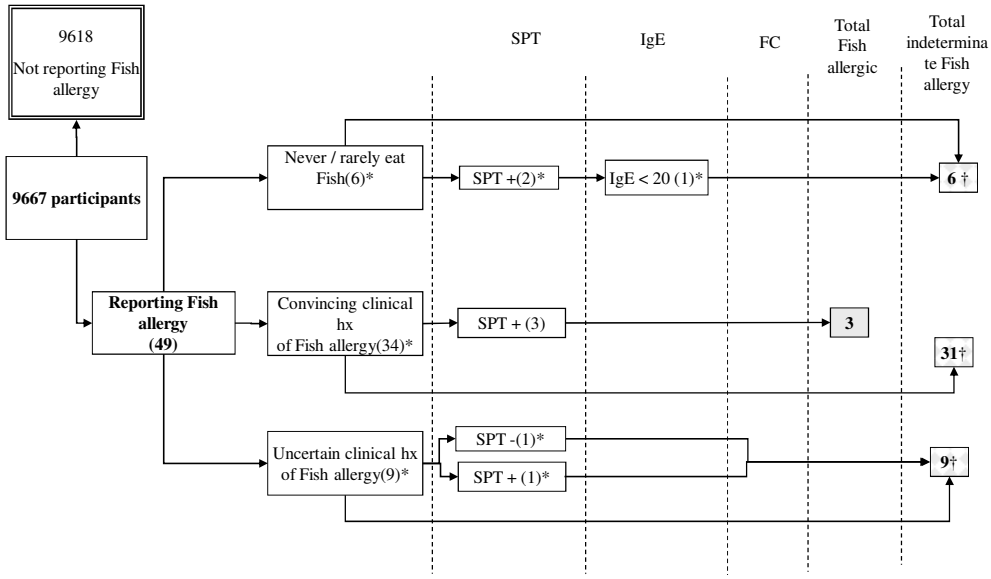

Figure Legend:

Hx, history

SPT, prick skin test

FC, food challenge

* The number of participants eligible for SPTs, measurement of fish-specific IgE levels, or FCs exceeds the number of available tests results because participants did not have the tests done, participants refused to release medical information from treating physician or because physicians did not provide tests results..

†Data provided not sufficient to establish the diagnosis of allergy.

Figure 1D: Algorithm for the diagnosis of confirmed shellfish allergy.

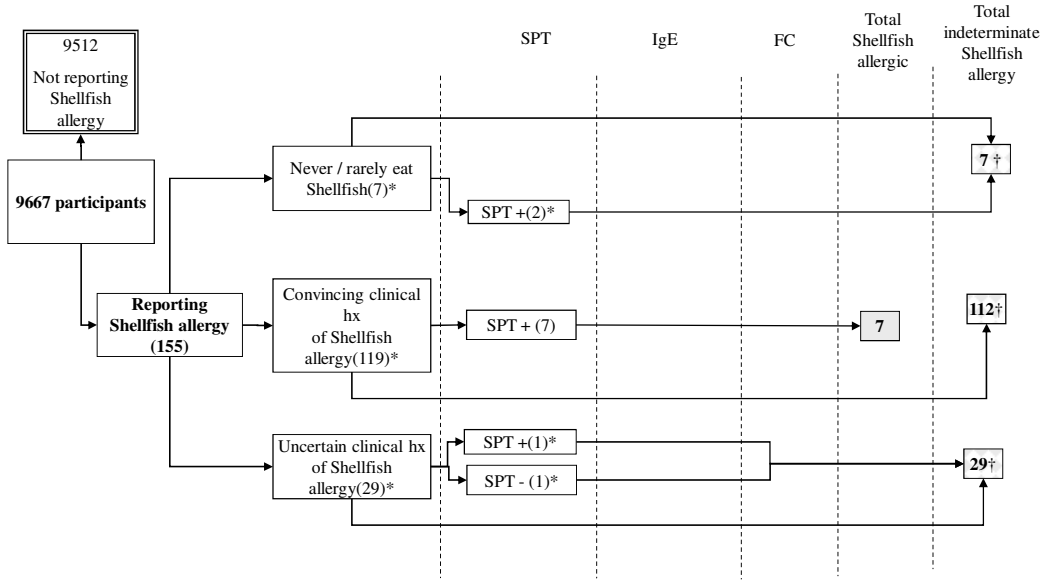

Figure Legend:

Hx , history

SPT , prick skin test

FC,food challenge

* The number of participants eligible for SPTs, measurement of shellfish-specific IgE levels, or FCs exceeds the number of available tests results because participants did not have the tests done, participants refused to release medical information from treating physician or because physicians did not provide tests results..

†Data provided not sufficient to establish the diagnosis of allergy.

Figure 1E: Algorithm for the diagnosis of confirmed sesame allergy.

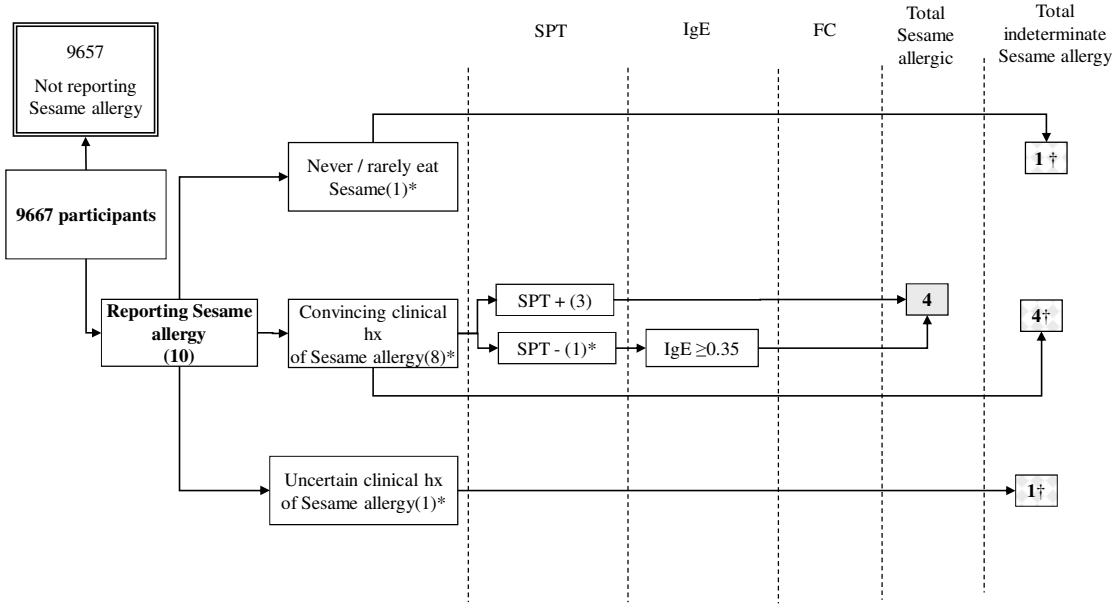

Figure Legend:

Hx, history

SPT, prick skin test

FC, food challenge

* The number of participants eligible for SPTs, measurement of sesame-specific IgE levels, or FCs exceeds the number of available tests results because participants did not have the tests done, participants refused to release medical information from treating physician or because physicians did not provide tests results..

†Data provided not sufficient to establish the diagnosis of allergy.

5.3 Manuscript 2: Demographic Predictors of Peanut, Tree Nut, Fish, Shellfish and Sesame Allergy in Canada.

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Key words: food allergy, gender, immigrants, socioeconomic status, parental education, urban.

Abbreivations:

SPT- skin prick test, CI- Confidence Interval, OR- Odds Ratio

Keywords : food allergy, peanut allergy, fish allergy, shellfish allergy , sesame allergy, predictors of food allergy.

Abstract:

Background: Studies suggest that the rising prevalence of food allergy during recent decades may have stabilized. Although genetics undoubtedly contribute to the emergence of food allergy, it is likely that other factors play a crucial role in mediating such short term changes.

Objective: To identify potential demographic predictors of food allergies.

Methods: We performed a cross-Canada, random telephone survey. Criteria for food allergy were self-report of convincing symptoms and/or physician diagnosis of allergy. Multivariate logistic regressions were used to assess potential determinants.

Results: Of 10,596 households surveyed in 2008/2009, 3666 responded, representing 9667 individuals. Peanut, tree nut and sesame allergy were more common in children [odds ratio (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)]. Tree nut and shellfish allergy were less common in males [OR 0.55 (95% CI, 0.36, 0.83) and 0.63 (95% CI, 0.43, 0.91)]. Shellfish allergy was more common in urban settings [OR 1.55 (95% CI, 1.04, 2.31)]. There was a trend for most food allergies to be more prevalent in the more educated [tree nut OR 1.90 (95% CI, 1.18, 3.04)] and less prevalent in immigrants [shellfish OR 0.49 (95% CI, 0.26, 0.95)], but wide CIs preclude definitive conclusions for most foods.

Conclusions: Our results reveal that in addition to age and sex, place of residence, socioeconomic status and birth place may influence the development of food allergy.

Word Count: 2190

Introduction

Among adults worldwide, 7.7% (Iceland) to 24.6% (US) are sensitized to food allergens.[299] Foods are the most common triggers for anaphylaxis, accounting for 33.2% to 56% of all

cases[6;300] with peanut, tree nut, fish and shellfish responsible for the majority of fatal reactions.[7] Studies suggest an increasing prevalence of food allergies in the past two decades,[56;230] with a recent stabilization in developed countries.[67;68] Although genetic factors undoubtedly contribute to the development of food allergies,[169] it is evident that they are not fully responsible for these relatively short term temporal trends in prevalence. Further, recent reports suggest that populations with similar genetic backgrounds may have different rates of food allergy, possibly due to different dietary habits,[137] and alternatively, populations with different genetic backgrounds may have the same relative prevalence of food allergies.[299] It is evident that the development of food allergy results from an interplay of genetic, environmental and demographic factors. However, little is known about which demographic factors are associated with food allergy. In the SCAAALAR study (**S**urveying **C**anadians to **A**ssess the Prevalence of Common Food **A**llergies and **A**ttitudes towards Food **LA**belling and **R**isk) launched in 2008, we determined the nationwide prevalence of peanut, tree nut, fish, shellfish and sesame allergy.[301] In this manuscript, we evaluate potential demographic factors that may influence the prevalence of these potentially severe food allergies in the SCAAALAR population.

Methods

As described in detail elsewhere,[301] households in the ten Canadian provinces were chosen by purchasing, from Info-Direct, a random selection of telephone numbers and their accompanying addresses from the electronic white pages. Interviews were conducted from May 2008 to March 2009 by trained interviewers from either McGill (Montreal, Quebec) or McMaster (Hamilton, Ontario) Universities, using Computer Assisted Telephone Interview (CATI) software (WinCati 4.2, Copyright 1986-2004 Sawtooth Technologies Inc, Northbrook Illinois). Eligible respondents were 18 years or older and living in the household, with no language-mental-hearing barriers. They were queried on whether any of the household members had any of the above 5 food allergies as well as on potential demographic predictors of food allergy.

To optimize response rates and minimize bias, a maximum of 10 attempts were made to contact households during different days and times between the hours of 9:30 AM to 9:00 PM

(local time) Monday through Friday and 10:30 AM to 5:00 PM on Saturdays and Sundays. Households were also advised of our survey a few weeks in advance of the phone call by a mailed information letter.

The study was approved by the Institutional Review Boards of the McGill University Health Centre and McMaster University.

Questionnaire

We used a standardized questionnaire developed by Sicherer et al as [63;230] in the US, and incorporated questions regarding sesame allergy. The questionnaire was translated into French and back-translated to English. If the eligible household respondent reported that he or she or any family member potentially had a food allergy, the respondent was queried on the history of the most severe allergic reaction, interval between exposure and symptom onset, if medical care was sought and if diagnosed by a physician. The eligible household respondent reported on the household sibship size, annual household income and the respondents' education level, marital status, and country of origin. The eligible household respondent also reported on the ages and gender of all household members.

Statistical analysis

The prevalence of probable food allergy was estimated by including all with a convincing history and/or self-report of a physician diagnosis of allergy. A convincing history was defined as at least 2 mild signs/symptoms or 1 moderate or 1 severe sign/symptom that occurred within 120 minutes after ingestion or contact (or inhalation in those with fish/shellfish allergy). Mild reactions included: pruritus, urticaria, flushing, or rhinoconjunctivitis; moderate: angioedema, throat tightness, gastrointestinal complaints, or breathing difficulties (other than wheeze); and severe: wheeze, cyanosis, or circulatory collapse.[67;90;301;302]

Univariate and multivariate logistic regression analyses were used to estimate the associations between the presence of probable food allergy and potential predictive factors including: sibship size, annual household income (low income level defined as an income at which families or unattached individuals spend at least 70% of before tax income on food, shelter and clothing and is determined according to family size and location), location of household (urban defined as

residing in Canadian metropolitan areas or in Canadian areas with a population ≥100,000), province of household (Atlantic provinces, Quebec, Ontario, Prairies or British Columbia), education level of household respondent (completed college or university), marital status of household respondent (living with partner/married), immigration status of household respondent (Canadian born), ages of each household member (< 18 years) and gender of each household member. Possible confounding factors were investigated by comparing univariate to multivariate results. Since the data were collected for randomly selected households rather than randomly selected individuals, all confidence intervals (CI) were corrected in order to account for clustering effects. In addition, a significant proportion of households (38%) did not provide any income data and hence multiple imputation techniques were applied, using all available data, in order to estimate the effect of low income over the largest possible sample. In the case of income-related questions, non-response may be due to non-ignorable factors. Therefore, two sensitivity analyses were also performed in which the predicted incomes used for imputations were either doubled or halved.

Results

Three thousand six hundred sixty six out of 10,596 households contacted responded (34.6% participation rate), of which 3613 completed the entire interview, providing data on 9667 participants.

Low income and immigrant populations were relatively underrepresented in SCAAALAR (8.9% of households in SCAAALAR were considered low income versus 14.5% in the Canadian population and 14.4% of household respondents in SCAAALAR were immigrants versus 19.4% in the Canadian population), while the SCAAALAR population had a higher proportion of household respondents with post-secondary education when compared to the general Canadian population (60.5% in SCAAALAR versus 32.9% in the Canadian population), The populations were similar with respect to urban versus rural location, province of residence and marital status.

Table 1: Multivariate Logistic Regression Examining Association between Specific Food Allergies and Respondent Characteristics (n = 8682*)

	Peanut Odds Ratio (OR) (95% CI)	Tree nut	Fish	Shellfish	Sesame
Age < 18 yo	2.24 (1.4, 3.59)	1.73 (1.11, 2.68)	0.17 (0.04, 0.72)	0.29 (0.14, 0.61)	5.63 (1.39, 22.87)
Male	1 (0.63, 1.58)	0.55 (0.36, 0.83)	0.96 (0.52, 1.78)	0.63 (0.43, 0.91)	1.04 (0.25, 4.23)
Urban	0.82 (0.5, 1.35)	0.99 (0.65, 1.5)	0.97 (0.51, 1.84)	1.55 (1.04, 2.31)	0.91 (0.18, 4.63)
Immigrant	0.62 (0.28, 1.38)	0.52 (0.25, 1.07)	0.45 (0.14, 1.46)	0.49 (0.26, 0.95)	0.73 (0.08, 6.65)
Post-secondary graduate	1.63 (0.94, 2.85)	1.9 (1.18, 3.04)	1.06 (0.56, 2)	0.69 (0.47, 1.01)	2.43 (0.56, 10.59)**

*this refers to participants providing complete data for the variables in this model; income level was provided by only 5,961 participants

** given the small number of sesame allergic individuals, the education variable is university graduate for this allergy

Peanut, tree nut and sesame allergy were more common in children [peanut: Odds ratio (OR) 2.24 (95% CI, 1.40, 3.59), tree nut: OR 1.73 (95% CI, 1.11, 2.68) and sesame: OR 5.63 (95% CI, 1.39, 22.87)], while fish and shellfish allergy were more common in adults [OR 0.17 (95% CI, 0.04, 0.72) and OR 0.29 (95% CI, 0.14, 0.61), respectively]. 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), respectively]. Shellfish allergy was more common in urban settings [OR 1.55 (95% CI, 1.04, 2.31)]. Higher household education was associated with increased likelihood of allergy to peanut, tree, fish, and sesame although it reached significance only for tree nut [OR 1.9 (95% CI,1.18, 3.04)]. All food allergies were less common in immigrants although large CIs preclude definitive conclusions except for shellfish [OR 0.49 (95% CI, 0.26, 0.95)]. Use of multiple imputation for income and the sensitivity analyses did not alter these associations.

Discussion

Consistent with other research, our study has demonstrated that peanut, tree nut and sesame allergy were more common in children, fish and shellfish more common in adults, and tree nut and shellfish allergy less common in males.[55;63;64;110;303] However, ours is the first North American study to examine the influence of education level, immigrant status, and geographic location on food allergy and we found that most food allergies are more prevalent in the more educated and those born in Canada and shellfish allergy in those residing in urban settings.

Our results suggest that a higher educational level may be associated with an increased risk of food allergy. These results are consistent with other studies suggesting an increased risk for allergic diseases, including food allergies, in families with higher parental education.[250] However, the mechanisms underlying these relationships are not yet well understood. Given that a higher education level may be associated with changes in family lifestyle,[254] the hygiene hypothesis may partially account for these findings. Consistent with the hygiene hypothesis, smaller family size, decreased exposure to pets and 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.[304] Other factors may also explain this association between education and food allergy. It is possible that more educated parents may be more likely to have followed American Academy of Pediatrics recommendations[184] regarding the restriction of

potentially allergenic foods in early life. This guideline has recently been retracted as research suggests that delayed introduction may promote, rather than reduce, the development of food allergy.[183] Further, educated parents have higher health literacy and may be more likely to consult a physician for suspected food allergies.[251] Hence, the actual prevalence may not be higher in the more educated, but may merely appear increased because of greater likelihood of seeking a diagnosis. The observed reduced risk of food allergy in immigrants might be due to genetic differences as well as environmental influences. Recent studies suggest an increased prevalence of allergic diseases commensurate with the length of stay in Westernized countries regardless of age at arrival, sex or atopic status.[246] Further, it was reported that asthma symptoms in Chinese adolescents were lowest among residents of mainland China, were greater for those in Hong Kong and those who had immigrated to Canada, and were highest among those born in Canada.[239] It was also 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.[147] These observations suggest a crucial role for environmental factors in the pathogenesis of allergic diseases in immigrants. Certain western dietary habits and lifestyles might contribute to the development of food allergies[136] including: omega-3 deficiency,[305] decreased consumption of fresh fruits and vegetables,[174] excess or inadequate vitamin D,[200;306] different food processing methods,[241] delayed introduction of foods,[137] low dose cutaneous sensitization to peanut,[307] and improved sanitation. [240] It is also possible that immigrants are less likely to consult a physician for a suspected allergy because of lower health literacy [308] and /or lack of a regular family doctor,[257] resulting in an apparent, rather than a real decrease in allergy prevalence in this population.

Although a higher prevalence of asthma[309] and eczema[310] in urban settings was previously reported, no population based studies have examined the association between urban/rural dwelling and food allergy. The higher prevalence of shellfish allergy in urban areas may be attributed to factors related to the hygiene hypothesis including less exposure to parasites and other infections,[311] higher use of antibiotics, less exposure to animals,[312] less overcrowding (in a house),[313] higher use of processed food,[314] and piped water intake (versus spring drinking water).[315] It is possible that only shellfish allergy was associated with living in an urban setting as it is reported that city dwellers consume more shellfish,[316] but not more of the other food allergens. Gender differences were observed for tree nut and shellfish allergy. Higher rates of

food allergy in post-pubertal females are consistent with other studies suggesting that anaphylaxis is more common in adult females [6] potentially due to the effect of estrogens that enhance mast cell activation and allergic sensitization, and progesterone that inhibits histamine release, but potentiates IgE induction.[317] The reduced risk for tree nut and shellfish allergies in males may only be apparent and attributable to a lower rate of physician diagnosis in males as adult males are known to be less likely to have a regular doctor.[257]

Our study has some potential limitations. Although our participation rate was only 34.6% with an underrepresentation of those of lower socioeconomic status and immigrants, this is consistent with other recent studies.[55] This low participation rate potentially resulted in selection bias with an overrepresentation of those with food allergy. However, given that our estimates for peanut allergy prevalence are consistent with our previous estimates in Montreal school children where the participation rate was 64.2%,[67] we anticipate that such a bias is likely to be minimal Yet, if such a bias does exist, it is likely to make the strength of the association between high socioeconomic status and allergy conservative. We anticipate that among the vulnerable populations, the presence of allergy will increase participation more than it would in the observed population. Hence, if the sample of the vulnerable populations was more representative, the prevalence of allergy in this sample would be even lower and the association between high socioeconomic status and allergy would be even stronger. Other limitations include the availability of data on education and birthplace on only a single household member (i.e. the eligible respondent), and our failure to explore other potential determinants. However, we have data on the education level and birthplace of the principal caregiver of the allergic individual and it is likely that the demographic characteristics of that caregiver play a major role in shaping the household lifestyle and the factors that may contribute to the emergence of food allergies in the household.[318]

In conclusion, our results reveal that demographic determinants such as education level, birthplace, and urban dwelling may influence the development of food allergy. Further studies examining the prevalence and pathogenesis of food allergy in vulnerable populations and exploring genetic and other environmental determinants will help disentangle the numerous factors mediating the development of food allergy.

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Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine, New York for sharing with us the food allergy telephone questionnaire.

The authors declare that they have no competing interests

6. Discussion

6.1. Interpretation and implications of results

Food allergy is perceived as a common problem, especially during childhood. Accurate estimation of the prevalence of confirmed food allergy in population based studies is extremely difficult due to a lack of consensus on appropriate threshold levels for either SPTs or specific IgE, inappropriate use of these tests to define food allergies, and ethical and practical issues surrounding food challenges. Prior to SCAAALAR, there was only one national population survey in Canada that inquired about food allergy; the Canadian Community Health Survey Cycle 3.1 (2005) included a single question on self-report of physician diagnosis of food allergy.[319] These data showed that 7.2% of Canadians report a food allergy with the prevalence of food allergy in those born in Canada (7.6%) exceeding that of immigrants (6.6% for immigrants residing in Canada for ≥ 10 years and 4.5% for recent immigrants).[319] However, it is well recognized that there is considerable discrepancy between self-perceived and physician-diagnosed food hypersensitivity.[52] In the first manuscript in the thesis, we provide the first nationwide Canadian estimates using a validated questionnaire for the prevalence of perceived, probable and confirmed peanut, tree nut, shellfish, fish and sesame allergy. The prevalence of probable allergy was 0.93% (95% CI, 0.74%, 1.12%) for peanut, 1.14% (95% CI, 0.92%, 1.35%) for tree nut, 0.48% (95% CI, 0.34%, 0.61%) for fish, 1.42% (95% CI, 1.18%, 1.66%) for shellfish and 0.09% (95% CI, 0.03%, 0.15%) for sesame.

Our estimates indicate a clear disparity between perceived and confirmed food allergies that is in line with previous studies in other parts of the world[19;53;54] as well as with previous studies done by our group.[265] This disparity is likely attributable to several factors. Some respondents reporting an allergy did not consult a physician. For those who did consult a physician, we were unable to obtain allergy testing results on almost 50% of respondents either because respondents refused to share their results or physicians did not provide results. In addition, even when testing results were provided, they did not always provide sufficient evidence to establish the diagnosis. However, absence of testing does not rule out the presence of a true food allergy. Given that our

probable estimates for peanut allergy in children are consistent with our previous estimates based on corroboration of clinical history with appropriate testing in Montreal school children (participation rate of 64.2%),[83] we anticipate that these probable estimates most likely reflect the presence of true food allergy. The difference between perceived and confirmed estimates certainly contributes to the wide range of published values for food allergy prevalence. Further, appropriate use of confirmatory tests is required not only to correctly diagnose those with allergy, but also to be able to appropriately follow the patients and predict the development of tolerance.[320]

In our second manuscript, we were able to identify demographic determinants such as higher education level, western birthplace, and urban dwelling that may contribute to the development of food allergy. Identifying demographic factors associated with disparities in food allergy prevalence enables better understanding of the pathogenesis of food allergies as well as helps to target diagnostic, management and prevention strategies to susceptible groups. Development of such strategies requires involvement of major policy makers including government, health and allied professionals and allergic patients themselves or their representatives.[321-323]

6.2. Strengths and limitations

A major strength of this study was the use of a validated food allergy questionnaire that allows both better clinical characterization of severe food allergies as well as comparison with other studies done world-wide[55;147;148;230] using identical methodologies. Such comparisons can identify disparities in food allergy prevalence between different populations and potentially help elucidate factors contributing to these differences. Other strengths of our study include our attempt to acquire confirmatory tests results that, despite being lacking in the majority of individuals, still elucidate the existing gaps between perceived /probable and confirmed allergies. A major limitation of our study is the potential for selection bias due to our low participation rate (34.6%) with an underrepresentation of those of lower socioeconomic status and immigrants. In addition, having received the letter prior to the survey and knowing the purpose of the survey might have contributed to selection bias due to increased the participation of those who have food allergies . Selection bias is defined as "any systemic error in the design, conduct or analysis of the study that results in a mistaken estimate of an exposure effect on the risk of disease.[226;324] Selection bias is present when individuals have different probabilities of being included in the study sample according to relevant study characteristics, i.e. the exposure and outcome of interest.[325] Selection bias may occur to some degree in all types of epidemiologic studies as in

the context of most sampling of human populations, there is unlikely to be a pure random sample from a clearly defined population. [326] However, recent studies suggest that high non-response rates are a much smaller threat to survey estimates than suggested by prior practical guidance. [327-329] In fact, Groves reviewed 59 different surveys in which data were collected to assess non-respondents for 959 different variables (this came from screening questions before the survey and from supplemental data) and showed that there is little or no relationship between the overall survey response rate and the degree of bias in the parameter estimated. Thus, he concludes that there is little empirical support for the notion that low response rate surveys de facto produce estimates with high non-response bias.[329] This is in line with the fact that our estimates in SCAAALAR for peanut allergy in Canadian and Quebec children (Canada: perceived 1.77% and probable 1.68%; Quebec: 1.69% and 1.69%, respectively) are consistent with our estimates for confirmed peanut allergy in Montreal school children (1.63%) where the participation rate was 64.2%.[83] Thus, we believe that our estimates for the prevalence of perceived and probable food allergy are valid and that such a bias is likely to be minimal. Regarding our reported associations with potential demographic determinants, we anticipate that if a bias does exist, it is likely to make the strength of the association between high socioeconomic status and allergy conservative. We anticipate that among the vulnerable populations, the presence of allergy will increase participation more than it would in the observed population. Hence, if the sample of the vulnerable populations was more representative, the prevalence of allergy in this sample would be even lower and the association between high socioeconomic status and allergy would be even stronger.

Due to the need to use a concise brief survey in a telephone interview, our study was also limited by our inability to include all potential confounders that might have an effect on our reported associations. These confounders may include family history of atopy and differences in various environmental factors such as diet.

6.3 Future research

Given our findings and the potential limitations discussed, there is a clear need for future studies assessing food allergies specifically in those of lower socioeconomic status, those living in the territories, New Canadians, as well as First Nations and Inuit. It is equally important to assess the prevalence of additional common food allergens that were not examined in SCAAALAR including milk, egg, soy and wheat. Extending the collection of data regarding prevalence to vulnerable populations and to other common food allergens is key to developing the full picture of the health, social, and economic burden of illness that food allergy represents in Canada. In addition, given that in the SCAAALAR study we were able to identify only

demographic factors related to food allergies, further studies should also explore how genes and the environment may interact to influence the development of food allergy.

7. Conclusion

In conclusion, we have shown that the prevalence of probable allergy was 0.93% (95% CI, 0.74%, 1.12%) for peanut, 1.14% (95% CI, 0.92%, 1.35%) for tree nut, 0.48% (95% CI, 0.34%, 0.61%) for fish, 1.42% (95% CI, 1.18%, 1.66%) for shellfish and 0.09% (95% CI, 0.03%, 0.15%) for sesame. Perceived food allergy estimates were similar to probable estimates. However, due to the infrequency of confirmatory tests and the difficulty in obtaining results if performed, the prevalence of confirmed allergy was much lower. These results indicate disparities between perceived and confirmed food allergy that might contribute to the wide range of published prevalence estimates. Wider use of confirmatory diagnostic testing could contribute to more accurate diagnosis in those who report they have food allergies.

This research highlights certain demographic factors including age, gender, socioeconomic and education levels as well as being an immigrant as potential factors associated with the presence of food allergies. Our findings may contribute to the development of policies and guidelines that will benefit those with food allergies and may serve as a platform for future research exploring the societal burden and pathogenesis of food allergies.

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