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Project Title: Assessing the relationship between maternal peanut consumption during pregnancy and the prevalence of peanut allergy in a birth cohort

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SUMMARY: (no more than 250 words single spaced)

Allergy is one of the most common chronic diseases of childhood and often presents early in life. Food allergies are typically the initial presentation of allergic disease. In the past, many medical/pediatric societies recommended avoidance or delayed introduction of certain foods, especially peanuts, in an attempt to reduce the risk of food allergy in children. However, it is now realized that this may not be the correct advice to give all mothers. The Canadian Healthy Infant Longitudinal Development (CHILD) study is a national, general population-based, longitudinal birth cohort study across four different centres in Canada: Vancouver, Edmonton, Winnipeg and Toronto. Data including maternal food frequency questionnaires and results of skin prick testing (SPT) to foods were collected. This data from the CHILD study was analyzed using a statistical analysis system (SAS) in order to determine the relationship between maternal consumption of peanut during pregnancy and the outcome of peanut sensitization as defined by SPT. Two mean wheal diameter cut-off points at 2 mm or greater or 3 mm or greater, which are commonly used in epidemiological studies, were used to indicate sensitization in this study. An unadjusted association was only found between maternal consumption of peanuts, other nuts and seeds and sensitization to peanut as indicated by development of a wheal measuring 3 mm or greater in diameter in response to skin prick testing.

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Introduction

Peanut allergy is increasingly common and characterized as "typically lifelong, often severe, and potentially fatal". [1] Two previous studies have illustrated that allergic reactions to peanut is the single most common cause of fatal, food-induced anaphylaxis. [2,3] In addition, a review of a ten-year history of food allergy-related emergency room visits to Uppsala University Children's Hospital in Sweden revealed that half of these visits were due to reactions to peanuts and tree nuts. [4] Unfortunately, the quality of life of peanut-allergic children and their families is significantly affected as a result of living with a peanut allergy. As described by Pansare and Kamat, "most families unfortunately live in a "constant state of fear" worrying about the occurrence of reactions". This is especially true considering that only trace amount of peanut proteins are required in order to induce a reaction. [5]

According to Jarvinen and Fleischer, "food allergy is defined as an adverse health effect arising from a specific immune response that is reproducible on exposure to a given food, and thus is an example of a defect in the development or a breakdown in the maintenance of oral tolerance". [6] Peanut allergy is an immediate hypersensitivity reaction, which presents clinically as a result of immunoglobulin E (IgE) production in response to an antigen. This particular class of hypersensitivity reactions require an initial antigen exposure in order to prime the immune system to respond to subsequent bouts of the same allergen exposure. Upon initial exposure, T_H2 reactions take place and IgE antibody production occurs. Fc receptors on mast cells are then bound by this allergen-specific IgE, which cross links on subsequent exposure to a specific allergen, leading to secretion of a wide range of biochemical and biologic mediators. These mediators act to produce signs and symptoms such as urticaria, flushing, bronchoconstriction, hypotension and laryngeal edema leading to compromised breathing. Individuals who tend to develop these types of IgE-mediated immediate hypersensitivity reactions are referred to as atopic. Anaphylaxis, which can occur in patients experiencing an allergic reaction to peanut, is "a systemic reaction characterized by edema in many tissues, including the larynx, accompanied by a fall in blood pressure". [7] It had been noted that 75% of peanut-allergic patients react to the allergen at the first overt exposure. [8] Based on this finding and the pathophysiology of an immediate hypersensitivity reaction, there must exist a route by which peanut-allergic patients are sensitized prior to initial, overt oral consumption.

The prevalence of peanut sensitization and peanut allergy has changed over time. Grundy et al. carried out a study looking at the change in the rate of peanut sensitization in two cohorts from the Isle of Wight, United Kingdom. Infants born between September 1, 1994 and August 31, 1996 were compared to infants born in 1989. The results of the study revealed that the rate of sensitization increased 3-fold from 1.1% in the 1989 cohort to 3.3% in the 1994-1996 cohort. [9] In the United States, Sicherer et al. researched the changes in peanut or tree nut allergy prevalence in children under the age of 18. The findings of the study revealed an increase in the prevalence of peanut or tree nut allergy over time, as the values were noted to be 0.6% in 1997, 1.2% in 2002 and 2.1% in 2008. [10] A Montreal school-based study performed by Ben-Shoshan et al. showed that the prevalence of peanut allergy was statistically unchanged with a minor numeric increase from 1.34% in a 2000-2002 cohort to 1.62% in a 2005-2007 cohort. [11]

The prevalence of peanut allergy has been noted to vary based on geographic area. In Canada, 1.68% of children have a peanut allergy. [12] In the United States, 2.1% of children under 18 years of age have an allergy to peanut, tree nut or both. [13] In France, between 0.30% and 0.75% of the general population have been noted to have a peanut allergy. [14] In Denmark, 0.2% of 3-year-old children and 0.4% of adults were noted to have a peanut allergy in a 2005 study. [15] In Singapore

and the Philippines, peanut allergy prevalence rates among children aged 4 – 6 years old was found to be 0.64% and 0.43%, respectively. [16]
As is true of many other diseases, genetics play a role in the development of food allergy. A study by Sicherer et al., which compared concordance rates between monozygotic and dizygotic twins, found that there is a strong genetic component that has an affect on the development of peanut allergy based on the fact that monozygotic twins were found to have a higher concordance rate than dizygotic twins. The study estimated the heritability of peanut allergy to be 82% to 87%, which is considered high. This estimate took into account both genetic and environmental contributions. [17]

A study by Du Toit et al. investigated the impact that early introduction of peanut into an infant's diet had had on the outcome of developing peanut allergy. The study looked at the differences in the timing of peanut introduction between two populations of similar heritable background; one was comprised of Jewish children living in the UK, while the other was Jewish children living in Israel. They found that Israeli infants consumed peanuts in significantly greater amounts and earlier in life than infants living in the UK. In fact, the median value for monthly peanut consumption among infants in the UK was 0 times per month, whereas the median value was 8 times per month with respect to Israeli infants. Overall, a 10-fold difference existed among peanut allergy prevalence rates; 1.85% peanut allergy among Jewish children in the UK and 0.17% in Israel. According to the authors, the difference in prevalence values could not be explained by "differences in atopy, social class, genetic background, or peanut allergenicity." These findings lead us to question whether or not earlier and more frequent consumption of peanut during infancy can induce tolerance to the allergen, as opposed to provoking sensitization. [18]

Over time, recommendations with respect to maternal consumption of peanut during pregnancy has changed. In 1998, the United Kingdom government's Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) advised pregnant and breastfeeding women with a history of atopic disease to avoid consuming peanuts and peanut products in an effort to decrease the incidence of peanut allergy in the population. The advice was directed at approximately 250, 000 women, all of which had a family history of atopic disease. Women who did not have a family history of atopic disease were not the target audience of this advisory. [19] In 2000, the American Academy of Pediatrics outlined recommendations for breastfeeding mothers of infants at high risk for developing allergy. The recommendations suggested that mothers of high risk infants remove peanuts and tree nuts from their diets, as well as consider eliminating eggs, cow's milk, fish, and perhaps other foods, while breastfeeding. It was also suggested that "solid foods should not be introduced into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts and fish until 3 years of age". In addition, the recommendations outlined that restrictions on maternal diet during pregnancy were not necessary with a possible exception of eliminating peanut. [20] In spite of general adherence to these recommendations, peanut allergy has increased.

In 2008, the American Academy of Pediatrics (AAP) published recommendations stating that "at the present time, there is lack of evidence that maternal dietary restrictions during pregnancy play a significant role in the prevention of atopic disease in infants". The AAP also stated that "although solid foods should not be introduced before 4 to 6 months of age, there is no current convincing evidence that delaying their introduction beyond this period has significant protective effect on the development of atopic disease regardless of whether infants are fed cow milk protein formula or human milk. This includes delaying the introduction of foods that are considered to be highly allergic, such as fish, eggs, and foods containing peanut protein".

In this particular publication, the AAP simply stated information based on previously published literature, rather than making specific dietary consumption recommendations for pregnant women. [21]
Currently, the Canadian Paediatric Society (CPS) advises against women avoiding peanut consumption during pregnancy due to the fact that "evidence to support maternal dietary restrictions during pregnancy is contradictory and insufficient to change best practice". [22]

Multiple studies have been conducted with the objective of determining whether or not an association exists between maternal consumption of peanut during pregnancy and peanut allergy or sensitization. Four previously published studies have been unable to show an association whereas two studies have shown a positive relationship between maternal peanut consumption during pregnancy and the outcome of peanut sensitization.

A prospective longitudinal study was carried out by Tariq et al., which focused on children born from the Isle of Wight between January 1989 – February 1990. 1218 subjects were studied and the authors found that maternal ingestion of nuts during pregnancy did not result in an increased number of sensitized children. A number of different factors were found to be risk factors for both allergy and sensitization to peanuts. These factors included family history of atopic disease, eczema as an infant, egg allergy at ages 1, 2 or both, as well as asthma, eczema and rhinitis at 4 years of age. [23] Lack et al. performed a case-control study in which peanut allergic children were compared to two unmatched control groups. One of the groups consisted of children who were atopic and did not have a diagnosis of peanut allergy, while the second group consisted of children without peanut allergies. The subjects in the first control group were considered to be atopic if both they and their mother had a diagnosis of eczema. The results of the study revealed that there were no significant associations between maternal consumption of peanuts and the outcome of peanut allergy. In addition, this study measured peanut-specific IgE in previously frozen cord blood from all of the children who were determined to be peanut allergic, and the results revealed that peanut-specific IgE could not be found in any of the samples. [24] Binkley et al. carried out a retrospective web-based case-control study in which information from the Anaphylaxis Canada Registry was used in order to compare 1300 children with reported peanut allergy with 113 control children with shellfish allergy. Mothers were asked to answer a questionnaire that included a question on recalling the amount of peanut or peanut containing products consumed during pregnancy. The results of the study revealed that reduction in maternal consumption of peanut during pregnancy "was associated with a non-significantly lower risk of peanut allergy in the offspring". [25] Hourihane et al. performed a prospective longitudinal study, which focused on children born between March 1999 and March 2000 in Southampton and Manchester, United Kingdom. The purpose of this study was to determine whether or not the guidelines put forth by the COT (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment) in the United Kingdom had any impact on the overall prevalence of peanut allergy. Overall, the prevalence of peanut sensitization in this particular cohort, at a value of 2.8% (95% confidence interval 1.8% to 3.8%), was found to be significantly greater than the prevalence of peanut sensitization in the 1989 cohort, at a value of 1.1% (95% confidence interval 0.5% to 1.6%). [26]

In 1996, Hourihane et al. published a study in which one of the focuses was on the prevalence of peanut allergies in families where one member was diagnosed with the allergy. One of the conclusions from the study was that at the time, peanut allergy was presenting earlier in life, and that may have been as a result of increased maternal consumption of peanuts during pregnancy and breastfeeding. [27]

There are two studies which have shown an association between maternal consumption of peanut during pregnancy and peanut sensitization. Sicherer et al. carried out a cross-sectional study focusing on 503 infant subjects ages 3 months to 15 months who had not been previously diagnosed with peanut allergy but were likely to have a milk or egg allergy. The enrollment criteria of this study included "(1) a history of a convincing immediate allergic reaction to cow's milk (and/or egg) and a positive skin prick test (SPT; 3 mm larger than the negative control) to cow's milk (and/or egg, if the clinical reaction was to egg), and/or (2) moderate to severe atopic dermatitis (AD), and a positive SPT to milk and/or egg". Peanut specific IgE was used in order to determine whether or not a child was likely to have a peanut allergy and the cut off level used in this study was peanut IgE $\geq$ 5.0 kU_A/L. The results of the study "showed peanut consumption during pregnancy…to be…associated with peanut IgE $\geq$ 5.0 kU_A/L". In summary, the authors "found that maternal ingestion of peanut during pregnancy had a dose-dependent association with peanut sensitization and likely peanut allergy in infants with likely egg or milk allergy". [28] In 1999, Frank et al. published a case-control study, which focused on consumption of peanuts and peanut-containing foods during both pregnancy and breastfeeding. This particular study gathered information from mothers with a family history of atopic disease. 43 children, whose ages ranged between 0 and 3 years old, were the subjects of focus for this particular study. 25 case subjects were sensitized to peanut, while 18 control subjects were sensitized to milk and/or egg but not peanut. The authors of this study reported that "mothers who consumed peanuts more than once a week during pregnancy were more likely to have a peanut-allergic child than mothers who consumed peanuts less than once a week (odds ratio = 3.97, 98% confidence interval 0.73-24)". In addition, children who developed a peanut allergy were fed peanuts or peanut butter at a significantly younger age. Both maternal consumption of peanut during pregnancy and the age at which peanut is introduced into the child's diet represent risk factors that could be modified. [29]

Materials and Methods

The Canadian Healthy Infant Longitudinal Development (CHILD) study, which is a national, general population-based, longitudinal birth cohort study, recruited pregnant women during the second or third trimester to participate in the study. [30] Overall, more than 3600 mothers were recruited from four different sites across Canada: Vancouver (University of British Columbia, Simon Fraser University, Child and Family Research Institute, St. Paul's Hospital, Women and Children's Hospital and BC Children's Hospital), Edmonton (University of Alberta, Alberta Health Services - Sturgeon, Royal Alexandra (Lois Hole Hospital for Women) and Stollery Children's Hospital, Covenant Health - Grey Nuns and Misericordia Hospitals), Winnipeg (Winnipeg Health Sciences Centre, St. Boniface General Hospital, Boundary Trails Health Centre, The Manitoba Institute of Child Health and The Birth Centre), and Toronto (The University of Toronto, Gage Occupational & Environmental Health Unit, The Hospital for Sick Children, Mount Sinai Hospital and Sunnybrook Hospital). Mothers were recruited in a number of different settings, which included malls, community centres, farmer's markets, baby shows, prenatal swimming classes and physician offices. Individuals contributing to the recruitment process included physicians, nurses, staff, students, volunteers and other members involved with the study. Mothers were recruited using posters, online resources or in person.

Inclusion criteria for the study included the following: (1) pregnant women aged 18 years and older (19 in Vancouver); (2) residence in reasonable proximity to the delivery hospital; (3) able to read, write and speak English; (4) willing to provide informed consent; (5) willing to consent to cord blood collection for the study; (6) planning to give birth at a designated recruitment centre participating hospital; (7) infants born at or after 35 weeks; (8) able to provide name, address and telephone numbers of two alternate contact individuals. Exclusion criteria for the study

included the following: (1) children born with major congenital abnormalities or respiratory distress syndrome (RDS); (2) expectation of moving away from a recruitment area within 1 year; (3) children of multiple births; (4) children results from in vitro fertilization; (5) children who will not spend at least 80% of nights in the index home; (6) children born before 35 weeks gestation. [30]

The sample size is fixed based on the original sample size calculation done for the full national study based on the development of asthma at age 5 years. Mothers provided written consent during pregnancy, and then subsequently were asked to complete health, stress and environmental exposure questionnaires. Mother's completed a detailed food frequency questionnaire (FFQ) that was used to assess their consumption of peanuts and other tree nuts during pregnancy. Food frequency questionnaires are well-validated methods of assessing nutritional intake. [31] We used the responses to the questions: "Peanuts and other nuts and seeds" and "Peanut butter". Father's were asked to complete a health-related questionnaire in order to provide information such as history of atopic disease. The children were followed from the time of their birth up until 1 year of age. During this year, the children's health was assessed via questionnaire at 3 months, 6 months and 1 year. Children were seen for a physician assessment in clinic at age 1. Data was collected with respect to maternal consumption of peanut, tree nuts, seeds and peanut butter during pregnancy, the age at which peanut and tree nut were introduced into the child's diet, family history of atopic disease, duration of breastfeeding, ethnicity, sex, as well as skin prick test results.

Ethics

Ethics was obtained from the Research Ethics Board of The University of Manitoba and the Regional Health Authority of Central Manitoba.

Skin Prick Testing (SPT)

At 1 year of age, skin prick (epicutaneous) testing was performed to foods including peanut, egg, milk and soy. Positive and negative controls included histamine and saline, respectively. A skin prick test to peanut was considered positive with a mean wheal diameter 2 mm or more or 3 mm or more than the negative control.

Statistical Analysis

Data was analyzed using a statistical analysis system (SAS). Chi-square tests of independence were performed in order to produce unadjusted comparisons between peanuts, other nuts and seeds consumption and production of a wheal measuring 2 mm or greater or 3 mm or greater in diameter, in response to peanut SPT, as well as between peanut butter consumption and production of a wheal measuring 2 mm or greater or 3 mm or greater in diameter, in response to peanut SPT.

Results

One hundred and forty seven out of 2927 (5.0%) children were found to be sensitized to peanut with a mean wheal diameter of 2 mm or greater in response to peanut (table 1). 109 out of 2926 (3.7%) children were found to be sensitized to peanut based on a mean wheal diameter of 3 mm or greater in response to peanut (table 2). With respect to peanuts, other nuts and seeds consumption, 661/3049 (21.7%) mothers never consumed or consumed less than once per month, 1085/3049 (35.6%) consumed 1 to 3 times per month, 687/3049 (22.5%) consumed 1 to

2 times per week, 486/3049 (15.9%) consumed 3 to 6 times per week, and 130/3049 (4.3%) consumed more than once per day. Data was missing from 376 subjects with respect to peanuts, other nuts and seeds consumption (table 3). With respect to consumption of peanut butter, 728/3049 (23.9%) never consumed or consumed less than once per month, 721/3049 (23.7%) consumed 1 to 3 times per month, 839/3049 (27.5%) consumed 1 to 2 times per month, 608/3049 (19.9%) consumed 3 to 6 times per week, and 153/3049 (5.0%) consumed more than once per day. Data was missing from 376 subjects with respect to peanut butter consumption (table 4).

A chi-square test of independence indicated that there is no significant unadjusted association between the frequency of peanuts, other nuts and seeds consumed and the outcome of developing a wheal measuring 2 mm or greater in diameter in response to peanut SPT, X^2 (4, N = 2711) = 8.79, p = 0.07. Data was missing for 714 subjects (table 5). A chi-square test of independence indicated that an unadjusted significant association exists between the frequency of peanuts, other nuts and seeds consumed and the outcome of developing a wheal measuring 3 mm or greater in diameter in response to peanut SPT, X^2 (4, N = 2710) = 12.0, p = 0.02. Data was missing for 715 subjects (table 6). A chi-square test of independence indicated that there is no significant unadjusted association between the frequency of peanut butter consumed and the outcome of developing a wheal measuring 2 mm or greater in diameter in response to peanut SPT, X^2 (4, N = 2711) = 1.35, p = 0.85. Data was missing for 714 subjects (table 7). A chi-square test of independence indicated that there is no significant unadjusted association between the frequency of peanut butter consumed and the outcome of developing a wheal measuring 3 mm or greater in diameter in response to peanut SPT, X^2 (4, N = 2710) = 1.73, p = 0.79. Data was missing for 715 subjects (table 8).

Discussion

We evaluated the relationship between maternal consumption of peanuts, other nuts and seeds, and specifically of peanut butter, during pregnancy and the outcome of sensitization to peanut on skin prick testing at 1 year of age. We did find an association between maternal consumption of peanuts, other nuts and seeds and sensitization to peanut as indicated by development of a wheal measuring 3 mm or greater in diameter in response to skin prick testing. This cut-off for considering a positive skin prick test is commonly viewed as clinically important. We did not find an association between maternal consumption of peanuts, other nuts and seeds and sensitization to peanut as indicated by development of a wheal measuring 2 mm or greater in diameter in response to skin prick testing. This cut-off for considering a positive skin prick test is commonly used in epidemiologic studies. We did not find an association between maternal consumption of peanut butter and sensitization to peanut as indicated by development of a wheal measuring 2 mm or greater in diameter in response to skin prick testing. We did not find an association between maternal consumption of peanut butter and sensitization to peanut as indicated by development of a wheal measuring 3 mm or greater in diameter in response to skin prick testing. There was a positive relationship between maternal consumption of peanuts, other nuts and seeds and sensitization to peanut as indicated by development of a wheal measuring 3 mm or greater in diameter in response to skin prick testing, but we have not yet adjusted the analysis for important confounding factors such as maternal allergy, breastfeeding and other factors associated with potential for allergy.

In clinical practice, the production of a wheal in response to a food allergen measuring at least 3 mm greater in diameter than the negative control is considered to be a positive response, while all wheals of smaller size are considered to constitute a negative response. Positive SPT results are simply an indication of a possible association between a particular food allergen and

production of allergen specific IgE. In general, the positive predictive value of a SPT is less than 50% in history negative subjects when compared to the gold-standard of food allergy diagnosis, which is the double-blind, placebo controlled food challenge (DBPCFC). As outlined by Sampson, the clinical implication of a positive SPT is that "responses only "suggest" the presence of symptomatic allergy". With that being said, a positive SPT "may be considered diagnostic in patients who experience a serious systemic anaphylactic reaction after the ingestion of an isolated food". On the other hand, the negative predictive value of a SPT is greater than 95%, which means that these tests are useful at ruling out an IgE-mediated food reaction. [32] In this particular study, a second cut-off value has been established at 2 mm. This particular cut-off was chosen based on the fact that it is commonly utilized in epidemiological studies and infants less than 2 years of age produce smaller wheals in response to skin prick testing with histamine (a positive control). [33]

Strengths of our study include the large number of children from whom data has been collected, as well as the ability to collect the information in a prospective manner. In addition, the study is representative of the Canadian population as the information is derived from a general population-based cohort from four different centres across the country.

Limitations to this study include lack of information in regards to maternal peanut consumption during breastfeeding, as well as an inability to determine the quantity of environmental peanut that a child may be exposed to during the first few months of life. Vadas et al. carried out a study with the objective of determining whether or not peanut protein could be present in the breast milk of mothers consuming dietary peanut. The study showed that peanut protein could be detected in the breast milk of 11 out of 23 women. [34] Therefore, maternal consumption of peanut during lactation may present as another source of sensitization and can act as a confounding variable as a result. Lack et al. published results showing that a significantly greater percentage of peanut-allergic children had been exposed to creams containing peanut oil during the first six months of life relative to children who were not peanut allergic. "84 percent of the children who were allergic to peanuts and 91 percent of those with a positive peanut-challenge test had been exposed to creams containing peanut oil during the first six months of life". These values were significantly greater than the 59 percent in a normal control group and 53 percent in a control group comprised of children whose mothers had a history of eczema and who had eczema themselves in the first six months of life ($P < 0.001$). These creams were used in an effort to treat rashes and their use occurred at a time prior to a history of peanut allergy symptoms. [24] In addition, the clinical assessment at age 1 does not query whether or not there is a probable, likely or certain diagnosis of food allergy. It is important to make the distinction between sensitization and allergy, as the terms describe two different entities. As outlined by Boyce et al., "the presence of sIgE, [which can be indicated by a positive skin prick test] reflects sensitization and not necessarily clinical allergy". [35] Osborne et al. provided a good illustration of this difference when the authors carried out a study in Australia that looked at 2848 infants. The results revealed that 8.9% of infants were sensitized to peanut, based on a positive SPT resulting in a wheal 1 mm or greater than the negative control, while 3.0% of infants were shown to be peanut-allergic based on oral food challenge (OFC) results. A positive oral food challenge was considered as such if it met the following criteria as outlined by the authors "the development of 1 or more of the following objective criteria was used to define a positive OFC: 3 or more concurrent noncontact urticaria persisting for at least 5 minutes, perioral or periorbital angioedema, vomiting (excluding gag reflex), or evidence of circulatory or respiratory compromise, occurring within 2 hours of ingestion of a dose during food challenge. This definition was also used if infants developed a reaction within 2 hours of ingestion of the food on subsequent days of home-based introduction if they had not reacted on day 1 of the challenge". [36]

Also, double-blind, placebo-controlled food challenges (DBPCFC), which are considered to be the "gold standard" of food allergy diagnosis, are not part of the study protocol. Another important factor that cannot be accounted for is history of peanut allergy in a peanut-allergic sibling, as this was not queried amongst the general cohort in the CHILD study. Liem et al. published results showing "that the sibling of a peanut-allergic child has a dramatically increased risk of developing peanut allergy". It was found that the risk of a child developing a peanut allergy was "nearly 7-fold greater than those who do not have a sibling with peanut allergy". [37] With respect to the clinical implications of these findings, there are a number of analyses that will need to be carried out on the data in order to produce results that are more inclusive of a wider array of factors that impact allergy development. The relationship between maternal consumption of peanuts, other nuts and seeds, as well as peanut butter, and the outcome of sensitization to peanut, needs to be adjusted for based on a number of confounding factors which include the following: duration of breastfeeding, timing of the introduction of peanuts and nuts into the child's diet, both maternal and paternal history of atopy (with a focus on peanut and/or food allergy), and presence of atopic dermatitis.

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Table 1. Number and percentage of children sensitized to peanut at 1 year based on a cut-off of ≥ 2mm wheal size

Sensitized to peanut	Number	Percent
No	2780	95.0%
Yes	147	5.0%
498 subjects missing		

Table 2. Number and percentage of children sensitized to peanut at 1 year based on a cut-off of ≥ 3 mm wheal size

Sensitized to peanut	Number	Percent
No	2817	96.3%
Yes	109	3.7%
499 subjects missing		

Table 3. Consumption frequency of peanuts, other nuts and seeds

Amount consumed	Number	Percent
Never or < 1 per month	661	21.7%
1 – 3 per month	1085	35.6%
1 – 2 per week	687	22.5%
3 – 6 per week	486	15.9%
1+ per day	130	4.3%
376 subjects missing		

Table 4. Consumption frequency of peanut butter

Amount consumed	Number	Percent
Never or < 1 per month	728	23.9%
1 – 3 per month	721	23.7%
1 – 2 per month	839	27.5%
3 – 6 per week	608	19.9%
1+ per day	153	5.0%
376 subjects missing		

Data from food frequency questionnaire modified from Fred Hutchinson Cancer Research Centre, Seattle, Washington
A) FFRQ25 – Peanuts and other nuts and seeds
B) FFRQ26 – Peanut butter

Table 5. Comparing consumption frequency of peanuts, other nuts and seeds with development of ≥ 2 mm wheal in response to peanut skin prick test

Frequency of peanuts, nuts and seeds consumption	Negative SPT result (wheal < 2 mm)	Positive SPT result (wheal ≥ 2 mm)
Never or < 1 per month	554	23
1 – 3 per month	919	42
1 – 2 per week	594	31
3 – 6 per week	402	33
1+ per day	109	4
714 subjects missing		

X^2 (4, N = 2711) = 8.79, p = 0.07

Table 6. Comparing consumption frequency of peanuts, other nuts and seeds with development of ≥ 3 mm wheal in response to peanut skin prick test

Frequency of peanuts, nuts and seeds consumption	Negative SPT result (wheal < 3 mm)	Positive SPT result (wheal ≥ 3 mm)
Never or < 1 per month	562	15
1 – 3 per month	933	28
1 – 2 per week	603	22
3 – 6 per week	408	27
1+ per day	109	3
715 subjects missing		

X^2 (4, N = 2710) = 12.0, p = 0.02

Table 7. Comparing consumption frequency of peanut butter with development of ≥ 2 mm wheal in response to peanut skin prick test

Frequency of peanut butter consumption	Negative SPT result (wheal < 2 mm)	Positive SPT result (wheal ≥ 2 mm)
Never or < 1 per month	607	30
1 – 3 per month	607	27
1 – 2 per week	710	41
3 – 6 per week	524	27
1+ per day	130	8
714 subjects missing		

X^2 (4, N = 2711) = 1.35, p = 0.85

Table 8. Comparing consumption frequency of peanut butter with development of ≥ 3 mm wheal in response to peanut skin prick test

Frequency of peanuts, nuts and seeds consumption	Negative SPT result (wheal < 3 mm)	Positive SPT result (wheal ≥ 3 mm)
Never or < 1 per month	619	18
1 – 3 per month	613	21
1 – 2 per week	722	28
3 – 6 per week	529	22
1+ per day	132	6
715 subjects missing		

X^2 (4, N = 2710) = 1.73, p = 0.79