PREVALENCE AND TREATMENT OF FOOD ALLERGY IN CANADA

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ABSTRACT

Recent studies suggest that the prevalence of food allergy is increasing; however, Canadian data on prevalence are sparse. Additionally, although there is unanimous agreement in the medical community that all individuals with a history of food-induced anaphylaxis should have an epinephrine auto-injector (EAI), there is much evidence to suggest that this is not the reality. Using a cross-sectional, randomized telephone survey of Canadian households, we sought to estimate the prevalence of food allergy in Canada and the proportion of allergic Canadians with the EAI, and to determine whether certain characteristics were associated with having the EAI. Of the 10,596 households contacted, 3,666 responded (34.6%), of which 3,613 households, representing 9,667 individuals, provided enough information to be included in the prevalence calculations. The prevalence of self-reported allergy to any food was 8.0%. Of those with probable allergy to at least one of peanut, tree nut, fish, shellfish, and sesame (3.21%), only about 50% had the EAI, and males, those who were older, and those who were single were even less likely to have an EAI. This research suggests that food allergy is a significant health problem, affecting 1 out of every 13 Canadians, and many of them are not adequately managed for their condition. These findings support the need for better education of the public and health care professionals regarding the importance of proper diagnosis and follow-up of individuals with food allergy, and the need to prescribe the EAI to all individuals with a history of an allergic reaction.

RÉSUMÉ

Des études récentes suggèrent que la prévalence des allergies alimentaires augmente; mais, les données canadiennes sur la prévalence sont éparses. En plus, même s'il y a un accord unanime dans la communauté médicale que tous les patients avec une histoire de l'anaphylaxie causée par un aliment devraient avoir un auto-injecteur d'épinephrine (AIÉ), l'ensemble de recherche démontre que cela n'est pas la réalité. En utilisant un sondage téléphonique auprès des canadiens, nous avons estimé la prévalence des allergies alimentaires chez les canadiens et la proportion des canadiens allergiques qui possèdent un AIÉ. De plus, nous avons déterminé s'il y a certaines caractéristiques qui sont associés avec la possession de l'AIÉ chez les individus souffrant d`allergies alimentaires. Des 10,596 maisons contactées, 3,666 ont répondus (34.6%), et 3,613 de ceux-là ont données assez d`information pour être inclus dans les calculs de prévalence, ce qui représente 9,667 individus. La prévalence des allergies alimentaires auto signalée était de 8.0%. Sur tout ceux avec une allergie probable aux arachides, aux noix, au poisson, aux fruits de mer, et/ou au sésame (3.21%), seulement environ 50% avait l'AIÉ, et les hommes, les adultes, et ceux qui vivait seule étaient encore moins susceptibles d'en avoir un. Cette recherche suggère que les allergies alimentaires sont un problème de santé important, qui touche environ un sur treize canadiens, et la plupart d'entre eux ne sont pas gérés de façon adéquate pour leur condition. Ces conclusions appuient la nécessité de l'éducation pour le publique et les professionnels de la santé en ce qui concerne l'importance d'un diagnostique et un suivi approprié pour les gens avec des allergies alimentaires, et la nécessité de préscrire un AIÉ pour chaque patient avec une histoire d'une réaction allergique.

DEFINITIONS

The following definitions are used throughout this thesis.

Low income cut-off: income level at which families or unattached individuals spend at least 70% of before-tax income on food, shelter and clothing, determined according to family size and geographic location of the household.

Urban: living in a household which is in a Canadian metropolitan area with a population greater than or equal to 100,000 individuals.

Post-secondary degree: completed a university or professional degree (all provinces) or college degree (Quebec only).

ABBREVIATIONS

EAI: epinephrine auto-injector
SPT: skin prick test
SCAAALAR: Surveying Canadians to Assess the Prevalence of Common Food Allergies and Attitudes towards Food Labelling and Risk
DBPCFC: double-blind, placebo-controlled food challenge
CI: confidence interval
OR: odds ratio
BIC: Bayes Information Criterion

CONTRIBUTION OF AUTHORS

- Lianne Soller acted as both a telephone interviewer and research coordinator for the study. She wrote both manuscripts for this thesis, and performed the data analysis and interpretation under the supervision of Lawrence Joseph, Yvan St. Pierre and Ann Clarke. The final version of the EAI Letter to the Editor was shared with the other authors and comments were incorporated before submission to JACI. The final version of the Prevalence Manuscript will be reviewed and submitted for publication following submission of this thesis.
- Joseph Fragapane input the survey questions into CATI (Computer-Assisted Telephone Interviewing), and ensured that the logic of the questions was correct. He also extracted the data from the database and sent it to all authors. Joseph also reviewed the EAI Letter to the Editor.
- Moshe Ben-Shoshan, pediatric allergist, adapted the food allergy prevalence questionnaire, based on questions employed by Scott Sicherer in the United States to estimate prevalence of allergy to peanut, tree-nut, fish and shellfish. The questionnaire was adapted for sesame. Lianne, Moshe and Dr. Clarke worked closely together in deciding on the content of the thesis. Moshe also reviewed the EAI Letter to the Editor.
- Daniel Harrington wrote the environmental risk and demographic section of the survey, using the wording of questions from the Canadian census. He also reviewed the EAI Letter to the Editor.
- Reza Alizadehfar provided valuable clinical input on the validity of the study results and suggestions regarding content of the thesis, manuscripts, and conference presentations. Reza also reviewed the EAI Letter to the Editor.
- Lawrence Joseph acted as co-supervisor for this thesis, and provided the statistical expertise for the study. He developed the sample size estimates and sampling strategy. He also provided valuable input during the data analysis stage. He helped Lianne Soller write the hierarchical logistic models with multiple imputations in WinBUGS. Lawrence also reviewed the EAI Letter to the Editor and Prevalence Manuscript.

- Yvan St. Pierre, statistician, checked that the data analysis performed by Lianne Soller was correct. He checked the dataset for coding of variables, and re-ran the logistic regressions. He worked with Lianne and Ann very closely to ensure the accuracy of the results. Yvan also reviewed the EAI Letter to the Editor.
- Samuel Godefroy and Sebastien La Vieille from Health Canada supported this initiative to estimate prevalence of food allergy in Canada, and provided input on the subject matter of the questionnaire. Samuel and Sebastien also reviewed the EAI Letter to the Editor.
- Ann Clarke and Susan Elliott conceptualized the idea for this nationwide study. They wrote the proposal for the study, submitted it to AllerGen NCE Inc., and received funding for the project. They also presented their idea to Health Canada, who approved the project and agreed to provide funding for employees. Ann and Susan also reviewed the EAI Letter to the Editor.
- Ann Clarke acted as supervisor for this thesis. She provided extensive input regarding content of the thesis and manuscripts, writing style, statistical analysis and interpretation of results. She encouraged and provided funding for Lianne to attend AllerGen and American Academy of Allergy, Asthma and Immunology annual conferences. She also provided Lianne with opportunities to present the SCAAALAR data to the Allergy Association of Quebec and the media. Ann also reviewed the Prevalence Manuscript.

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- Rebecca Wickett, who spent countless hours testing and re-testing the computerized questionnaire and training me to take over as project coordinator (McGill University).
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- Scott Sicherer, who kindly provided our research team with the prevalence questionnaires he used for his research on prevalence in the United States (Mount Sinai Medical Center, New York).

THESIS CONTENT

This thesis focuses on the prevalence and treatment of food allergy in Canada. Chapter I provides an introduction to the subject of food allergy prevalence, including background information on this topic and the objectives of this thesis. Next, chapter II summarizes the literature on food allergy prevalence. Chapter III provides data on the prevalence of food allergy in Canada based on the results from the SCAAALAR project (Surveying Canadians to Assess the Prevalence of Common Food Allergies and Attitudes towards Food Labelling and Risk), the first nationwide study to estimate the prevalence of food allergy. Chapter IV provides a review of the literature on the role of the epinephrine auto-injector (EAI) for the treatment of anaphylaxis, which motivates the results in Chapter V regarding possession of the EAI by Canadians with food allergies again using data from SCAAALAR. Chapter VI will provide a final discussion of the research.

The present thesis has been prepared according to the McGill University guidelines for a Manuscript-Based Thesis. The results are summarized in two manuscripts, as follows:

- Soller L, Joseph L, Clarke AE. Prevalence of food allergy in Canada. (Not yet submitted for publication)
- Soller L, Fragapane J, Ben-Shoshan M, Harrington DW, Alizadehfar R, Joseph L, St. Pierre Y, Godefroy SB, La Vieille S, Elliott SJ, Clarke AE. Possession of epinephrine auto-injectors by Canadians with food allergies. Published in: Journal of Allergy and Clinical Immunology, Volume 128, Issue 2, Pages 426-428, August 2011 (1).

I: INTRODUCTION

Background

Food allergy has become a topic of increasing interest in today's society because of its unknown aetiology, unpredictable progression, difficult diagnosis, and potentially devastating consequences on the quality of life of affected individuals (2). It has been posited by some researchers that the prevalence of food allergy is increasing (3), while others suggest it has stabilized (4, 5). Several studies have been conducted in various countries, including the United States (6, 7), Europe (8, 9), and Israel (10), all with conflicting results with regards to prevalence of food allergy. Two systematic reviews published in 2007-2008 (11, 12) emphasize the wide range of prevalence estimates in terms of both overall prevalence (3-35%) and prevalence of specific food allergies.

Since there is no widely-accepted cure for food allergy, the only way to prevent an allergic reaction is to avoid the known allergen. Avoidance is often difficult for patients because of unclear or absent precautionary statements on packaged foods (13), and accidental exposures continue to occur even if the patient takes all the necessary precautions. Patients must therefore rely on effective treatment in the case of an accidental exposure. This involves the prompt administration of epinephrine as soon as symptoms appear or exposure to the known allergen is suspected (14, 15). Since allergic reactions occur outside the hospital, allergists recommend that all individuals with a history of anaphylaxis, a severe allergic reaction, carry the EAI (16-23). However, even with specific guidelines from allergists, the EAI is still under-prescribed by physicians (24), and, in cases where it is prescribed, the patient often does not know how or when to use it (25-27). It is therefore very important to know how many allergic individuals have the EAI, and to identify those individuals who are particularly unlikely to have it, to be able to accurately target public health campaigns about the importance of the EAI for food-allergic individuals.

Objectives

The SCAAALAR project is the first Canadian study to estimate the prevalence of food allergy. The objectives of this thesis are as follows:

1. To estimate the prevalence of self-reported allergy to any food, as well allergy to milk, egg, wheat, soy, fruits and vegetables among Canadians.
2. To identify socio-demographic characteristics associated with self-report of food allergy in Canada.
3. To estimate the percentage of Canadians with probable food allergy to peanut, tree nut, fish, shellfish and/or sesame that have an EAI.
4. To identify demographic and other factors associated with possession of the EAI in Canadians with probable food allergy to peanut, tree nut, fish, shellfish and/or sesame.

Objectives 1 and 2 will be addressed in Chapter III and objectives 3 and 4 will be addressed in Chapter V.

II: LITERATURE REVIEW - PREVALENCE OF FOOD ALLERGY

Introduction to food allergy

Food allergy is an adverse reaction arising from a specific immune response that occurs reproducibly upon exposure to a food (28). Allergic reactions to food can be either IgE-mediated or non-IgE-mediated (29). For the purpose of this thesis, "food allergy" will include IgE-mediated allergic reactions only. A food allergen is defined as the specific component of a food or an ingredient in the food (usually a protein) that elicits the allergic reaction (28).

Symptoms of an IgE-mediated allergic reaction involve several organ systems including the skin (pruritis, urticaria, erythema, angioedema), eyes (pruritis, edema), respiratory tract (nasal congestion, rhinorrhea, sneezing, cough, chest tightness, wheezing), oral cavity (angioedema of the palate, lips and tongue), gastrointestinal tract (nausea, abdominal pain, reflux, diarrhea, vomiting) and cardiovascular system (tachycardia, hypotension, dizziness, fainting, loss of consciousness) (28). Symptoms of an allergic reaction almost always occur within a few minutes to a few hours after ingestion of the allergenic food (28).

Although allergic reactions to a large variety of foods have been reported (28), the majority of reactions in North America are caused by nine main allergens: peanut, tree nut, fish, shellfish, sesame, milk, egg, wheat, and soy (11, 12, 30, 31). Although not extensively studied in North America, fruits and vegetables are important allergens in Europe, especially in the adult population (32).

Several studies have estimated the prevalence of food allergy in various populations and in different countries. In 2007-2008, a series of systematic reviews by Rona (11) and Zuidmeer (12) were published in an attempt to synthesize and understand the literature on food allergy prevalence. A total of 51 articles were included in Rona's paper, which provided data on the prevalence of food allergy for any food, milk, egg, peanut, fish, and shellfish (11). Zuidmeer's

article featured a total of 36 studies and summarized prevalence data for fruit, tree nut, vegetable, wheat, soy, and sesame allergy, among others (12). The majority of studies included in the two review articles defined food allergy as any case of self-reported food allergy, while others diagnosed food allergy based on the results of confirmatory tests such as skin prick tests (SPT), blood tests, or food challenges. In the next few paragraphs, these definitions will be elaborated and the issues surrounding their use in determining the prevalence of food allergy will be discussed.

Definitions of food allergy in the literature

The double-blind, placebo-controlled food challenge

The gold standard for the diagnosis of food allergy is the double-blind, placebo-controlled food challenge (DBPCFC) (11). A food challenge is a procedure whereby a patient ingests the suspected allergen under physician supervision in a hospital setting (33). In double-blind challenges, neither the patient nor the physician is aware of what the patient is ingesting. The patient is fed increasing amounts of the food (or placebo) over several hours, and symptom assessment is performed throughout the procedure. Although the DBPCFC is of clinical value for diagnosing food allergy because it provides objective results, very few studies use it because the procedure is time-consuming and may potentially cause severe, and even fatal, reactions in individuals with food allergy (34). Furthermore, physicians are often reluctant to subject a patient who they believe is very likely allergic to a challenge, and parents are even more unwilling to permit their child to participate in such a potentially risky procedure. For these reasons, using DBPCFC data alone to estimate prevalence of food allergy may lead to an underestimate of prevalence because individuals who do not undergo a food challenge, but who may in fact be allergic, would not be counted in the final prevalence estimate (34). Some studies may also use open challenges, which are acceptable if performed by a trained healthcare professional, especially in young patients (35). Open challenges are also used by the physician where the risk of

allergy is relatively low to reassure the parent that the child is tolerant to the suspected allergen.

The skin prick test

Although less reliable than the food challenge, most physicians will perform an SPT to establish a diagnosis of food allergy as results are available in 15 minutes and the procedure is minimally invasive (36). To perform this test, a food extract is applied to the arm of the patient, along with a negative and positive control (saline and histamine). A lancet is used to prick the skin through the extract, and the results are read approximately 15 minutes later. A positive SPT is usually defined as a wheal diameter size of at least 3 millimetres larger than the negative control (36, 37). Allergen extracts used in SPTs are not standard across companies, and may change over time (11), causing the results to vary. Furthermore, the SPT has a specificity of only 50%, and in the absence of a convincing clinical history of an IgE-mediated reaction, the test is of little clinical value (30, 37). Despite these well-recognized limitations, patients without convincing clinical histories of an allergic reaction continue to receive diagnoses of food allergy based on positive SPTs alone, sometimes leading to overestimates of prevalence (38, 39).

The allergen-specific blood test

Blood tests can also be used to detect the presence of IgE antibodies to specific foods in the blood. The level of allergen-specific IgE in the serum is measured using fluorescence enzyme labelled assays which involve an enzyme that is linked to an antibody which binds specific IgE and emits a signal that is detectable through a fluorochrome. For the IgE tests, positive predictive values greater than 95% have been obtained with IgE levels of 7kU/L for egg, 15kU/L for milk and peanut, and 20kU/L for fish (40). This means that individuals with IgE levels equal to or higher than these thresholds are 95% likely to have an allergic reaction if they are exposed to the allergen, and therefore a food challenge is not necessary to confirm the allergy. The authors of this study also found that patients with an

IgE level less than 0.35kU/L for any of these foods are very unlikely to have an allergic reaction. For those with IgE levels between these values, food challenges should be done to confirm the presence or absence of food allergy.

Self-report

The least conservative definition of food allergy, and the one which tends to overestimate the prevalence the most, is that based on self-report alone, i.e., perceived food allergy (11). Self-report refers to a situation where an individual reports having a food allergy, but the individual is not necessarily assessed by a physician and confirmatory testing may not have been performed. There is no well-established definition of self-report in the literature; some researchers simply ask whether the participant has a food allergy without any further questioning, while others may ask the participant to describe their clinical history including symptoms of previous allergic reactions. Many researchers base prevalence estimates on self-report because it does not require that each patient be assessed by a physician and it allows large populations to be included. However, prevalence estimates based on self-report are often higher than those based on stricter criteria such as the requirement of a clinical history compatible with an IgE-mediated reaction combined with a positive diagnostic test result such as SPT, IgE, or DBPCFC. Research has shown that individuals tend to report diseases even if these diseases were never diagnosed clinically, and food allergy is not exempt from this phenomenon. In fact, one American study found that almost one-third of mothers with young children reported at least one food allergy in the household (41). The trend extends beyond North America to Europe, where a Dutch study found that 12.4% of adults thought they had a food allergy, but upon further investigation with diagnostic testing, the prevalence dropped to 2.4% (9). In Britain, the prevalence of food allergy was found to be 19.9% based on self-report, but when diagnostic tests were employed to confirm the allergy, the prevalence was found to be between 1.4% and 1.7% (42).

Summary

From the above, it is clear that the choice of definition of food allergy employed by the researcher can affect the results of the study. In Chapter III of this thesis, data will be presented from the SCAAALAR project, the first nationwide Canadian study to estimate the prevalence of food allergy. Although the study design, which involved telephone interviews with participants across Canada, precluded evaluation of each participant by a physician, we did ask detailed questions regarding the reaction experienced to some of the most common allergens (peanut, tree nut, fish, shellfish and sesame). However, because we wanted to keep the survey time to a minimum, we were unable to evaluate reactions to all food allergens with such rigor (milk, egg, wheat, soy, fruits, vegetables, and other allergies). Therefore, our prevalence estimates for these foods are based on self-report alone, which, as seen in the paragraph above, may lead to an overestimate. We were able to create more accurate estimates for peanut, tree nut, fish, shellfish and sesame which were based on symptoms and/or self-report of physician-diagnosis of food allergy (probable food allergy) (43). The prevalence estimates for perceived (i.e., self-report only) and probable food allergy for these five foods were very similar; hence, our perceived estimates for other foods are probably not huge overestimates.

Definitions of food allergy for this thesis

Food allergy was defined in different ways throughout this thesis, depending on the information available for the different food allergens.

Perceived food allergy

Any self-report of food allergy by the primary respondent during the telephone survey, used throughout the thesis interchangeably with self-reported allergy, used for overall food allergy, milk, egg, wheat, soy, fruits and vegetables (Chapter III).

Probable food allergy

Convincing history of an IgE-mediated allergic reaction* and/or self-report of physician diagnosis of food allergy. Probable food allergy could only be determined for peanut, tree nut, fish, shellfish, and sesame allergies because they required detailed questions regarding symptoms and physician diagnosis (Chapter V).

Diagnosed food allergy

Convincing history of an IgE-mediated allergic reaction and self-report of physician diagnosis, or self-report of diagnosis without a convincing history, could only be assessed for peanut, tree nut, fish, shellfish, and sesame allergies for the same reason as above (Chapter V).

Ben-Shoshan et al. employed three definitions in his previous publication: perceived, probable and confirmed (43). Confirmed required confirmatory test results from the treating physician, which were very difficult to obtain, and hence this definition was not used in this thesis.

Before presenting the SCAAALAR data, the current literature on food allergy prevalence will be summarized below.

Prevalence of food allergy

The overall prevalence of food allergy

The overall prevalence of food allergy varies considerably in the literature; in the studies included in Rona's article, prevalence ranged from 3% to 35% based on self-report (11). These estimates decreased with the use of results of diagnostic

* A convincing history of an allergic reaction 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 2 hours of ingestion or contact (or inhalation for fish and shellfish). Mild symptoms include pruritus, urticaria, flushing, or rhinoconjunctivitis; moderate includes angioedema, throat tightness, gastrointestinal complaints, or breathing difficulties (other than wheeze); and severe includes wheeze, cyanosis, or circulatory collapse.

tests; estimates based on food challenges (1% to 10.8%) were generally lower than those based on SPTs or blood tests (2% to 5%), but there was still inconsistency in the rate of allergy across studies (11). There is only one North American study that reported the overall prevalence of food allergy; this study was performed in the United States by Altman in 1996 using a questionnaire-based survey, which was mailed out to a demographically-representative sample of households. Altman reported the overall prevalence of food allergy to be 16.2% in 1989, 16.6% in 1992, and 13.9% in 1993 (42) based on self-report; however, no information on diagnostic testing was obtained.

Peanut allergy

Peanut allergy is one of the most severe food allergies and causes the majority of fatal anaphylactic reactions from food in the United States. Peanut allergy is usually life-long, with a resolution rate of only about 20% (44). Many studies have attempted to estimate the prevalence of peanut allergy; in fact, it is one of the most studied food allergens in the literature. In Rona's review article, the prevalence of peanut allergy ranged from 0% to 2% based on self-report, and 0.5% to 2.5% for SPTs or blood tests (11). Rona's article consisted primarily of European studies on peanut allergy prevalence; only two groups in the United States (Altman (42) and Sicherer (1999, 2003, 2010)) and our group in Canada have conducted peanut allergy prevalence studies in North America. Using a cross-sectional approach, Sicherer in the United States estimated the prevalence of peanut allergy in children to be 0.4% in 1997 (45), 0.8% in 2002 (6) and 1.4% in 2008 (3), according to self-report. He did not seek diagnostic test results from participants. Our group at McGill estimated the prevalence of peanut allergy in Montreal schoolchildren using questionnaires, SPTs, blood tests, and food challenges, and estimated the prevalence to be 1.5% in 2000-2002 (46) and 1.63% in 2005-2007 (4). Comparing these two studies, it appears that peanut allergy is more prevalent in Canadians than in Americans. However, the American and Canadian studies are not comparable. The American studies were nationwide, whereas the Canadian study was in a single city (Montreal), and the American

studies estimated prevalence based on self-report of peanut allergy, whereas the Canadian study established peanut allergy using the results of confirmatory tests in addition to self-report.

Tree nut allergy

Tree nut is the second most common food allergen involved in fatal anaphylaxis, after peanut. Like peanut, tree nut allergy usually does not resolve with time; one study by Fleischer found that only 9% of children with tree nut allergy outgrew their allergy (47). There are different types of nuts which are classified as tree nuts, and some are more allergenic than others. Hazelnuts, walnuts, cashews and almonds are more commonly involved in allergic reactions than pecans, chestnuts, brazil nuts, and pine nuts (48). Zuidmeer's article found that the rate of tree nut allergy varied from 0.1% to 4.3% when based on food challenge, less than 1% when defined by SPT or blood tests, and 0% to 7.3% for perceived allergy (12). However, some authors did not mention whether they classified peanuts in the same group as tree nuts, so it is difficult to determine whether some of the prevalence estimates include peanuts or not. The highest prevalence for a specific tree nut was 4% for hazelnut according to food challenge and SPTs and 4.1% for almond based on self-report. Using a cross-sectional telephone survey in the United States, the perceived prevalence of tree nut allergy was estimated at 0.5% in 1997 (45), 0.7% in 2002 (6) and 0.6% in 2008 (3). It is possible that some patients reporting allergy to tree nut with symptoms limited to itching or swelling of the mouth following oral contact with the food actually have pollen-food allergy syndrome. Pollen-food allergy syndrome occurs where an individual has an allergy to a flower or tree pollen which shares a common antigen with pollen from a specific food, causing oral symptoms similar to those of an allergic reaction upon ingestion of that food (49). This syndrome occurs with nuts, fruits, and vegetables, and patients with pollen-food allergy syndrome are usually less likely to experience severe anaphylaxis compared to those with true IgE-mediated food allergy (50). However, Sicherer's study did not address this issue; therefore it cannot be determined whether or not his prevalence estimates for tree nut are accurate.

Fish allergy

Fish allergy usually develops later in life and persists over time, affecting more adults than children according to some studies (7). There are several types of fish, but those which cause the majority of reactions include salmon, tuna and halibut (7). Very few studies have estimated the prevalence of fish allergy due to the difficulty in establishing a clinical diagnosis and the lack of established thresholds for SPT or blood test results; in fact, only 5 studies were found which used diagnostic tests to confirm fish allergy: 3 for SPTs or blood tests and 2 for food challenges (11). Rona's review article found that the prevalence of fish allergy according to self-report ranged from 0% to 2%, 0.5% or less using SPTs or blood tests, and near 0% for food challenge. Using a general population telephone survey in the United States, Sicherer found the prevalence of fish allergy to be 0.1% for children and 0.4% for adults according to self-report (7). Some individuals reporting a single reaction to fish may have experienced scromboid fish poisoning due to a bacterial contamination which causes the production and release of histamine which may resemble an IgE-mediated allergic reaction (51). Alternatively, an allergy to anisakis simplex, a worm found in fish, may occur upon consumption of raw fish (52, 53). However, patients reporting recurrent reactions or positive diagnostic tests to fish likely do not have scromboid poisoning or anisakis allergy. Unlike with other food allergens, allergic reactions to fish can be triggered through inhalation because the allergenic protein found in fish is airborne (54).

Shellfish allergy

Allergy to shellfish, like fish, tends to develop in adulthood. According to Sicherer, the prevalence of perceived shellfish allergy in American children is very low, at 0.1%, whereas in adults, it is 2%, making it the leading cause of IgE-mediated food allergy in adults in the United States (7). The authors also found that the most common types of shellfish causing allergic reactions were crab and lobster (7). Rona's review article reported prevalence estimates ranging from 0%

to 10% for perceived allergy, 0% to 1.4% for SPTs and blood tests, and near 0% for food challenge (11). Like fish allergy, shellfish allergy is difficult to diagnose because there are no established cut-off levels for SPTs or blood tests. Therefore, the only reliable diagnostic test is the food challenge, which can be dangerous for patients who are allergic. As with fish, airborne shellfish allergens can elicit an allergic reaction through inhalation (54).

Sesame allergy

When Zuidmeer's article was published in 2008, there were only 5 studies examining the prevalence of sesame allergy. In the last few years, the number of studies looking at sesame allergy has increased, which might be due to the observation that sesame seed allergy seems to have become more common. Most recently, Osborne et al. in Australia estimated that sesame allergy affected 2.5% of 12-month-old children according to SPT, but this number dropped to 0.8% after food challenges were performed (55). Three studies to estimate the prevalence of sesame allergy were performed in the United Kingdom, one of which found a prevalence of 0.6% for self-report in those over 15 years old (56), while two other studies which used SPTs found prevalences of 0.2% in 7 year-olds (57), and 0.6% and 0.9% in 11 and 15 year-olds, respectively (58). In Israel, Dalal and colleagues found a perceived prevalence of 0.05% among infants up to 2 years old, and 0.2% using SPT (59). In the United States, Sicherer et al. found that the prevalence of sesame allergy was 0.1% according to self-report (3). From the data that exists in the literature, sesame allergy appears to be quite rare.

Milk allergy

Milk allergy is the most common food allergy among children, with a prevalence of 2.2% to 2.8% at 12 months of age (60, 61). Milk represents 10% to 19% of all food-induced anaphylaxis cases seen in the pediatric emergency room, behind peanuts and tree nuts (62-65). Children outgrow their milk allergy in the majority of cases (61), hence, it is rarely seen in adults. According to Rona's review article, which included 28 studies on milk allergy, the self-reported prevalence of milk allergy ranged from 1.2% to 17%; the high prevalence estimate of 17% was

perhaps due to the fact that studies which did not perform diagnostic testing on participants could not differentiate between milk allergy and lactose intolerance, which is often mistaken for food allergy. Lactose intolerance results from an enzyme deficiency, specifically lactase, which is responsible for digesting milk products (66). Patients reporting an allergic reaction where the symptoms are localized to the gastrointestinal tract likely suffer from lactose intolerance and not IgE-mediated allergy (66). Another issue which complicates the diagnosis of milk allergy is the fact that some patients with milk allergy can tolerate cooked milk in baked goods but cannot tolerate raw milk or dairy products, whereas those with lactose intolerance can tolerate small amounts of some dairy products such as cheese and yogurt. Given that many participants probably have lactose intolerance and not IgE-mediated milk allergy, it is not surprising that the range of prevalence estimates in the literature for milk allergy based on SPTs or blood tests (0% to 2%), or based on oral food challenge results (0% to 3%), was much lower than the perceived estimates (11). Although a few studies in the literature employed a general population approach, only three involved individuals of all ages (42, 67, 68). The remaining studies included adults only (9, 69-71) or children only (60, 72). The majority of studies involved cohorts of individuals from a specific area (55, 58, 73), a hospital or clinic (74, 75), or a school (76, 77), and the age range of the participants varied considerably. Only one study estimated the prevalence of milk allergy in the United States: 29.3% in 1989 and 30.7% in 1993, based on self-report (42). These numbers are extremely high, and may be explained by a possible confusion with lactose intolerance. In Canada, one study from 1973 estimated the prevalence of milk allergy based on oral food challenge to be 7.5% in the first year of life (78); this study is extremely outdated and only represents young infants, therefore it cannot be used to make any inferences regarding the prevalence of milk allergy in the general population of Canada.

Egg allergy

After milk, egg is the second most common food allergen in young children (31, 79). According to Rona's article, 0.2% to 7% of individuals have egg allergy,

based on self-report (11). Although most studies in Rona's paper used self-report to estimate prevalence, some use SPTs and blood tests, and only three used food challenge data (72, 77, 80). As with milk allergy, prevalence estimates varied between studies, but decreased slightly with the use of SPTs and blood tests (0.5% to 2.5%) and even more so with the use of food challenges (0% to 1.7%). For those studies using food challenges, the prevalence of egg allergy among a cohort of German children up to 17 years old, was 0.5% (72); similar testing performed on nursery school children in Mexico found a prevalence of 0.6% (77), and, among 3 year-old children in Denmark, a prevalence of 1.6% was reported (80). Eggesbo in Norway (79) and Sampson in the United States (37) reported prevalence estimates in children similar to those from Denmark, 1.5% and 1.3% respectively. Many patients with egg allergy can tolerate cooked egg in baked goods but not raw egg. This issue may help explain the differences in the prevalence of egg allergy in the studies above, although the studies do not report whether the patients were challenged with raw or cooked egg, except for the Denmark study, where we know that cooked egg was used. A few studies have estimated the prevalence of egg allergy among adults (42, 81), even though egg allergy is outgrown in more than two-thirds of patients by the age of 16 (82). Only a few studies were population-based-Altman in the United States (42), Falcao in Portugal (81), Gislason in Iceland (69), Woods in Australia (71), Roehr (72) and Zuberbier (68) in Germany, and Young in the United Kingdom (67)-while others were cohorts of patients from a specific town (83), daycare (77), school (84), or clinic (85). There are no data on egg allergy prevalence from Canada.

Wheat allergy

Wheat allergy, like milk and egg allergy, is said to decrease in prevalence with age; the BAMSE (Barn Allergi Miliõ Stockholm Epidemiologi) cohort of Sweden reported a prevalence of 4% for wheat sensitization in children 4 years of age (86, 87), and a decrease in prevalence from 1 to 8 years of age (88). This rate may be too high because the authors do not differentiate between IgE-mediated allergy and sensitization to wheat, and may have therefore included patients who are not

truly allergic in their calculations. The majority of children outgrow their wheat allergy by 3 to 5 years old, which is why wheat allergy is much less common in adults(89). A study from the United States found that the self-reported prevalence of doctor-diagnosed wheat allergy in adults was 0.4% (90), a 10-fold difference compared to the Swedish report of 4% for 4 year-old children. In Zuidmeer's review article, two population-based studies from the United Kingdom and Germany found prevalences as high as 0.5% in children undergoing food challenge tests (12). Most studies included in Zuidmeer's article were not population-based; the prevalence of wheat allergy in Zuidmeer's systematic review was 0% to 3.6% for SPTs and blood tests, and 0.2% to 1.3% for self-report (12). The estimate of 3.6% stems from a study performed on blood samples from volunteer donors in the United States (91); there was no attempt to combine IgE levels with a clinical history of an allergic reaction to wheat, therefore one can only comment on sensitization, i.e., evidence of wheat-specific IgE, and not clinical allergy. The other American study by Altman found a perceived prevalence of 0.3% for wheat allergy in 1996 (42). The authors did not comment on the possibility that some patients who self-report wheat allergy may actually suffer from celiac disease, an autoimmune condition whereby consumption of gluten-containing products causes inflammation of the bowel, leading to symptoms such as diarrhoea, vomiting, anaemia, and others (92). The gastrointestinal symptoms involved in celiac disease may be confused with an allergic reaction. If not taken into consideration when determining the prevalence of wheat allergy, the results may be overestimated.

Soy allergy

Soy allergy apparently resolves with time, and should therefore be more common in children than in adults(93). However, prevalence data from the literature shows the opposite trend, suggesting that perhaps soy allergy persists. This is likely due to the use of different criteria to define food allergy in various studies. For example, using food challenge results, Osterballe in Denmark found a prevalence of 0% for soy allergy in children 3 years of age (80), and Roehr in Germany found

a prevalence of 0.7% in children 0-14 years of age (72). Four studies included in Zuidmeer's review performed SPTs on children to assess allergy to soy, and again, the prevalence was low, with a range of 0.03% to 0.2%. In adults, three studies using blood tests found the prevalence to be from 0.2% to 2.9%. Self-report of soy allergy was examined in 9 studies, and the prevalence ranged from 0% to 1.3%. The highest prevalence estimates for soy allergy were from 3 Swedish studies: 2.1% (94) and 2.9% (95) in 20-44 year-olds, using blood test results, and 1.3% in 13-21 year-olds based on self-report (84); it was lower in other countries regardless of the age of participants or the definition of food allergy used (12). There are no data on soy allergy from the United States or Canada.

Fruit allergy

Although not one of the nine main food allergens in North America, fruit allergy is apparently one of the most common food groups involved in adult allergy in Europe. Studies looking at the prevalence of fruit allergy are sparse; Zuidmeer's review found a total of 8 studies which estimated the self-reported prevalence of allergy to all fruits. The perceived prevalence estimates ranged from 0.4% in individuals under 61 years old (96), to 11.5% in 2 year-old children (79). Most studies examined specific fruits, and the prevalence estimates for these varied as well. For food challenge, the prevalence of apple allergy was the highest, with one study by Roehr from Germany reporting a prevalence of 4.3%, and the prevalence of other fruit allergies, regardless of age, was less than 1% (12). All studies looking at food challenge results, with the exception of two, were performed in Germany. Only 3 studies used SPTs, one in Germany, one in France, and one in Israel. Again, apple was the most prevalent of the fruit allergies, at 4.2% (68), while all other fruit allergies had a prevalence of less than 1%. For perceived fruit allergy, there were several studies included in Zuidmeer's report, most of which were conducted in Europe, one in Israel (59) and one in Russia (83). Five studies were population-based, and all were from Europe. To interpret these prevalence estimates for fruit allergy, it is important to consider pollen-food allergy

syndrome which may be mistaken with food allergy because the oral symptoms are very similar to those found in food allergy. Without specifically asking about symptoms of the allergic reaction and performing diagnostic allergy testing, it is impossible to tell whether an individual has pollen-food allergy syndrome or IgE-mediated food allergy. This issue may help to explain the extremely high prevalence of perceived fruit allergy found in some of the studies included in Zuidmeer's article. In North America, the only study to estimate the prevalence of fruit allergy was by Altman in the United States in 1996, and he found a prevalence of 1.4% for allergy to all fruits(42). There is no recent American or Canadian data on fruit allergy prevalence.

Vegetable allergy

Several vegetables have been implicated in food-induced allergic reactions, but carrot and tomato seem to be the most common and also the most studied of the vegetable family, especially in Europe. In Zuidmeer's review article, the prevalence of self-reported tomato allergy was 13.7% in Swedish children 18 months of age, whereas in Icelandic children of the same age, the perceived prevalence was 3.1% (74). Carrot was also quite prevalent; a Russian study found a prevalence of 6% based on self-report in children under 1 year of age (83), and a Swedish study found a prevalence of 3% in individuals 13 to 21 years of age (84). Pollen-food allergy syndrome is also an issue with vegetables. Therefore, it is possible that the prevalence estimates for perceived allergy to vegetables are inflated by inclusion of those with pollen-food allergy syndrome. Studies which used SPTs or food challenge to estimate prevalence of vegetable allergy all found prevalences less than 1% for all vegetables, except one German study that reported a prevalence of 2.7% for carrot allergy using SPTs (68). As with fruits, an American study by Altman found a prevalence of 1.4% for vegetable allergy(42). No Canadian data exists for vegetable allergy.

In the next section of this literature review, demographic characteristics which may be associated with food allergy are discussed.

Demographic predictors of food allergy

Age

Several studies have shown that the prevalence of food allergy varies according to age, with children having more food allergies than adults. Food allergy affects up to 2.5% of adults and 4% to 8% of children (31, 97-100). Children tend to develop food allergies at a young age and outgrow them as they mature. As noted previously in the review, milk (101), egg (82, 102), wheat (103), and soy (104) allergy tend to resolve over time, while fish and shellfish allergy tend to develop in adulthood, and are usually life-long (28). A minority of those with peanut (44) and tree nut (47) allergy may also develop tolerance.

Sex

Sex has also been shown to have an effect on the prevalence of allergic diseases such as asthma (105, 106) and allergy. The 2005-2006 National Health and Nutrition Examination Survey in the United States found that males were more likely to have food allergy than females (107), whereas Ben-Shoshan et al. in Canada showed that tree nut and shellfish allergy are more common in females than in males (108). In a 2010 publication by Sicherer et al., allergies to peanut, tree nut and sesame were more common in males under the age of 18 years and more common in females over 18 years (3). The difference observed between these studies is likely due to the definition of food allergy that was used. Ben-Shoshan and Sicherer relied on self-report of symptoms during the most severe reaction, with or without self-report of physician diagnosis and testing to establish the diagnosis of food allergy, whereas the National Health Survey used self-report of symptoms and performed food-specific serum IgE blood tests on 80% of the sample. As was mentioned previously, using self-report alone to ascertain whether an individual has a certain condition may be problematic. Females tend to over-report medical conditions and seek consultation with a physician for their ailments more often than males (109). There may also be genetic reasons for differences in

prevalence of food allergy between men and women. For example, the presence of estrogens, which enhances mast cell activation and allergic sensitization, and progesterone, which potentiates IgE induction, in women, may influence the development of allergies (110).

Western versus non-western birthplace

Studies have shown that the rate of allergic disease is higher in developed than in developing countries. For example, the rate of peanut allergy is between 0.43% and 0.64% in Asian schoolchildren (111, 112) compared to North American and European children, where the prevalence is 1.8% in Canada (43), 1.4% in the United States (3), and between 1.2% and 1.8% in the United Kingdom (5, 113). A study from Asia compared the prevalence of peanut, tree nut and shellfish allergy among children born in Asia and children of western ex-patriates who had immigrated to Asia (111). They found a higher prevalence of peanut and tree nut allergy in western-born children compared to Asian-born children. A recent paper by our group at McGill suggests that food allergy may be less common among immigrants to Canada compared to individuals born in Canada, although the difference was only significant for shellfish allergy (108). Prevalence of food allergy may differ between immigrants and non-immigrants for genetic (114) or dietary reasons (10), but may also appear to be different because of the lack of family doctors and consequent under-diagnosis among recent immigrants to Canada (109) compared to individuals born in Canada.

Socioeconomic status

Socioeconomic status may also be associated with food allergy. A study by Pawlinska-Chmara et al. found a higher prevalence of food allergy in children with highly-educated parents who lived in more favourable economic conditions (115). Our group has also shown that those with higher education had a higher prevalence of food allergy, particularly for peanut and tree nut allergy (108). It is possible that highly educated and wealthier parents were more likely to follow the guidelines from the American Academy of Pediatrics which, until recently,

recommended restriction of allergenic foods during pregnancy, lactation, and in infancy (116). It is now thought that these precautions may actually increase the likelihood of developing food allergy (117), which may explain the higher prevalence of food allergy observed in the middle and upper class. The higher prevalence of allergic disease in those of higher socioeconomic status may also be explained by a phenomenon known as the hygiene hypothesis. The idea is that individuals of higher socioeconomic status are exposed to less bacteria and suffer from less infections, which causes a skewing of the immune response away from Th1, the immune cells that fight infection, towards Th2, which leads to an increase in allergy (118). As well, more affluent households are more likely to seek medical attention for their ailments (109), and hence may be more likely to obtain a physician diagnosis of food allergy than those of lower socioeconomic status, thereby causing an artificially inflated prevalence of food allergy in this group (109).

Marital status

The link between marital status and food allergy has never been explored; however, one study found that individuals who are married are more likely to have a family doctor (109), and hence, would seek physician diagnosis for food allergy more often than those who are single. This may lead to an apparent, but perhaps not real, increase in diagnosed food allergy in those who are married compared to those who are single.

Geographic location

Studies have shown that individuals living in urban areas have more asthma (119) and eczema (120) than in rural areas. Recently, Ben-Shoshan et al. showed that shellfish allergy is more common in urban areas (108). Urban lifestyle is usually associated with less exposure to infections and animals, higher antibiotic use, and a higher consumption of processed foods, all of which may lead to increased prevalence of allergic disease, including food allergies. It is also possible that a higher number of specialists in urban areas would lead to more diagnoses of food

allergy than in rural areas, thereby creating an artificially inflated prevalence in urban compared to rural settings. Although the distribution of food allergy across Canadian provinces has not been specifically studied, Quebec has been identified as the province with the lowest percentage of individuals having regular family doctors and Ontario with the highest (109). It would not be surprising, therefore, to find different rates of food allergy across Canada.

Conclusion

The SCAAALAR project is the first Canadian study to provide prevalence estimates for overall food allergy and specific foods using a cross-sectional study design and random selection of households. The estimates of perceived prevalence for peanut, tree nut, fish, shellfish, and sesame allergy (43), as well as demographic predictors of these five allergies, have already been published by Ben-Shoshan (108). In Chapter 3, we extend this work by presenting the proportion of Canadians reporting at least one food allergy and provide prevalence estimates for individual foods not discussed by Ben-Shoshan (milk, egg, wheat, soy, fruits, and vegetables), as well as demographic predictors of food allergy.

III: PREVALENCE OF FOOD ALLERGY IN CANADA

Abstract

Background

Food allergy prevalence estimates vary considerably across studies, as documented in a series of systematic reviews from 2007-2008 (11, 12). Although our research team has generated recent estimates for the prevalence of peanut, tree nut, fish, shellfish, and sesame in Canada (43), the prevalence of food allergy overall has never been reported.

Objectives

To estimate the overall prevalence of food allergy and the prevalence of specific food allergies (milk, egg, wheat, soy, fruits and vegetables) among Canadians, and to identify demographic predictors associated with self-reporting food allergy.

Methods

We performed a cross-sectional, randomized telephone survey of Canadian households. Respondents were asked whether any household member had a food allergy, and to what food(s). The prevalence of perceived allergy to any food was ascertained, and multivariate logistic regression performed to identify socio-demographic characteristics associated with self-reporting food allergy.

Results

Of 10,596 households surveyed, 3,666 responded (35% response rate), of which 3,613 provided data on food allergies, representing 9,667 individuals. Of these, 8.0% (95% CI, 7.5%, 8.6%) self-reported at least one food allergy. When adults reporting only milk, egg, wheat and/or soy allergy were omitted, the prevalence dropped to 6.6% (95% CI, 6.1%, 7.1%). After adjusting for non-responders, the prevalence increased to 8.2% (95% CI, 7.6%, 8.8%). Children and individuals living in a household where the primary respondent was born outside of Canada

were less likely to report a food allergy than adults and those born in Canada [OR 0.79 (95% CI, 0.64, 0.97)] and OR 0.71 (95% CI, 0.55, 0.91)], respectively. Individuals living in a household where the primary respondent was a post-secondary graduate were more likely to self-report food allergy than non-post-secondary graduates [OR 1.27 (95% CI, 1.06, 1.53)]. . In addition, individuals living in Western Canada had the highest prevalence of self-reported food allergy [OR 1.44 (95% CI, 1.17, 1.77)], and those living in Quebec had the lowest [OR 0.64 (95% CI, 0.53, 0.79)].

Conclusions

This is the first nationwide study to estimate the prevalence of food allergy among Canadians. Food allergy is an important health problem, affecting 1 in 13 Canadians. Further research is necessary to help explain these differences in the prevalence of food allergy.

Introduction

Food allergy is a significant health problem in the western world, and some studies suggest it is increasing (3) while others say it has stabilized (4, 5). Prevalence estimates vary considerably between studies, with estimates for overall prevalence ranging between 3% and 35% (11, 12). This variability is likely due to multiple factors, including study design, study population, and methodology for assessing the definition of food allergy.

In 2008-2009, our research team conducted the SCAAALAR study (Surveying Canadians to Assess the prevalence of food Allergies and Attitudes towards food Labelling and Risk) and published the first Canadian data on the prevalence of peanut, tree nut, fish, shellfish and sesame allergy (43). However, there are no published data on the overall prevalence of food allergy in Canada. In the SCAAALAR study, we did inquire about the presence of other food allergies, but unlike peanut, tree nut, fish, shellfish, and sesame, we did not collect any data about symptoms after ingestion of the allergen or diagnostic testing to confirm the allergy. Although this would have been optimal to develop an estimate of overall food allergy prevalence, such detailed data collection would have considerably lengthened the telephone survey and made it infeasible. Hence, in this manuscript, we provide estimates for the overall prevalence of food allergy in Canada using self-report of food allergy only without requiring a characteristic history of allergy. We also provide estimates stratified by demographic characteristics, estimates adjusted for non-response and estimates for specific foods not previously reported in SCAAALAR.

Methods

Study design

To estimate the prevalence of food allergy in Canada, we performed a nationwide cross-sectional telephone interview of households in the 10 Canadian provinces. The territories (Northwest, Yukon and Nunavut) were purposely excluded due to

expected cultural differences between individuals living in the territories and those living in the rest of Canada. It was thought that these areas would be harder to sample because there are fewer landlines and many individuals living in Nunavut may not speak English or French. Household telephone numbers and their corresponding mailing addresses were randomly selected from the electronic white pages by Info Direct, a company who maintains an updated list of telephone numbers and mailing addresses for Canadian households listed in the white pages.

Survey methodology

Four trained interviewers based at McGill University in Montreal, Quebec, Canada, and three at McMaster University in Hamilton, Ontario, Canada, contacted households using Computer Assisted Telephone Interviewing (CATI) software (WinCati 4.2, Copyright 1986-2004 Sawtooth Technologies Inc, Northbrook, Illinois) between May 2008 and March 2009. Participants were eligible to respond to the telephone survey if they were 18 years of age or older, lived in the household, and appeared to have no mental, language, and/or hearing barriers to understanding the interviewer's questions. Once eligibility of the primary respondent was ascertained, they were invited to participate in the telephone survey. The respondent was asked whether they or another household member had any food allergies, and demographic information was also obtained.

To optimize response rates and minimize selection bias, interviewers contacted each household up to a maximum of ten times, at different hours and on different days of the week. Calling was done between 9:30am and 9pm local time on weekdays (Monday to Friday), and between 10:30am and 5pm on weekends (Saturday and Sunday). An information letter was sent to all selected households informing them that they would be contacted to participate in a telephone survey (see Appendix A).

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

Questionnaire

To estimate the prevalence of food allergy, the questionnaire first asked if there were any food allergies in the household, and if so, to which food(s). Although detailed data on the symptoms post-ingestion and diagnostic allergy testing were collected for participants reporting a suspected allergy to peanut, tree nut, fish, shellfish, and sesame, this information was not collected for any other foods. The prevalence estimates based on the detailed history have been previously published (43). All prevalence estimates in this manuscript are based on self-report of allergy only and are referred to as "perceived prevalence."

At the end of the questionnaire, the primary respondent was asked to provide the age of all household members, country of origin and highest level of education of the primary respondent, and annual household income.

Because the survey was performed across Canada, the full questionnaire was translated into French and back-translated to English (see Appendix B for the prevalence and demographics questionnaire).

Sample size

Given that our group previously estimated the prevalence of peanut allergy in Montreal school-children (4, 46), and data already exist on the prevalence of allergy to tree nut, fish, and shellfish in the United States (6, 7), we based our sample size calculation on these previous estimates. From our Montreal study, the prevalence of peanut allergy in children is 2.0 % (95% CI, 1.4%, 2.7%); from Sicherer's studies in the United States, the prevalence of tree nut allergy is 0.5%, the prevalence of fish allergy is 0.4% (95% CI, 0.3%, 0.5%), and the prevalence of shellfish allergy is 2.0% (95% CI, 1.8%, 2.3%). If we assume that the prevalence of these allergies in the general Canadian population is similar to these previous estimates, a sample of approximately 9,000 individuals (or 3,000 households assuming there is an average of 3 persons per household(121)) will enable us to estimate the prevalence of peanut allergy to within ± 0.30%, nut

allergy to within ± 0.15%, fish allergy to within ± 0.175 %, and shellfish allergy to within ± 0.30% using 95% CIs.

Statistical analysis

i. Crude prevalence estimates for overall food allergy

The prevalence of perceived food allergy was estimated as the number of individuals who self-reported at least one food allergy divided by the total number of participants. We developed two estimates of perceived prevalence and calculated 95% CIs:

1) The numerator included all individuals self-reporting at least one food allergy
2) The numerator excluded all adults self-reporting an allergy to milk, wheat, egg, and/or soy but no other food allergies

Exclusion of these adults was based on studies showing that individuals allergic to these four foods have usually outgrown the allergy by the time they reach adulthood (122), and therefore it is unlikely that they continue to have true IgE-mediated allergy to these foods. In adults, adverse reactions to milk often represent lactose intolerance(66), and to wheat, celiac disease(123).

ii. Overall food allergy prevalence estimates adjusted for household non-response and clustering

Due to a relatively low response rate (35%), we also calculated an adjusted perceived prevalence estimate to account for non-responding households, i.e., those households who refused to participate in the survey. This additional prevalence estimate also enabled us to account for household clustering, which is important since there is a genetic component to food allergy. To calculate an adjusted prevalence estimate for food allergy which would account for non-responding households, we needed to impute the probability that non-respondents were allergic based on the data they provided. Since the only data available was the postal code and province of residence, this is what was used. We used

WinBUGS to calculate the adjusted prevalence estimate (see Appendix C) using the technique of multiple imputation to account for the missing allergy status of all individuals in the non-responding households. Multiple imputation is the gold standard for adjusting for missing data (124). It involves filling in missing values with a "best guess", which is based on other data from the dataset, in this case, the 3-digit postal code and province of residence of the non-responding households. Multiple versions of the complete dataset (usually thousands) are formed and data analysis is carried out on each one. To make final inferences from the data, an average of the results is used as a point estimate, with overall variance equal to the sum of within and between imputation variances (124). The model in WinBUGS was a three-level hierarchical model; the highest level was the provincial level, which contained 10 provinces, followed by the postal code level, which contained 1,372 postal codes, and finally the household level, which contained 10,596 households. The household level was included in the model to account for within-household clustering, i.e., multiple individuals living in the same household.

iii. Prevalence of allergy to specific foods

For prevalence of allergy to specific foods, we calculated the proportion of individuals reporting an allergy to milk, egg, wheat, soy, fruits and vegetables divided by the total number of individuals in the study, and calculated the 95% CIs for the prevalence of each reported food allergy.

iv. Socio-demographic predictors of perceived food allergy to any food

We also performed multivariate logistic regression to identify potential socio-demographic predictors associated with self-report of food allergy. The first analysis involved all individuals with any food allergy (main analysis), while the second excluded adults with milk, egg, wheat or soy allergy but no other allergies (sensitivity analysis). The following characteristics were included in our analyses: age of the allergic individual (adult versus child), country of birth (Canada versus outside of Canada) and education level (post-secondary degree versus no post-

secondary degree) of the primary respondent, household income (at or above low income cut-off versus below), and geographic location (Quebec vs. Atlantic Canada and Ontario, and Western Canada vs. Atlantic Canada and Ontario).

Results

Participation rate

Of the 10,596 households who were contacted to complete the survey, 3,666 responded (35% response rate) of which 3,613 completed the survey, representing 9,667 individuals (2198 children and 7469 adults).

Perceived prevalence of food allergy in Canada

Responses indicated an allergy to one or more foods in 860 individuals [8.0% (95% CI, 7.5%, 8.6%)] reported an allergy to one or more foods. Excluding adults reporting milk, egg, wheat, or soy allergies, the overall prevalence dropped to 6.6% (95% CI, 6.1%, 7.1%). After adjusting for non-response, the perceived prevalence for any food allergy was 8.2% (95% CI, 7.6%, 8.8%). The perceived prevalence of allergy to milk, egg, wheat, soy, fruits, and vegetables, in addition to previously published estimates for peanut, tree nut, fish, shellfish, and sesame, are presented in Table 1.

Table 1: Perceived prevalence of food allergy in Canada

Food/Food group	Children (%) (95% CI)	Adults (%) (95% CI)	Entire study population (%) (95% CI)
Reporting at least one food allergy	7.1 (6.0, 8.2)	8.3 (7.7,9.0)	8.0 (7.5, 8.6)
Excluding adults with milk, egg, wheat, soy allergy	7.1 (6.0, 8.2)	6.5 (5.9, 7.1)	6.6 (6.1, 7.1)
Adjusted for non-response	7.1 (6.1, 8.3)	8.6 (7.9, 9.1)	8.2 (7.6, 8.8)
Peanut	1.8 (1.2, 2.3)	0.78 (0.58, 0.97)	1.0 (0.80, 1.2)
Tree nut	1.7 (1.2, 2.3)	1.1 (0.84, 1.3)	1.2 (1.0, 1.4)
Fish	0.18 (0.00, 0.36)	0.60 (0.43, 0.78)	0.51 (0.37, 0.65)
Shellfish	0.55 (0.21, 0.88)	1.9 (1.6, 2.2)	1.6 (1.4, 1.9)
Sesame	0.23 (0.030, 0.43)	0.070 (0.010, 0.13)	0.10 (0.04, 0.17)
Milk	2.2 (1.6, 2.9)	2.1 (1.8, 2.4)	2.1 (1.8, 2.4)
Egg	1.3 (0.83, 1.8)	0.66 (0.49, 0.87)	0.80 (0.63, 0.99)
Wheat	0.43 (0.20, 0.81)	0.86 (0.66, 1.1)	0.77 (0.60, 0.96)
Soy	0.32 (0.080, 0.56)	0.16 (0.070, 0.25)	0.20 (0.11, 0.29)
Fruits	1.1 (0.70, 1.6)	1.6 (1.3, 1.9)	1.5 (1.3, 1.7)
Vegetables	0.45 (0.17, 0.73)	1.3 (1.0, 1.6)	1.1 (0.90,1.3)

*Note: these are not mutually exclusive groups, i.e., individuals can have more than one allergy

Socio-demographic characteristics associated with perceived food allergy

The perceived prevalence of food allergy varied according to the birthplace of the primary respondent for both the main and sensitivity analyses; individuals residing in a household where the primary respondent was born in Canada had more food allergies than those where the respondent was born outside of Canada as shown in Table 2. Education level of the primary respondent was also associated with a difference in the rate of self-reported allergy; individuals residing in a household where the primary respondent had a post-secondary degree were more likely to report food allergy than those where the respondent did not have a post-secondary degree. Household income was not associated with self-report of food allergy. Those living in Western Canada were more likely and Quebec was less likely to report food allergy than Ontario and Atlantic Canada. Children (age < 18 years) were less likely to have perceived food allergy in the

main analysis compared to adults, but the difference changed direction after excluding adults reporting an allergy to one of milk, egg, wheat, or soy allergy but no other foods.

Table 2: Multivariate logistic regression model examining the association between perceived food allergy and socio-demographic characteristics

Characteristic	**OR (95% CI) for main analysis**	**OR (95% CI) for sensitivity analysis**
Characteristics of primary respondent		
Immigrant	0.71 (0.55, 0.91)	0.68 (0.52, 0.90)
Post-secondary graduate	1.27 (1.06, 1.53)	1.24 (1.03, 1.51)
Location of household		
Ontario and Atlantic Canada	1.00 (referent)	1.00 (referent)
Quebec	0.64 (0.53, 0.79)	0.73 (0.59, 0.90)
Western Canada	1.44 (1.17, 1.77)	1.30 (1.04, 1.63)
Individual characteristics		
Child (< 18 years)	0.79 (0.64, 0.97)	1.03 (0.84, 1.28)

Discussion

Although we have published nationwide estimates for the prevalence of peanut, tree nut, fish, shellfish, and sesame allergy (43), there were no data on the overall prevalence of food allergy in Canada. In this paper, we provide the first estimates of overall prevalence. According to our study, 8% of Canadians self-report at least one food allergy. However, this is likely an overestimate as many adults reporting milk, egg, wheat, and/or soy allergy have likely outgrown their allergy. In addition, many adults reporting milk allergy may actually have lactose intolerance (66) and many reporting wheat allergy may have celiac disease (123). To account for these issues, we created a more conservative prevalence estimate where we excluded adults reporting one or more of these allergies but no others, and obtained a prevalence of 6.6%. This prevalence estimate likely represents the lower bound since some adults may not have outgrown their allergy. Further, we adjusted for non-responders by imputing the probability that they were allergic

(based on postal code and province of residence) and obtained an estimate of 8.2%, suggesting that individuals who did not participate have similar rates of food allergy compared to those who did participate.

Our study is limited in that we were only able to inquire about the symptoms related to the ingestion and diagnostic testing performed for peanut, tree nut, fish, shellfish and sesame. Characterizing adverse reactions to other foods in such detail would have substantially lengthened the questionnaire and made it completely infeasible to administer over the telephone. We only obtained a 35% response rate with our existing questionnaire; it would have almost certainly been lower with an even longer version. We were therefore forced to rely on self-report of food allergy for most foods, likely leading to an overestimate of the prevalence of true food allergy. However, our previous publication by Ben-Shoshan (43), which reported perceived and probable allergy, compared prevalence estimates based on self-report versus estimates based on a convincing history of an IgE-mediated reaction to a food or self-report of a physician diagnosis, and found only slight differences. Therefore, it is likely that the perceived prevalence of food allergy of 8% is only a slight overestimate.

Although our prevalence estimates for milk, egg, wheat, and soy allergy in adults are likely inflated for the reasons previously discussed, our estimates for these allergies in children are likely more robust and agree with estimates generated in other countries. For milk allergy, one other Canadian study estimated a perceived prevalence of 7.5%, but the study was published in 1973 and only looked at infants less than one year of age (78). Two population-based studies from Europe show a prevalence of milk allergy between 2.2% and 2.8% among children (60, 61), much closer to the estimate of 2.2% that we obtained in our study. For egg, Eggesbo in Norway (79), Osterballe in Denmark (80), and Sampson in the United States (37) reported estimates of 1.5%, 1.6%, and 1.3%, respectively, in children, which are comparable to our rate of 1.3%. A recent study by Gupta et al. in the United States (125) reported prevalence estimates for wheat (0.4%), and soy

(0.4%) allergies in children which were very similar to those from our study (0.43% for wheat and 0.32% for soy). Although fruits and vegetables are not priority allergens in Canada, they appear to be relatively common in adults, which is line with current thinking of researchers in Europe (32). A nationwide American study found a perceived prevalence of 1.3% to 1.4% for fruit allergy and 1.2% to 1.4% for vegetable allergy in individuals of all ages (42), similar to our estimates of 1.5% and 1.1% respectively.

Our data reveal an association between the prevalence of food allergy and country of birth of the primary respondent; those born in Canada are more likely to report an allergy than those born outside of Canada. Our previous paper found an increased risk of shellfish allergy among Canadian-born individuals compared to those born outside of Canada (108) Shek reported a higher risk for peanut and tree nut allergy in western-born compared to Asian-born individuals (126). This trend was also observed by Leung et al (127).

Our study found a higher rate of perceived food allergies among individuals living in a household where the primary respondent was highly educated. A previous study reported a higher prevalence of food allergy in families with highly-educated parents living in favourable economic conditions (115). In a recent paper by our group at McGill, we showed that individuals who live in a household where the primary respondent has a post-secondary degree are more likely to have a tree nut allergy (108). There are a few potential reasons for the increased prevalence of self-reported food allergy in those of higher socioeconomic status: 1) more education may lead to higher health literacy and a higher likelihood of seeking consultation with a physician for a diagnosis of food allergy (128), and 2) having more education and more disposable income may precipitate changes in family lifestyle including fewer children and pets, increased use of antibiotics and improved sanitation, leading to a Th2-predominant immune system which is responsible for causing allergic disease (129). Unlike other studies, however, we did not observe a higher prevalence of self-reported food

allergy in those with a higher household income, possibly due to the fact that one third of participants refused to provide their annual household income.

We also identified differences in self-reported food allergy according to geographic location. Using Atlantic Canada and Ontario as the referent group, the province with the lowest rate of reported allergies was Quebec and the highest was Western Canada.

Contrary to other published research (31), our main analysis reveals a higher perceived prevalence of food allergy for adults compared to children. However, since we expect that most adults with milk, egg, wheat, or soy allergy have either outgrown the allergy (130) or have intolerance to the food (66, 123), we excluded them in our sensitivity analysis and obtained an association which was on the other side of the null compared to that in the main analysis, although not significant. The change in direction of the Odds Ratio is to be expected given that the main analysis is contaminated by adults who do not have true allergy, while the sensitivity analysis removes those without true allergy and is hence more robust.

The SCAAALAR project is the first cross-sectional study to estimate the prevalence of common food allergies in the general Canadian population. We recognize that although 1 in 13 Canadians self-report food allergy, fewer are likely to have a true food allergy. Despite not being diagnosed with food allergy, those who merely believe they are allergic are still adversely affected; they follow the same dietary restrictions, possibly leading to malnutrition (42), and experience the same anxiety and uncertainty as those who are truly allergic. Hence, it is critical to encourage all who suspect they have a food allergy to seek appropriate medical care to ensure correct diagnosis and follow-up.

IV: LITERATURE REVIEW - POSSESSION OF EPINEPHRINE AUTO-INJECTORS BY CANADIANS WITH FOOD ALLERGIES

Management of food allergy

We have already seen that food allergy affects between 7.6% and 9.6% of Canadians based on self-report, representing a significant health concern. Despite the risk of severe and potentially fatal allergic reactions, there is currently no cure for food allergy. For this reason, the recently-published National Institute of Allergy and Infectious Diseases (NIAID) guidelines for the diagnosis and management of food allergy in the United States (28) state the importance of seeking medical attention and receiving proper education and follow-up for all individuals who experience an adverse reaction to food. The guidelines also address the need for a management and prevention plan for patients with food allergy. Specifically, avoidance of the known allergen and nutritional counselling are recommended, age and culturally-appropriate information on food allergen avoidance and emergency management of allergic reactions should be provided, and a prescription for the epinephrine auto-injector (EAI), as well as instructions on its use, should be given at the time of diagnosis (28). However, there is much evidence to suggest that these recommendations are often not practiced; a substantial proportion of individuals who report food allergy have not been diagnosed by a physician and are therefore not equipped with the knowledge or the tools necessary to prevent or treat an allergic reaction. In fact, a national survey from the United States found that 74% of children and only 44% of adults with peanut and/or tree nut allergy sought a diagnosis for food allergy, and that less than half of these were given a prescription for an EAI (6).

Treatment of food allergy

What is epinephrine?

Currently, the World Health and World Allergy Organizations consider epinephrine to be an essential medication for the treatment of anaphylaxis (131).

Epinephrine is an alpha- and beta- adrenergic agonist that affects many of the body's organ systems, causing a response referred to as "fight-or-flight," which can cause symptoms such as anxiety, heart palpitations, sweating, and pupil dilation. It also leads to a decrease in the release of inflammatory mediators, which play an important role in anaphylaxis (28). Epinephrine is always present in the human body, but there is also an injectable form of epinephrine that is used as a pharmacological agent. Initially, synthetic epinephrine was used to treat asthma in humans, but in the 1960s, several reports were published demonstrating the effectiveness of epinephrine for treatment of anaphylactic reactions in the community (132).

The use of epinephrine in the treatment of anaphylaxis

Although epinephrine is the treatment of choice for food-induced allergic reactions, studies have shown that many allergic reactions are left untreated, are treated with other therapies which are not as effective as epinephrine, such as antihistamines or steroids (133, 134), or are treated too late, causing death in some cases (135-137). A recent systematic review by Canadian researchers identified the infrequent treatment of allergic reactions with epinephrine as a major gap in anaphylaxis management (138). One study included in this review surveyed daycares in the suburbs of Chicago and found that only 24% of centers would administer the EAI for a severe allergic reaction, even though each center had an average of seven children with food allergies (139). This statistic is alarming, especially since children rely on their caregivers to administer the EAI in case of an allergic reaction. A multicenter study involving twenty-one North American emergency departments found that only 19% of all patients admitted to hospital for a food-induced allergic reaction and only 24% of patients admitted for a severe reaction were treated with epinephrine (25). Even more worrisome is that between 1993 and 2004, the use of epinephrine for allergic reactions in emergency departments in the United States decreased from 19% to 7% (140).

Timing of administration of epinephrine

Studies have shown that rapid administration of epinephrine during an anaphylactic reaction can be life-saving. Sampson et al. documented deaths and near-deaths in children and adolescents caused by accidental exposure to a known food allergen (137). Of the thirteen children included in the study, 6 died following complications of their anaphylactic reaction and 7 survived but required intubation. Only two of the 6 patients who died received epinephrine in the first hour following the onset of symptoms, but neither received it before the onset of severe symptoms. Of the 7 who survived, all but one patient received epinephrine before the onset of severe symptoms. Yunginger et al. (141) assessed adults who experienced fatal anaphylactic reactions due to food, and concluded that the primary reason for these deaths was failure to administer epinephrine immediately after the onset of symptoms. Bock (135) and Pumphrey (142) also attributed fatal episodes of anaphylaxis to delayed administration of epinephrine. These studies all came to the same conclusion: individuals who receive epinephrine early are less likely to experience a fatal reaction than those who receive it late or not at all.

The importance of the epinephrine auto-injector for the treatment of food-induced anaphylaxis

Given that anaphylactic reactions occur in the community, and that injection of epinephrine soon after the onset of symptoms reduces the risk of fatality, an emergency form of epinephrine was warranted. In the 1980s, the EAI was introduced. The EAI is a pen-like device that is used to inject an emergency dose of epinephrine, usually to treat anaphylaxis. The device is composed of a needle that delivers the dose of epinephrine, and a compartment where the epinephrine dose is held. When the EAI is needed, the patient must remove the safety cap, press the pen down against the mid-outer thigh until the device clicks, and leave the device in place for several seconds to allow the medication to be delivered into the body. The device is very practical for patients with food allergy, because it is small and can therefore be easily carried by the allergic person. It also allows

for the delivery of an emergency dose of epinephrine outside of a hospital setting much before the paramedics arrive.

Physician indications for prescription of the epinephrine auto-injector

Health care professionals generally agree that the EAI should be prescribed to all patients with a history of respiratory symptoms, hypotension, or anaphylaxis to common food allergens (peanut, tree nuts, and shellfish particularly), insect stings, exercise, or those with idiopathic anaphylaxis (20, 143). However, there are certain situations where the indications for prescription of the EAI are less clear. For example, patients who experience a reaction where their only symptom is a single hive may not necessarily warrant prescription of an EAI. However, some patients with previously mild reactions may experience severe reactions upon subsequent exposure to an allergen. Additional issues that the physician must consider include age of the patient, co-morbid diseases like asthma and cardiovascular disease, and medications, all of which affect the likelihood of severe anaphylaxis (135). For example, the risk for food-induced anaphylaxis is elevated in teenagers, because they are more risk-seeking than younger children (144), and in individuals with asthma, because they are more likely to experience a severe or fatal anaphylactic episode due to exacerbation of the allergic reaction by asthma symptoms (135).

Prescription and possession of the epinephrine auto-injector by food-allergic individuals

The first opportunity for a physician to prescribe an EAI is when the patient presents to a healthcare facility for treatment of their first allergic reaction; in some cases, the patient may not seek medical attention for their first reaction and may see their family doctor or paediatrician after the symptoms have resolved or they may mention the reaction only in the context of a visit for another issue. Prescription of an EAI and education regarding how to use it during the first visit with a physician is critical to ensure adequate treatment of subsequent reactions (145); further, referral to an allergist for appropriate diagnostic testing to identify

the causative factor is also important. Studies have shown that emergency physicians often discharge patients following an anaphylactic reaction without a prescription for an EAI, education regarding avoidance of the suspected food allergen, or a referral to an allergist (145, 146).

Even more surprising is that even after consultation with an allergist, patients with a history of anaphylaxis are still not always prescribed an EAI (6). Sicherer et al. performed a cross-sectional, random digit dial telephone survey of households in the United States to assess the prevalence of peanut and tree nut allergy, and the percentage of allergic individuals who have the EAI. They found that only 46% of children and 23% of adults with a diagnosed peanut and/or tree nut allergy were prescribed an EAI (6). In Japan, Imai et al. asked physicians to describe situations in which they would prescribe the EAI to a patient. Of the physicians who had ever prescribed the EAI (47% of the participants), only 41.6% agreed that cases with a history of at least one anaphylactic episode should have an EAI, and 88% agreed that repeated cases of anaphylaxis warranted prescription of the EAI (147). The authors did not report on the percentage of individuals with food allergy who were prescribed the EAI or the type of physician participating in the survey.

A few studies looking at prescription and possession of the EAI have focused on specific age groups. A Dutch study looked at the frequency of EAI ownership among 168 adolescents aged 11 to 20 years old from 4 high schools in 4 provinces of the Netherlands (148). All participants were asked questions regarding symptoms and diagnosis of food allergy, and 48 were identified as probably allergic based on their clinical history. Of those considered probably allergic, 23 were considered candidates for the EAI, but only two reported having the device. Although this statistic cannot be generalized to the entire Dutch population because it focuses on only a few schools and does not cover all age groups, the results are alarming, especially because adolescents are more likely to experience anaphylactic reactions due to risk-taking behaviour such as ignoring precautionary labels on packaged foods. In addition to studies on children, one Italian study

explored the rate of EAI prescription among adults with food allergy in 19 allergy clinics (149). The authors reported that only 13% of adults with food allergy were prescribed the EAI, and that prescription was associated with a history of a previous anaphylactic episode, as well as an allergy to fish and tree nuts, regardless of clinical history. This figure is particularly disturbing as these adults have all consulted an allergist; it is likely to be much lower among those with anaphylaxis who are not referred to allergists.

In Canada, only one study has assessed the rate of EAI prescriptions. Using the Drug Programs Information Network in Manitoba, a database containing information on 279,638 children, the authors found that 1.2% of children included in this database were dispensed an EAI (150). However, this study did not address whether prescribing practices were appropriate as it does not link prescription with diagnosis. Hence, it provides no information on whether those prescribed an EAI actually require one or on the percentage of allergic individuals who were actually prescribed an EAI. Further, this study provides no information on adults and, as it was performed in Manitoba, it may not provide an accurate representation of EAI dispensation rates across Canada.

Demographic and reaction characteristics associated with possession of the EAI

To improve the management of food allergy, it is important to know which groups are the least likely to own the EAI, so that education campaigns can be targeted towards these groups. There are very few studies looking specifically at the rate of EAI prescription among different demographic groups; a Canadian study did not specifically address this issue, but it did examine the factors associated with having a family physician (109). Using the National Population Health Survey from 1994-1995, researchers asked 15,777 Canadians over the age of 20 if they had a regular medical doctor, and performed logistic regression to determine which groups were less likely to report having a doctor. The study found that males, immigrants, those who were single, those who had a lower income, and

those living in Quebec were the least likely to have a regular doctor (109). Not having access to a regular family doctor would probably make these individuals less likely to receive a diagnosis of food allergy or a prescription for an EAI from a physician. Although we cannot directly conclude that the characteristics identified in this study coincide exactly with Canadians who do not have EAIs, we can speculate that some of the characteristics may be similar.

Age and sex

Gender and age differences in EAI prescription have also been reported. In a Canadian study by Simons et al. (151), males were more likely to have an EAI during childhood and adolescence, whereas females were more likely to have one during adulthood, and there was no gender difference in the elderly. This study used an administrative pharmaceutical database of persons living in Manitoba to calculate the percentage of EAIs dispensed during a 5-year period. This study did not specifically look at the reason for dispensation of the device; therefore we cannot make any conclusions on the percentage of EAIs dispensed for food allergy. In addition, this study is not representative of the Canadian population, as it only looks at individuals living in Manitoba. Another study from Singapore looking at hospital records of individuals with food allergies who were prescribed the EAI found that males (OR = 1.36) and children under the age of 15 (OR = 2.593) had more EAIs (152); however, there was no subgroup analysis performed to see if the association between sex and possession of the EAI changed with age.

Western versus non-western birthplace

Studies done outside of Canada show that certain demographic characteristics are predictive of having an EAI. Individuals born in non-western countries are less likely to have a family doctor or consult a health care professional due to lower health literacy levels compared to individuals born in a western country (153). Due to this problem, immigrants may be less likely to receive a physician diagnosis of food allergy and hence a prescription for an EAI if needed. One study from Singapore found that Eurasians and Caucasians, i.e., those born in western

countries, were more likely to have the EAI than those native to Singapore (OR = 15.873) (152).

Socioeconomic status

Socioeconomic status (income and education) is a predictor of having an EAI; those of lower socioeconomic status have less EAIs than more affluent individuals. One Canadian study by Frost et al. in Toronto found that the percentage of children with the EAI was lower in schools located in areas where more than 20% of the population was low income (154). The authors also inquired about the number of allergic children in each school, and did not find a difference in prevalence of food allergy between the schools in an area with less than 20% low income versus those with more than 20% low income. Therefore, the rate of EAI possession in schools does not seem to be attributed to a difference in food allergy prevalence in these two school districts. Another study from Massachusetts examined three school districts: two in affluent neighbourhoods and one in a low income neighbourhood (155). Nurses in these schools recorded the age, sex, ethnicity, and offending allergen for each student dispensed an EAI for use in school. The study found the rate of EAI dispensation, particularly for nut allergy, was much lower in schools from the low income neighbourhood compared to the high income neighbourhoods (0.17% versus 1.23%). The authors point out that this difference in EAI dispensation rate may be explained by a difference in the prevalence of food allergy according to socioeconomic status. It is possible that there is a higher prevalence of food allergy in individuals of higher socioeconomic status compared to those of lower socioeconomic status, which may be due to genetic (156-158) or environmental differences. It is also possible that there is not a real, but only an apparent, increased prevalence in those of higher socioeconomic status as they may have higher health literacy and a greater likelihood of seeking medical attention for a food allergy (153). Another reason is that the cost of an EAI device, which is more than 100$ per year, may deter those of lower socioeconomic status from purchasing it; therefore, individuals with more disposable income would be more likely to have the EAI.

Availability of the EAI

As highlighted previously, many individuals with food allergies are not prescribed the EAI. Further, of those who are prescribed the EAI, many do not fill the initial prescription or do not renew their prescription (159). Even more surprising is that those who do have the EAI seldom carry the device when they leave home. Research has shown that many accidental exposures to food occur outside of the home (160, 161), highlighting the importance of carrying the EAI at all times. Ben-Shoshan et al. showed that although 98.5% of Quebec children with an allergist-diagnosed peanut allergy had an EAI, only about half actually carried the EAI at school (162). In most cases, the EAI was kept in the nurse's office. This study only looked at Quebec and is therefore not representative of the Canadian population. In addition, it only examined EAI availability among children who had been assessed by an allergist and did not provide any information on allergic children and adults in the general population who had not seen an allergist or who may never have even consulted a physician for their allergy. Another study by Pouessel et al. in France (163) found that the EAI was available at school in 82% of preschool children, 72% of elementary school children, and 55% of high school children. There have not been any studies done to assess the availability of the EAI among adults with food allergies. However, based on other studies showing that allergic adults tend to be less cautious than allergic children (144) and are less likely to own an EAI (6), it is likely that the rate of EAI self-carry in adults is even lower.

Knowledge regarding use of the EAI

We have already seen that many allergic individuals do not have the EAI, and even if they do, many either do not know how or when to use it, or are afraid to do so. Several studies have assessed reasons for the lack of knowledge in patients with food allergy, and have identified a few issues. The role of the physician is not only to provide a diagnosis of food allergy, but also to educate the patient on how and when to use the EAI. However, many doctors do not know the proper technique for administration of the EAI (24), or do not show the patient how to

use the EAI for various reasons. A recent study by Paek et al. found that although physicians said that they knew how to administer the EAI, only one of approximately 40 physicians was able to correctly demonstrate the steps (164). Another study by Mehr et al. reported that only 2% of physicians correctly demonstrated the EAI administration technique (165). In the same study, only 3 of 45 physicians who reported prescribing the EAI provided education on the proper technique to administer the device.

If physicians do not instruct patients and their caregivers on the proper administration technique for the EAI, they will not know how to inject the device or when to do so, or will be fearful of using it (163, 166, 167). Healthcare professionals agree that food-allergic individuals and their families should be educated on how to recognize an anaphylactic reaction, and if they are in doubt, they should inject the EAI to avoid a potential fatality caused by delay in treatment (137, 142, 168). In a study by Kim et al. examining individuals who were prescribed the EAI, 42% of children had an episode of anaphylaxis. Of these, 20% received the EAI injection from their parent during the anaphylactic episode (167). Those parents who had previously injected the EAI or received instruction by the allergist regarding its use said they felt comfortable administering the EAI to their child. Gold et al. found that only 29% of individuals who had been prescribed the EAI used it during a recurrent anaphylaxis episode. The reasons for not injecting the device were lack of knowledge regarding how to use the EAI or how to recognize symptoms of anaphylaxis (166). A study by Sicherer et al. found that the majority of parents of children with food allergies were unable to demonstrate the correct technique for administration of the EAI when asked to do so by the allergist (24). Arkwright et al. showed that prior hands-on education from a physician, especially an allergist, was associated with proper administration technique (169). These results emphasize the essential role that the treating physician should play in educating food-allergic patients and their families.

Conclusion

Although several researchers from around the world have attempted to determine the percentage of individuals who were prescribed or who currently have the EAI, there are still considerable gaps in the literature. Many studies report the proportion of individuals with the EAI, but do not focus specifically on individuals with food allergy. Other studies include only those suffering from food allergy, but are not population-based.

The next chapter of this thesis (Chapter V) will attempt to bridge these gaps in the literature through the presentation of the first nationwide data from Canada to estimate the proportion of individuals with food allergy who have the EAI. This study encompasses individuals of all age groups, i.e., both adults and children, and includes only individuals with probable food allergy to peanut, tree nut, fish, shellfish and sesame. It is also the first study in Canada to explore demographic and reaction characteristics that are associated with the possession of the EAI.

CHAPTER V: POSSESSION OF EPINEPHRINE AUTO-INJECTORS BY CANADIANS WITH FOOD ALLERGIES

Introduction

In this chapter, data will be presented on possession of the EAI by Canadians with food allergies. Specifically, data on the percentage of Canadians with probable allergy to peanut, tree nut, fish, shellfish, and/or sesame who have the EAI, and demographic and reaction characteristics associated with having the EAI will be presented. Before we present these results which were published in Journal of Allergy and Clinical Immunology(1), a few details regarding the methodology for this work, which were omitted from the Letter due to the word limit, will be described.

Methods

Survey methodology

As previously described in the first manuscript on prevalence of food allergy in Canada in Chapter III, our research team conducted a nationwide telephone survey in which household respondents were asked to report whether any household member had one or more food allergies. To further characterize these households, demographic information was obtained. In households reporting allergy to peanut, tree nut, fish, shellfish and sesame, detailed questions were asked to assess whether the allergy was IgE-mediated (see Appendix B). These questions were based on those employed by Sicherer and his group in the United States (3, 6, 7, 45). Households self-reporting an allergy to one or more of these five foods were re-contacted within four months following completion of the telephone survey and asked if the allergic individual(s) currently had an EAI. A research nurse based at McGill University contacted all households who gave permission to be re-contacted during the initial telephone survey. There was no differentiation made between EAI formulations currently available in Canada (EpiPen® and Twinject™).

Definitions

Two groups of allergic respondents were created for the Letter: the probable group and the diagnosed group. Our first category, termed "probable" employs exactly the same definition as the "probable" group in our previously published study by Ben-Shoshan et al. (43), i.e. self-report of a convincing history and/or physician diagnosis of allergy.

We also created two additional groups of allergic individuals in order to perform a sensitivity analysis; however, we did not include these groups in the Letter due to the word limit. The first group, termed "convincing history", included all individuals with an allergy to peanut, tree nut, fish, shellfish and/or sesame who had a convincing history of an IgE-mediated allergic reaction. This group included 223 individuals; 160 with convincing history and diagnosis, and 63 with convincing history but no diagnosis. The other group, termed "convincing history + diagnosis", included those with both a convincing history and self-report of physician diagnosis (n=160 individuals).

Statistical analysis

i. Point estimates

Point estimates and corresponding 95% CIs were calculated for the percentage of allergic individuals with the EAI for each of the four groups defined above, i.e., the probable group, the diagnosed group, the convincing history group, and the convincing history + diagnosis group.

ii. Logistic regression

Univariate and multivariate logistic regression models were fit for each group of allergic respondents, to identify predictors of having an EAI, as well as to adjust for any confounding between co-variates.

Confounding occurs when two variables are associated with one another as well as the outcome. If either of the two variables is excluded from the regression model, the association with the outcome (Odds Ratio, OR) can change. In order to ascertain whether confounding is an issue in a regression model, one must compare the results with and without the co-variate, to see if the OR changes with the addition of this co-variate to the model. If there is evidence of confounding between two variables, then it is better to keep both in the model, in order to estimate effects for each variable adjusted for the confounding effect from the other.

Bayesian hierarchical logistic regression models were fit for all groups of allergic individuals. We used a hierarchical model with 2 levels (household-level and individual-level) because our survey collected data both at the household and individual level (see Letter for a list of these variables). To identify the best multivariate model for predicting possession of the EAI, we used the Bayes Information Criterion (BIC) results. The BIC selects potential multivariate models in terms of how precisely they can predict the outcome (170). The BIC also allows you to examine the effect of adding or removing a co-variate from the model, which aids in identifying any potential confounding that may occur between variables.

iii. Missing data

As in many surveys, our dataset contained variables for which information was missing for some of our participants. There was very little missing data for most variables, but a substantial percentage of households refused to provide their annual household income. In the probable group, 86 of 261 individuals (33%) did not provide their income, and in the diagnosed group, 63 of the 198 (31.8%) did not provide their income. We felt that removing these households from the data analysis would substantially decrease statistical power, so we used multiple imputation to adjust for this missing data (see Prevalence Manuscript for details on the basic idea of multiple imputation).

For the low income variable, we created multiple complete data sets and then created a final complete dataset which used the average of estimates across these data sets as an overall point estimate, with overall variance equal to the sum of within and between imputation variances. We used the final complete data for the low income variable in WinBUGS to identify predictors of having the EAI (Appendix D).

Below, data from the SCAAALAR project are presented in the form of a Letter to the Editor, entitled “Possession of the epinephrine auto-injector in Canadians with food allergies”. This Letter is published in the August 2011 issue of The Journal of Allergy and Clinical Immunology (1).

Letter to the editor: Possession of epinephrine auto-injectors in Canadians with food allergies

To the Editor:

Although there is unanimous agreement that epinephrine is the first-line treatment for anaphylaxis (162), many with food allergy have not been prescribed an epinephrine auto-injector (EAI).

As part of our nationwide Canadian study on the prevalence of food allergy (43), households from the 10 Canadian provinces were randomly selected from the electronic white pages and were telephoned between May 2008 and March 2009. Households self-reporting an allergy to peanut, tree nut, fish, shellfish, and/or sesame were recontacted within four months of the telephone survey and asked whether the individual(s) with allergy currently had an EAI. There was no differentiation between EAI formulations currently available in Canada (EpiPen® and Twinject™).

Two categories of respondents with allergy were defined: 1) those reporting a convincing history of an IgE-mediated allergic reaction[†] and/or a physician diagnosis of an allergy to peanut, tree nut, fish, shellfish, or sesame, termed probable group (43), and 2) those reporting a physician diagnosis of an allergy to peanut, tree nut, fish, shellfish, or sesame, termed diagnosed group.

Multivariate logistic regression models were performed for each group of respondents to identify factors associated with having an EAI; multiple imputation techniques were used to adjust for missing data for the low-income variable. Both models were hierarchical using the following household-level

[†] A convincing history of an allergic reaction 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 2 hours of ingestion or contact (or inhalation for fish and shellfish). Mild symptoms include pruritus, urticaria, flushing, or rhinoconjunctivitis; moderate includes angioedema, throat tightness, gastrointestinal complaints, or breathing difficulties (other than wheeze); and severe includes wheeze, cyanosis, or circulatory collapse.

variables: postsecondary education of household respondent (attained college/university degree), low-income household[‡], marital status of household respondent (married/living with partner), urban location of household[§], and birthplace of household respondent (not born in Canada). The following individual-level data of the participants were also included: age (< 18 years), sex, type of allergy (peanut, tree nut, or sesame), multiple allergies (allergy to > 1 of peanut, tree nut, sesame, fish, or shellfish), age at most severe reaction, treatment with epinephrine during most severe reaction, multiple allergic reactions, and self-report of diagnostic allergy testing.

Of 10,596 households contacted, 3666 responded (35% participation rate), of which 3613 completed the entire interview, representing 9667 individuals. Of these 9667 individuals, 310 (3.2%) were considered to have a probable food allergy to at least one of the following: peanut, tree nut, fish shellfish, and/or sesame. Of those with probable food allergies, 261 (84%) could be recontacted and queried on the EAI (convincing history only, n=63; diagnosis only, n=38; convincing history and diagnosis, n=160). These were similar to the 49 with a probable allergy who could not be contacted (Table 3).

[‡] Low Income Cut-off, defined as income level 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 in a Canadian metropolitan area with a population ≥ 100,000

Table 3: Socio-demographic characteristics of allergic responders and non-responders

Characteristic	**Responders (n=261) %, (95% CI)**	**Non-responders (n= 49) %, (95% CI)**
Household characteristics		
Post-secondary education	66 (60, 72)	69 (52, 83)
Low income household	5.1 (2.4, 9.5)	8.3 (1.0, 27)
Married/living with partner	83 (78, 88)	82 (66, 92)
Urban location of household	68 (62, 74)	54 (39, 69)
Not born in Canada	9.2 (5.9, 14)	9.8 (2.7, 23)
Individual characteristics		
Child (< 18 years)	22 (17, 28)	16 (7.3, 30)
Female	58 (52, 65)	54 (37, 71)
Allergy to peanut, tree-nut and/or sesame	57 (51, 63)	45 (31, 60)
Multiple allergies	24 (19, 29)	10 (3.4, 22)
Mean age at most severe reaction, in years	24 (22, 27)	29 (23, 34)
Treated with epinephrine during most severe reaction	26 (21, 32)	16 (7.3, 30)
Multiple allergic reactions	73 (67, 79)	61 (46, 75)
Self-report of diagnostic testing	69 (63, 75)	69 (55, 82)

Of the 261 with probable allergy, 45% (95% CI, 39%, 51%) had an EAI. One hundred ninety-eight of the 261 with probable allergy (76%) formed the diagnosed group (diagnosis only, n=38; convincing history and diagnosis, n=160) and 55% (95% CI, 48%, 62%) of these reported having an EAI.

In a multivariate model for the probable group, individuals with allergy residing in a household where the respondent was married/living with a partner were more likely to have an EAI (Table 4). Furthermore, children, females, those with multiple allergies, those who experienced their most severe reaction at a younger age, those who had been treated with epinephrine during the most severe reaction, and those who reported having had confirmatory testing were more likely to have an EAI. The same factors were associated with having an EAI in the diagnosed group.

Table 4: Multivariate logistic regression model examining the association between owning an epinephrine auto-injector and household and individual characteristics

Characteristic	**OR (95% CI) for probable group**	**OR (95% CI) for diagnosed group**
Household characteristics		
Married/ Living with partner	3.8 (1.4, 9.1)	3.6 (1.1, 9.4)
Individual characteristics		
Child (< 18 years)	5.1 (1.5, 13)	5.1 (1.4, 15)
Female	2.8 (1.3, 5.6)	4.0 (1.5, 8.7)
Multiple allergies	2.6 (1.1, 5.3)	2.9 (1.2, 6.4)
Age at most severe reaction	0.96* (0.93, 0.98)	0.95* (0.91, 0.98)
Treated with epinephrine during most severe reaction	5.2 (2.1, 11)	5.1 (1.9, 12)
Self-report of diagnostic allergy testing	6.5 (2.4, 16)	13 (1.7, 64)

* For every 1-year increase in age of most severe reaction, the likelihood of having the EAI decreases by 4% (probable group) and 5% (diagnosed group)

While it is recommended that because of the potential for anaphylaxis, all with food allergy have an EAI, our results show that only 45% to 55% report having the device. On the basis of previous research by our group in school-age children reporting that less than 50% owning an EAI actually have it available at all times (162), we suspect that many of the 45-55% of respondents in SCAAALAR (Surveying Canadians to Assess the prevalence of common food Allergies and Attitudes towards food LAbelling and Risk) who own an EAI do not have it readily accessible.

Individuals with food allergy who resided in a household where the primary respondent was married or living with a partner were more likely to own an EAI potentially because such households have higher health literacy and are more likely to seek appropriate medical attention and be more compliant with suggested management. It has been shown that single people are less likely to have a family

doctor (109), making them less likely to consult a physician for a suspected food allergy and hence less likely to be prescribed an EAI. Furthermore, such households may be less able to afford the EAI.

It was not surprising that children, individuals experiencing their most severe reaction at a younger age, and females were more likely to have an EAI. Parents are usually very diligent with their children's health and would therefore ensure that they are properly assessed and managed for food allergy (171). As it is already known that males are less vigilant regarding their health, are less likely to have a family doctor (109), and are more likely to engage in risk-taking behaviours, it would be expected that they were less likely to have an EAI.

Characteristics of the food allergy itself were also associated with greater likelihood of having an EAI; those with multiple allergies, those treated with epinephrine during their most severe reaction, and those reporting diagnostic allergy testing were more likely to own an EAI. These characteristics may be associated with a greater likelihood of seeing an allergist and hence obtaining a prescription for an EAI (98, 172). These results are consistent with those of previous studies showing that physicians are more likely to prescribe an EAI to individuals with more than one food allergy (173) possibly because of the increased risk of accidental exposure associated with having multiple allergies. We have also shown in a previous study that those who self-carry the EAI are more likely to have had a previous allergic reaction requiring epinephrine (162).

Our study is limited by our relatively small sample size and moderate response rate. Consequently, our sample was not fully representative of the Canadian population in that it consisted of a higher percentage of households having a postsecondary education and income exceeding the low-income cut-off (43), potentially resulting in an overestimation of the percentage owning an EAI. Furthermore, we did not ask detailed questions regarding the accessibility of the

EAI. For those without an EAI, we do not know whether it was not prescribed or whether they failed to fill or renew their initial prescription.

It is a matter of concern that only 55% of Canadians who were diagnosed by a physician as having a food allergy have an EAI. Hence, based on known knowledge gaps (138), we anticipate that it is not only individuals with food allergy and their families who require more effective education on the recognition and management of anaphylaxis but likely health care providers as well. Certain individuals with food allergy are particularly unlikely to own an EAI (those residing in households where the household respondent is single, adults, and males) and merit additional attention. The recently published guidelines regarding diagnosis and management of food allergy (28) should be disseminated among all health care providers, and the essentials should be distilled and made accessible to food allergy advocacy organizations and the public. Furthermore, education campaigns and action plans regarding the management of food allergy should be implemented not only in schools but also in the workplace and should target groups who are particularly unlikely to have an EAI, that is, those who are single, adult, or male. Such strategies should reduce the number of individuals with allergy without EAIs and minimize the number of potentially fatal anaphylactic reactions in Canada.

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Additional results and Discussion

Percentage of allergic individuals with the EAI: results of sensitivity analysis

In addition to the results presented in the Letter to the Editor above, we created two other groups of allergic individuals to determine whether there was a significant difference in the percentage of individuals with the EAI if the participants were grouped differently. Of those in the convincing history group, 44% (95% CI, 37%, 51%) had the EAI, 14% (95% CI, 5.4%, 23%) of those with a convincing history but without a diagnosis had the EAI, 53% (95% CI, 36%, 69%) of those with a diagnosis but no convincing history had the EAI, and 56% (95% CI, 48%, 63%) of those with a convincing history and diagnosis had the EAI.

Potential predictors of having an EAI: univariate results for all groups of allergic individuals

In addition to the multivariate results which were presented in the Letter to the Editor, we performed univariate logistic regressions as well. We could not include them in the Letter due to space constraints, but thought they were important to include as supplemental information. The univariate results for the probable group found that those living in a household where the primary respondent was married or living with a partner, children, those with peanut, tree-nut, and/or sesame allergies, those with multiple allergies, those who experienced their most severe reaction at a younger age, those who had been treated with epinephrine during the most severe reaction, and those who reported having had confirmatory testing were more likely to have the EAI. In the diagnosed group, the same factors were associated with having the EAI except that the 95% CI for the OR for marital status crossed the null. In addition, the ORs were different in the univariate results for the diagnosed group compared to the probable group. In the convincing history group, the same factors were associated with having the EAI as in the probable group, and the ORs were very similar. In the convincing history+diagnosis group, the same factors were associated with having the EAI as

in the diagnosed group, except that having multiple reactions gained significance (see Table 5 for ORs and 95% CIs).

Table 5: Univariate logistic regression model examining the association between owning an epinephrine auto-injector and household and individual characteristics

Characteristic	**OR (95% CI) for probable group**	**OR (95% CI) for diagnosed group**	**OR (95% CI) for convincing history group**	**OR (95% CI) for convincing history+diagnosis group**
Household characteristics				
Post-secondary education	1.7 (0.93, 2.9)	1.6 (0.81, 3.0)	1.5 (0.80, 2.8)	1.4 (0.65, 2.8)
Low income household	0.83 (0.25, 2.7)	0.62 (0.16, 2.4)	0.82 (0.22, 3.0)	0.57 (0.12, 2.7)
Married/ Living with partner	2.8 (1.3, 6.1)	2.4 (0.96, 5.8)	2.4 (1.1, 5.4)	2.1 (0.81, 5.3)
Urban location of household	1.0 (0.57, 1.8)	1.1 (0.61, 2.2)	1.0 (0.56, 1.9)	1.3 (0.63, 2.6)
Not born in Canada	0.42 (0.15, 1.2)	0.65 (0.31, 2.0)	0.47 (0.14, 1.6)	1.1 (0.22, 4.9)
Individual characteristics				
Child (< 18 years)	10 (3.9, 26)	7.3 (2.6, 20)	13 (3.5, 47)	9.7 (2.1, 45)
Female	1.5 (0.89, 2.5)	1.5 (0.80, 2.6)	1.5 (0.82, 2.6)	1.4 (0.69, 2.8)
Peanut, tree-nut, and/or sesame allergy	4.2 (2.4, 7.5)	2.9 (1.5, 5.6)	4.1 (2.2, 7.7)	2.6 (1.3, 5.3)
Multiple allergies	3.5 (1.8, 6.7)	2.8 (1.3, 5.8)	3.6 (1.8, 7.2)	2.7 (1.2, 5.9)
Age at most severe reaction*	0.95 (0.93, 0.97)	0.95 (0.93, 0.97)	0.95 (0.93, 0.97)	0.95 (0.92, 0.97)
Treated with epinephrine during most severe reaction	4.2 (2.2, 7.9)	2.7 (1.4, 5.3)	5.1 (2.5, 10)	3.1 (1.4, 6.5)
Multiple allergic reactions	0.57 (0.32, 1.0)	0.51 (0.25, 1.0)	0.56 (0.28, 1.1)	0.35 (0.14, 0.90)
Self-report of diagnostic allergy testing	12 (5.4, 27)	11 (2.5, 52)	11 (5.0, 26)	8.3 (1.8, 39)

*For every 1-year increase in age of most severe reaction, the likelihood of having the EAI decreases by 5%

Potential predictors of having an EAI: multivariate results for convincing history and convincing history+diagnosis groups

The variables included in the best multivariate model for the probable and diagnosed groups included: being female, being a child, experiencing your most severe allergic reaction at a younger age, reporting confirmatory testing, having been treated with epinephrine for the most severe reaction, having multiple allergies, and living in a household where the primary respondent was married or living with a partner. When we performed a multivariate logistic regression for the convincing history group using these same variables in the model, all variables remained significant except for multiple allergies. For the convincing history+diagnosis group, three variables were no longer predictive of having the EAI: being a child, having multiple allergies, and living in a household where the primary respondent was married or living with a partner (see Table 6 for ORs and 95% CIs).

Table 6: Multivariate logistic regression model examining the association between owning an epinephrine auto-injector and household and individual characteristics

Characteristic	**OR (95% CI) for probable group**	**OR (95% CI) for diagnosed group**	**OR (95% CI) for convincing history group**	**OR (95% CI) for convincing history+diagnosis group**
Household characteristics				
Married/ Living with partner	3.8 (1.4, 9.1)	3.6 (1.1, 9.4)	4.1 (1.4, 10)	3.3 (0.88, 9.0)
Individual characteristics				
Child (< 18 years)	5.1 (1.5, 13)	5.1 (1.4, 15)	5.3 (1.2, 17)	5.0 (0.87, 17)
Female	2.8 (1.3, 5.6)	4.0 (1.5, 8.7)	2.7 (1.1, 5.6)	4.2 (1.4, 11)
Multiple allergies	2.6 (1.1, 5.3)	2.9 (1.2, 6.4)	2.3 (0.89, 5.1)	2.6 (0.92, 6.2)
Age at most severe reaction*	0.96 (0.93, 0.98)	0.95 (0.91, 0.98)	0.95 (0.92, 0.98)	0.93 (0.89, 0.97)
Treated with epinephrine during most severe reaction	5.2 (2.1, 11)	5.1 (1.9, 12)	6.4 (2.4, 14)	6.8 (2.2, 17)
Self-report of diagnostic allergy testing	6.5 (2.4, 16)	13 (1.7, 64)	7.1 (2.4, 17)	17 (1.9, 70)

*For every 1-year increase in age of most severe reaction, the likelihood of having the EAI decreases by 4% (probable and convincing history group), 5% (diagnosed group), and 7% (convincing history+diagnosis group).

Summary

Through the use of a sensitivity analysis, we found that the percentage of individuals with a convincing history and no diagnosis who own an EAI was significantly lower than for any other group of allergic individuals included in our analysis. This was not surprising, because without a physician diagnosis, it would be almost impossible to get a prescription for the EAI, unless an emergency room physician prescribed the device during a visit to the hospital for an anaphylactic reaction. However, as we have already seen, the majority of emergency room physicians do not prescribe the EAI (145, 146), and it is on the onus of the allergist to do so. The percentage of individuals with the EAI was similar for the other groups of allergic respondents.

Looking at the logistic regression results, we notice a few things. The sex variable is non-significant in the univariate analyses for all groups of allergic respondents, but gains significance for all groups in the multivariate model. This suggests that there may be some confounding between sex and one or more of the other variables included in the multivariate model. Most significant variables in the multivariate model are also significant in the univariate analysis, however, the ORs and 95% CIs change for many of the variables. If we compare the regression results for each group of allergic patients, we see that most of the associations hold, except that the magnitude of the association, i.e., the OR, changes.

Although we could not include the results of our sensitivity analysis in the Letter to the Editor due to space constraints, the information gained is very useful. We found that individuals who do not have a physician-diagnosed food allergy but who do have a convincing history of an allergic reaction will most likely not have an EAI. This is alarming given that allergic reactions can be fatal if not treated rapidly with epinephrine. It is therefore critical to educate those without physician diagnoses on the importance of seeking consultation with an allergist and obtaining a prescription for the EAI.

VI: CONCLUDING DISCUSSION AND SUMMARY

Summary and interpretation of results

Even though food allergy is an important health concern in the western world, we still know very little about its prevalence and how those who are affected manage their condition. In 2007 and 2008, a group of researchers in Europe published a series of papers summarizing the literature on food allergy prevalence at the time (11, 12). The main finding was that the prevalence of food allergy varied considerably across studies, and that the study population and methodology used by the researchers may influence results. Specifically, studies which employed diagnostic tests to confirm food allergy generally yield prevalence estimates which are lower than those using self-report alone. In 2008-2009, our group conducted the first nationwide Canadian study to estimate the prevalence of common food allergies. In the summer of 2010, data on the prevalence of peanut, tree nut, fish, shellfish, and sesame allergy from this study were published in the Journal of Allergy and Clinical Immunology (43).

To complete the picture of food allergy prevalence in Canada, Chapter III of this thesis presents the first Canadian estimates for the overall prevalence of food allergy. Because we collected data using a telephone survey, we were unable to confirm self-reported food allergies with convincing history and physician diagnosis for all foods, as this would considerably lengthen the questionnaire. Hence, we have relied on self-report alone to establish our prevalence estimates, even though previous research has shown that this may lead to an overestimate of prevalence compared to studies which corroborate self-report with symptoms and diagnostic testing. However, our previous publication found that the perceived prevalence estimates of peanut, tree nut, fish, shellfish, and sesame allergies were similar to those which combined self-report with a convincing history and/or a physician diagnosis of food allergy (43). Therefore, the prevalence estimates presented in this thesis are probably not huge overestimates.

In our study, 8.0% of participants reported an allergy to one or more foods. Using perceived food allergy as our definition, children appeared to have less food allergies than adults. However, previous research suggests that 79% of children outgrow their milk allergy (101) and 68% their egg allergy (174) by the age of 16 years, 65% outgrow their wheat allergy by the age of 12 years (89), and 69% of children outgrow their soy allergy by the age of 10 years (93). In addition, many adults may mistakenly report food allergy when they actually have food intolerance. Given this information, we created a second, more conservative prevalence estimate which excluded all adults who reported one or more of these allergies but no other allergies, and found a prevalence of 6.6%. Using this more robust definition, the prevalence of self-reported food allergy was found to be slightly higher in children than in adults, which is consistent with other research (31). Given that a few adults may still have one of these allergies, excluding all adults with milk, egg, wheat and soy allergies probably underestimated the prevalence of food allergy, and 6.6% likely represents a lower bound for perceived food allergy prevalence in Canada. We performed a third calculation of prevalence which accounted for non-response and household clustering, and found a prevalence of 8.2%, which is not very different from the prevalence of 8.0% which includes only responders. The use of multiple imputation in creating this adjusted estimate was helpful in that it allowed us to estimate what the prevalence of food allergy would be if our response rate was 100%. However, using only three-digit postal code and province of residence to impute allergy status may not be very robust since other unavailable variables may be important in reporting of food allergy, and hence, we cannot be sure that our imputed estimate is accurate. In addition, imputation assumes that there is no selection bias. Since we do not know if familiarity with allergies or having allergies would increase participation in our study, we cannot rule out at least minimal selection bias.

We also estimated the prevalence of perceived allergy to foods which were not included in our previous publication (43), notably, milk, egg, wheat, soy, fruits

and vegetables. Our estimates for milk, egg, wheat, and soy allergies may be inflated in adults due to the fact that children usually outgrow these allergies by the time they reach adulthood (130), and also because adults may actually have lactose intolerance or celiac disease rather than milk allergy or wheat allergy. We believe that our estimates for children are probably more accurate, since they agree with other findings from researchers in the United States and Europe. The prevalence of milk allergy in children was found to be 2.2%, 1.3% for egg, 0.43% for wheat, and 0.32% for soy. Since there is no specific data on the percentage of and age at which individuals tend to outgrow allergies to fruits and vegetables, it is difficult to comment on the accuracy of our age-specific estimates. However, our estimates do coincide with other previously published values. The perceived prevalence of fruit allergy is 1.1% for children, 1.6% for adults, and 1.5% overall, and for vegetables, the prevalence is 0.45% for children, 1.3% for adults, and 1.1% overall. These data support current thinking that fruit and vegetable allergies are common allergies in adulthood, as documented by Moneret-Vautrin in Europe (32).

Demographic characteristics associated with food allergy included country of birth, education, and province of residence. Our findings are in line with previously published studies, except that we did not find a difference in prevalence of perceived food allergy according to household income, which may be due to a large percentage of missing data (33%) on household income in our survey. In addition, due to the fact that we did not collect data on the sex of allergic individuals in our survey, we were unable to determine the prevalence of self-reported allergy stratified by sex.

There is general consensus in the medical community that those who have a history of food-induced anaphylaxis should carry the EAI. However, research shows that many with serious allergic reactions have never seen a physician for their allergy, and hence, have not been prescribed the EAI. In Chapter V of this thesis, we present the first data on possession of the EAI among Canadians with

probable food allergy to peanut, tree nut, fish, shellfish and/or sesame, and predictors of having the EAI. Only about half of individuals with food allergy who participated in our study have the EAI, which is alarming given that delay in administration of epinephrine during an anaphylactic reaction can have fatal consequences. In addition, males, those who are single, and those who are older are even less likely to have the EAI. Although we did not specifically query respondents on whether they self-carried the EAI, previous research by our team demonstrates that many who report owning the EAI actually do not carry it with them when they leave their home (162). We also performed a sensitivity analysis to document any differences in predictors of having the EAI when the allergic participants were grouped differently. As expected, the percentage of allergic individuals with the EAI was lower in those without a physician diagnosis than in those with a diagnosis, emphasizing the need for all individuals who experience an adverse reaction upon exposure to a food to consult a physician for appropriate testing and treatment.

Final conclusions

Our study indicates that food allergy is an important health problem in Canada, affecting 1 in 13 Canadians according to self-report. Even though many of these individuals may not suffer from true IgE-mediated food allergy, they often practice the same dietary restrictions as those who do, which may cause malnutrition and anxiety. In addition, we found that many allergic Canadians, even those who have received a physician diagnosis of food allergy, do not have an EAI. Although our study did not collect information regarding the reasons for not having the EAI, we can speculate that it is not only the fault of the physician who fails to prescribe the EAI, but the patient who believes that he or she can avoid the offending allergen and therefore does not feel that the EAI is necessary. Given these results, education campaigns on the importance of physician diagnosis for a potential food allergy as well as the need for adequate follow-up

and prescription of the EAI in those diagnosed as allergic is crucial to ensure a better quality of life for Canadians with food allergies and their families.

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APPENDIX A-INFORMATION LETTER TO HOUSEHOLDS

Centre universitaire de santé McGill

McGill University Health Centre

McMaster University

Nationwide study on Food Allergies, Food Labelling and the Environment

Your household has been randomly selected to take part in an important Canadian study that involves a short telephone survey that will ask you your experiences with food allergies, food labelling, and the environment. **Even if you do not have food allergies, your opinions on food labelling and the environment are really important to us.** The study is funded by Health Canada and the AllerGen NCE (www.Allergen-nce.ca/) and has been approved by the ethics boards at the McGill University Health Centre (Montreal), and McMaster University (Hamilton).

In the next few weeks you will be contacted by a university researcher to complete the survey over the phone. Your participation is entirely voluntary. The survey should take between 15 and 20 minutes to complete, depending on your experiences with food allergies. You will be asked if anyone in your household has a food allergy and some important information about the food allergy. We would also like to know your opinion on some common precautionary statements on food labels such as "May contain traces of nuts". And finally**,** we will ask you a few questions regarding environmental impacts on your health and the health of fellow Canadians.

If you should choose to participate in this study, all the information you provide will be kept secure and confidential. **If you would like more information, or do not wish to participate, please call our toll-free number, 1-866-431-7344, between the hours of 9am and 4pm or send an e-mail to SCAAALAR@epimgh.mcgill.ca**. We look forward to your participation in this very important study.

Sincerely,

Principal investigators for this research study:
Ann Clarke, MD, McGill University Health Centre - Montreal, Quebec
Susan Elliott, PhD, McMaster University - Hamilton, Ontario

Santé Canada Health Canada

AllerGen

Centre universitaire de santé McGill

McGill University Health Centre

Étude nationale sur les allergies alimentaires, l'étiquetage des aliments et l'environnement

Votre maison a été sélectionnée au hasard pour participer à cette étude nationale qui consiste en un court sondage téléphonique portant sur l'expérience que vous avez des allergies alimentaires, de l'étiquetage des aliments et de l'environnement. **Même si vous n'avez pas d'allergies alimentaires, nous accordons beaucoup d'importance à vos réponses.** L'étude est parrainée par Santé Canada et *AllerGen NCE* (www.Allergen-nce.ca/) et a été approuvée par le Comité de bioéthique du Centre universitaire de santé McGill (Montréal) ainsi que celui de l'Université McMaster (Hamilton).

Au cours des prochaines semaines, un chercheur de l'Université communiquera avec vous pour procéder au sondage téléphonique. Votre participation est entièrement volontaire. Le sondage devrait durer entre 15 et 20 minutes selon votre expérience des allergies alimentaires. On vous demandera si des membres de votre ménage ont des allergies alimentaires. Nous aimerions aussi connaître votre opinion sur certaines mises en garde courantes apparaissant sur les étiquettes des aliments par exemple, « Peut contenir des traces de noix ». Enfin, nous vous poserons quelques questions sur votre opinion de l'environnement et son impact sur votre santé et la santé des canadiens.

Si vous décidez de participer à cette étude, toute l'information que vous fournirez demeurera strictement confidentielle et sécurisée. **Pour obtenir de plus amples renseignements ou si vous ne voulez pas participer à l'étude, veuillez communiquer avec nous au numéro sans frais 1-866-431-7344, entre 9 h et 16 h, ou envoyez-nous un courriel à SCAAALAR@epimgh.mcgill.ca**. C'est avec plaisir que nous anticipons votre participation à cette importante étude.

Sincères salutations,

Chercheurs principaux de cette étude de recherche :
Ann Clarke, M.D., Centre universitaire de santé McGill – Montréal (Québec)
Susan Elliott, Ph. D., Université McMaster – Hamilton (Ontario)

Santé Canada Health Canada

AllerGen

APPENDIX B-QUESTIONNAIRE

Allergies in household

Q: IF_ALLERGY

Do you or anyone in your household have a food allergy?
- Yes
- No
- Refused
- Don't know

Q: WHO_ALLERGY

Is it you?
- Yes
- No

Are there any other adults in your household that have food allergies?
- Yes
- No
- Refused
- Don't know

INTERVIEWER NOTE: Refuses=-1, Don't know=-2
How many adults?

Are there any children in your household that have food allergies?
- Yes
- No
- Refused
- Don't know

INTERVIEWER NOTE: Refuses=-1, Don't know=-2
How many children?

Are you the best person to speak with about the child(ren) allerg(y/ies)?
- Yes
- No
- Refused
- Don't know

Q: WHICH_ALLERGY

Ok, I will now speak to you about your food allergy. Is your allergy to:
FOR INTERVIEWER: Read each and check all that apply. Do not give list of examples unless asked.

Peanut
Tree Nut
EXAMPLES: almond,brazil nut,cashew,hazelnut macadamia,pecan,pine nut,pistachio,walnut
Fish
Shellfish

EXAMPLES:lobster,crab,clams,oysters,mussels,scallops,shrimp
Sesame
Milk
Egg
Wheat
Soy
Other(please specify)

Peanut Prevalence

Q: PN1
FOR INTERVIEWER: Introduction to peanut survey
Now I am going to ask you a few questions about your experience with peanuts.
1.0) Have you ever had a reaction to TOUCHING peanuts?

1.1) Have you ever had a reaction to SMELLING peanuts?

1.2) Have you ever had a reaction to EATING peanuts?

1.3) So is it true to say that you have never had an allergic reaction to peanuts?

1.4) Have you ever eaten peanuts?

1.5) So is it true to say that you have never eaten peanuts?

Q: PN2

FOR INTERVIEWER: If Refused=>-1, Don't know=>-2, Never had a rxn=>-3
1.6a) How many allergic reactions have you had to peanut in your lifetime?

1.6b) It's important that we try to get an estimate for the number of reactions, can you at least tell me if it was...

Only 1 reaction	5-10 reactions	Don’t know
2-5 reactions	More than 10 reactions	Refused

1.7) About how old where you when you had your FIRST allergic reaction to peanuts?

1.8) It's important that we try to get an estimate...if you're not sure, can you at least tell me if it was...

Before you started school	In High school
In Elementary school	After High school
In Middle school	

2.0) How old were you when you had your MOST SEVERE reaction to peanut?

2.1) It's important that we try to get an estimate...if you're not sure, can you at least
tell me if it was...

Before you started school	In High school
In Elementary school	After High school
In Middle school	

2.2) Was the most severe reaction caused by eating, touching, or inhaling peanuts?

Eating	Refused
Touching	Don't Know
Smelling	

Q: PN3
I am going to read a list of symptoms that may or may not have occurred during the MOST SEVERE reaction, please indicate which one(s) occurred.

3.0) Did you have hives (skin rash, welts, urticaria)?

3.1) Did you have swelling (edema)?

3.2) Where did you have the swelling? (Click on all that apply)

Eyes(eyelids)	Refused
Tongue	Don't know
Lips	Other(specify)
Face	

3.3) Did you have nausea or stomach pain?

3.4) Did you vomit?

3.5) Did you have diarrhea?

Q: PN4

3.6) Did you start coughing?

3.7) Did you have trouble breathing?

3.8) Did you start wheezing?

3.9) Did you have an itchy mouth?

3.10) Did you feel any closing or tightening of the throat?

3.11) Did you feel lightheaded or as if you were going to faint?

3.12) Did you have any other symptoms?

Q: PN5

3.13) Now I would like you to think back to your most severe reaction. We would like to know how long it was from when you were exposed to peanuts and when your symptoms started?
INTERVIEWER NOTES: Exposed = eat,inhaled,touched

HH--MM--SS
-- --

Record time
Immediately
Refused
Don't Know

3.14) It's really important that we get an estimate...if you're not sure, can you at least tell me if the symptoms started...

In less than an hour	Refused
More than an hour	Don't know

3.15) How often have you had an allergic reaction after being exposed to peanuts? Would you say... INTERVIEWER: Please read all the responses

Never	Always
Less than half the time	refused
Half the time or more	Don't know

3.16) Why do you think you can sometimes be exposed to peanuts without having an allergic reaction? For example: Does it depend on how well it is cooked? Or did you "outgrow" the allergy?

Don't Know
Refused
Record answer:

Q: PN6

4.0) Have you ever used or been treated with a medication for an allergic reaction to peanut?

4.1) Was it epinephrine, an epipen, Twinjet or adrenaline?

4.2) Was it an antihistamine, like Benadryl, Reactin, Dimetapp or Atarax ?

4.3) Was it an inhaled medication such as Ventolin?

4.4) Was it steroids such as prednisone?

4.5) Have you ever used or been treated with any other medications for your peanut allergy?

4.6) Can you tell me more about those treatments?

Q: PN7

Now we would like to talk to you about how your peanut allergy was diagnosed.

5.0) Has your allergy to peanuts ever been confirmed by a doctor?

5.1) Did the doctor do a skin test?

5.2) Did the skin test show that you are allergic to peanut?

5.3) Did the doctor do a blood test?

5.4) Did the blood test show that you are allergic to peanut?

Q: PN8

5.5) Did the doctor do a food challenge?

5.6) Did the test show that you are allergic to peanut?

5.7) Could we contact your doctor to get a copy of the test results?
5.8) We will send you a consent form in the mail, could we have your mailing address now?

No Yes(ENTER ADDRESS):

Q: PN9

I am now going to ask you about what you have done AFTER your diagnosis with a peanut allergy. Do you agree with the following statements:

6.0) Since my diagnosis, I have stopped eating peanuts completely.

6.1) Since my diagnosis I continue to eat peanuts occasionally and I do not have a reaction.

6.2) Since my diagnosis I continue to eat peanuts occasionally and I do have a reaction.

Q: PN10

6.3) Since my diagnosis I sometimes eat foods that are labeled "may contain traces of peanuts" and I do not have a reaction.

6.4) Since my diagnosis I sometimes eat foods that are labeled "may contain traces of peanuts" and I do have a reaction.

7.0) Do you think you still have a peanut allergy?

7.1) How do you know that you no longer have a peanut allergy?

A doctor told me
Another health prof told me
Other(ie self-diagnosed)

Demographics

Q: DEMO1

1.0) If you are unsure, please ask "Can I confirm your gender".

Male
Female

Finally, we would just like to collect some general background information about you. Please be ensured that this information will remain confidential throughout the research process and that you have the option of not answering any question.

1.1) In what year were you born?

1.2) What is the highest level of education that you completed?

Never attended school	Some University
Some elementary school	University with degree
Elementary school	University with masters degree
Some secondary school	University with doctorate
Secondary school	Professional degree
Trade certificate or diploma	Refused
Some college	Don't Know
College with diploma	

1.3) What is your country of origin?

1.4) How long have you lived in Canada?

Number of years: Refused

Don't know

1.4a) Has it been... (FOR INTERVIEWER: READ THE RESPONSES)

More than 5 years

More than 10 years

More than 20 years

Q: DEMO2

In order to get a better picture of your household, we would like to ask you a couple of questions about each person in your household. This information will allow us to compare different types of households.

1.5) Starting with the oldest person in your household, REMEMBER to include yourself, what is their gender?

1.5) Now for the second oldest person in your household, what is their gender? ..(**up to ten times)**.

Male

Female

Refused

Don't know

1.6) How old is that person?

FOR INTERVIEWER: Refused= -, Don't Know= -2

Q: DEMO3

2.0) At present are you married, living with a partner, widowed, divorced, separated, or have you never been married?

Married
Living with a partner
Widowed
Divorced
Separated
Never married
Don't know
Refused

2.1) Is your dwelling owned or being bought by you or a member of this household,
or do you rent it?

Owned
Rented
Refused
Don't know

2.2) May I have your postal code?

Postal code
No (Ask: Can I just have the first 3 digits?)
Refused
Don't know (Ask: What city do you live in?)

2.3)For statistical purposes only, we need to know the total gross household income, from all sources, for 2007?

FOR INTERVIEWER: Refused = -1 and Don't know = -2

2.3a) We do not need to know your specific household income. Could you please indicate from the following list, the income range for your household.

Under $10,000
$10,000 - $19,000
$20,000 - $29,000
$30,000 - $39,000
$40,000 - $49,000
$50,000 - $59,000
$60,000 - $69,000
$70,000 - $79,000
$80,000 - $89,000
$90,000 - $99,000
More than $100,000
Refused
Don't know

APPENDIX C-WINBUGS PROGRAM FOR PREVALENCE MANUSCRIPT

```
model
{
for (i in 1:10596) #households
{
logit(p[i]) <- alpha.postal[postal[i]]
allergic[i]~dbin(p[i],individuals[i])
}
for (j in 1:1372) #postal codes
{
alpha.postal[j]~dnorm(mean.prov[prov[j]], tau.postal)
}
for (k in 1:10) #provinces
{
mean.prov[k]~dnorm(mu.prov,tau.prov)
}
#  Priors
mu.prov ~ dnorm(0, 0.05)
sd.postal ~ dunif(0.001, 7)
sd.prov ~ dunif(0.001, 7)
tau.postal <- 1/(sd.postal*sd.postal)
tau.prov <- 1/(sd.prov*sd.prov)
p.bar <- mean(p[])
for ( i in 1:10596)
{
household[i] ~ dnorm(0,1)
}
}
DATA
```

APPENDIX D-WINBUGS PROGRAM FOR EAI MANUSCRIPT

```
model
{
for (i in 1:233)      # individuals
{
logit(epipen.p[i])<-alpha0+alpha[y[i,1]]+ b.hadrx*y[i,3]+b.female*y[i,4]+
b.child*y[i,5]+b.age_ms*y[i,6]+b.mult_aly*y[i,7]+b.skin_blood*y[i,8]+b.epi_use
d*y[i,9]
y[i,2]~dbern(epipen.p[i])
}
for (j in 1:215)     #households
{
alpha[j] <-b.married*w[j,1]
}
alpha0~dnorm(0,0.05)
# Distributions for household data
b.married~dnorm(0,0.05)
b.canborn~dnorm(0,0.05)
# Distributions for individual data
b.hadrx~dnorm(0,0.05)
b.female~dnorm(0,0.05)
b.child~dnorm(0,0.05)
b.age_ms~dnorm(0,0.05)
b.mult_aly~dnorm(0,0.05)
b.skin_blood~dnorm(0,0.05)
b.epi_used~dnorm(0,0.05)
# Odds Ratios
or.female<-exp(b.female)
or.child<-exp(b.child)
or.age_ms<-exp(b.age_ms)
or.mult_aly<-exp(b.mult_aly)
or.skin_blood<-exp(b.skin_blood)
or.epi_used<-exp(b.epi_used)
or.married<-exp(b.married)
or.canborn<-exp(b.canborn)
}
DATA
```