

Timing of Introduction, Sensitization, and Allergy to Highly Allergenic Foods at Age 3 Years in a General-Population Canadian Cohort



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What is already known about this topic? Early dietary introduction of highly allergenic foods has been associated with decreased risk of food allergy in high-risk infants. Further information is needed regarding the importance of early introduction to highly allergenic foods in population-based cohorts.

What does this article add to our knowledge? This study examined associations between age of dietary introduction of peanut, egg, and cow's milk in general-population infants and sensitization and possible or probable clinical IgE-mediated allergy to the specific highly allergenic food being introduced.

How does this study impact current management guidelines? General-population infants introduced to peanut before age 12 months showed lower peanut sensitization and allergy, even after exclusion of high-risk infants. Introduction of egg and cow's milk before 12 months showed no increased risk.

BACKGROUND: Early dietary introduction of highly allergenic foods has been associated with decreased risk of food allergy in high-risk infants.

OBJECTIVE: Early introduction of highly allergenic foods for lower risk infants was examined using Canadian Healthy Infant Longitudinal Development (CHILD) Study data.

METHODS: CHILD participants were recruited from the general population before birth. Every 6 months, caregivers reported food introduction and allergic reactions. At ages 1 and 3 years, sensitization to peanut, egg, and cow's milk was measured by skin prick testing (SPT) and atopic dermatitis diagnosed at clinical visits. Multivariable logistic regression was used to examine associations between timing of introduction to peanut, egg, and cow's milk and the presence at 3 years of sensitization (positive SPT) and probable clinical IgE-mediated

allergy (sensitization with no current consumption and convincing history of allergic reaction to the specific food).

RESULTS: Among 2669 CHILD participants at age 3 years, 101 (3.80%) showed sensitization to peanut, 59 (2.21%) to egg, and 30 (1.12%) to cow's milk; 46 (1.78%) showed probable clinical IgE-mediated allergy to peanut, 4 (0.16%) to egg, and 2 (0.08%) to cow's milk. Infants introduced to peanut after 12 months had increased odds of sensitization (odds ratio [OR]: 2.38, 95% confidence interval [CI]: 1.39-4.07) and probable clinical allergy (OR: 4.04, 95% CI: 1.66-9.85) to peanut at 3 years. Associations persisted after exclusion of high-risk infants with moderate-to-severe atopic dermatitis in the first year/egg sensitization at 1 year.

CONCLUSIONS: General-population infants introduced to peanut after age 12 months were more likely to have

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This study was funded by the Manitoba Medical Service Foundation, Children's Hospital Foundation, and University of Manitoba. The Allergy, Genes and Environment (AllerGen), Network of Centres of Excellence (NCE), and the Canadian Institutes of Health Research (CIHR) provided core funding for CHILD.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication January 23, 2019; revised September 28, 2019; accepted for publication September 30, 2019.

Available online October 31, 2019.

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<https://doi.org/10.1016/j.jaip.2019.09.039>

Abbreviations used

CHILD Study- Canadian Healthy Infant Longitudinal Development Study

CI- Confidence interval

LEAP- Learning Early about Peanut

OR- Odds ratio

PAF- Population attributable fraction

SPT- Skin prick testing

sensitization and probable clinical allergy to peanut at 3 years. © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:166-75)

Key words: Food allergy; Peanut; Egg; Cow's milk; Food introduction; Sensitization; IgE-mediated; Pregnancy cohort; Multivariable logistic regression

Prevention of food allergy in infants and young children has become a central goal of food allergy management at the population level. Early dietary introduction of highly allergenic foods has been shown to decrease the likelihood of sensitization^{1,2} and allergy³⁻⁷ to the particular food in some populations of children. At age 1 year, Canadian Healthy Infant Longitudinal Development (CHILD) cohort participants were more likely to be sensitized to peanut (odds ratio [OR]: 1.76, 95% confidence interval [CI]: 1.07-3.01), egg (OR: 1.89, 95% CI: 1.25-2.80), and cow's milk (OR: 3.69, 95% CI: 1.37-9.08) if they had not introduced the corresponding highly allergenic food during the first 12 months of life.¹ Children at high risk for peanut allergy because of egg allergy and/or severe atopic dermatitis have been shown by randomized control trial to be less likely to develop persistent peanut allergy with introduction to peanut before age 12 months.^{5,6} However, other studies have not shown benefit of early introduction of highly allergenic foods. Conditions such as atopic dermatitis⁸⁻¹² remain associated with a higher risk of food allergy and have been implicated in increasing the risk of food allergy development.^{13,14}

The Learning Early about Peanut (LEAP) trial of high-risk infants enrolled 4- to 11-month-old infants with moderate-to-severe eczema and/or egg allergy who were skin prick tested to peanut and, if they were not sensitized (0 mm skin prick testing [SPT]) or minimally sensitized (≤ 4 mm SPT) to peanut, were randomized to consume peanut regularly or not consume peanut until age 5 years.⁵ Nonsensitized and minimally sensitized infants who consumed peanut up to age 5 years were less likely to have a persistent peanut allergy at age 5 years.⁵ The protective effect of early peanut consumption persisted after 12 months of peanut avoidance⁶ and was specific to peanut and not protective against other allergic conditions.¹⁵

Early introduction of highly allergenic foods is increasingly being recommended for all infants. Potential benefits of early introduction among infants who are not at high risk of food allergy should be better understood so that optimal recommendations can be made to health care providers and families of children for whom the timing of introduction is important.

In the CHILD pregnancy cohort of infants recruited before birth from the general population, we examined the associations between timing of introduction of 3 highly allergenic foods,

peanut, egg, and cow's milk, and the presence at age 3 years of sensitization, possible IgE-mediated food allergy, and probable clinical IgE-mediated food allergy to each of these foods.

We hypothesized that children introduced to peanut, egg, and cow's milk after age 12 months would have greater odds at age 3 years of sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy to the food whose introduction was delayed.

METHODS

Study population

Between 2008 and 2012, inclusive, healthy infants were enrolled in the CHILD Study (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org) before birth from the general population at 4 sites (Vancouver, Edmonton, Winnipeg/Morden-Winkler, and Toronto).¹⁶ In this observational study, families of the 3455 participating infants were not provided with specific information about when or how they should introduce highly allergenic foods to their infants. At the time of recruitment, consensus still recommended delayed introduction of highly allergenic foods,¹⁷ although individual studies suggested that delayed dietary peanut introduction was contributing to the increased prevalence of peanut allergy.^{18,19} Research Ethics Board approval was obtained at all study sites.

Highly allergenic foods: earliest age of introduction, current consumption, and allergic reactions

Every 3 to 6 months until age 36 months, parents and caregivers of CHILD participants provided detailed, prospectively collected information regarding their child's consumption of peanut, egg, and cow's milk. The earliest reported consumption of peanut, egg, and cow's milk was used as the age of introduction; where reported ages of introduction differed between questionnaires completed at different times, the timing reported on the earliest-completed questionnaire was used. Formula introduction and type of formula were also reported at birth and ages 3, 6, and 12 months. Parents and caregivers reported their child's current consumption of peanut, egg, and cow's milk at age 3 years using a validated Food Frequency Questionnaire. The reasons for introducing or not introducing or continuing to consume or no longer consuming highly allergenic foods at a particular time were not reported. Caregivers reported allergic reactions to highly allergenic foods every 6 months from ages 6 to 36 months.

Sensitization to highly allergenic foods and atopic dermatitis diagnosis

At the 1-year-old visit, sensitization to peanut, egg white, and cow's milk was determined by SPT with allergens (ALK-Abello Pharmaceuticals, Mississauga, ON, Canada) applied with Duotip II devices (Lincoln Diagnostics, Decatur, Ill). Sensitization was defined as mean wheal diameter at least 2 mm larger than the saline control (Methods section, available in this article's Online Repository at www.jaci-inpractice.org).¹⁰ At age 1 year, a clinical diagnosis of atopic dermatitis was also made by a CHILD Study health care professional and was based on the parental history of chronic, recurring, itchy rashes in a typical distribution over the past year and physical examination at age 1 year. Mild atopic dermatitis was defined as being present at no more than 2 sites, minor itching, rubbing, crusting or papules, without excoriations or oozing, and not needing frequent medical attention. Severe atopic dermatitis was defined as being at multiple sites, with extensive crusting, papules,

excoriations, oozing or lichenification, sleep loss, needing frequent medical attention, and a major concern to parents. Moderate atopic dermatitis was defined as being neither mild nor severe. Between ages 30 and 42 months, 2669 children had sensitization to peanut, egg, and cow's milk measured by SPT at their 3-year-old study visit.

Sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy

This study's 3 primary outcomes were sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy:

- (1) Sensitization: all children sensitized to peanut, egg, and cow's milk at age 3 years.
- (2) Possible IgE-mediated allergy: all children sensitized to peanut, egg, and cow's milk at age 3 years and not consuming the food to which they were sensitized at least once per month at age 3 years.
- (3) Probable clinical IgE-mediated allergy: all children sensitized to peanut, egg, and cow's milk at age 3 years and not consuming the food to which they were sensitized at least once per month at age 3 years and having any convincing history of signs or symptoms of an allergic reaction to the food to which they were sensitized and that they were not consuming.

These definitions were sequential rather than mutually exclusive. Children with a possible IgE-mediated allergy were also included in the sensitization group and children with a probable clinical IgE-mediated allergy were also included in both the possible allergy and sensitization groups. Each outcome was evaluated separately for peanut, egg, and cow's milk. Children who were sensitized but clinically tolerant were evaluated separately in a sensitivity analysis.

Covariables

In the prenatal questionnaires, mothers and most fathers reported their history of asthma, nasal allergy and food allergy symptoms, race/ethnicity, socioeconomic status, and education. They also reported the number of older siblings and food allergies in older siblings of the CHILd participants.

Statistical analysis

Multivariable logistic regression was used to examine if first introduction to peanut, egg, and cow's milk after ages 6, 9, and 12 months was associated with sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy for each specific food. For cow's milk, non-formula and formula cow's milk products were also considered separately.

The associations with peanut introduction were evaluated further by separately excluding 2 high-risk groups of infants: (1) those with moderate-to-severe atopic dermatitis, which is associated with food allergy,⁹⁻¹⁴ in the first year of life and (2) those with moderate-to-severe atopic dermatitis in the first year of life and/or egg white sensitization above 6 mm at age 1 year or above 3 mm with a history suggestive of an allergic reaction to egg in the first year of life, comparable with the high-risk infants studied in the LEAP trial.^{5,8} Too few children in the CHILd cohort had moderate-to-severe atopic dermatitis in the first year of life to permit an analysis of this subgroup. Population attributable fraction (PAF) of sensitization, possible allergy, and probable clinical IgE-mediated allergy to peanut associated with dietary peanut introduction delayed beyond 12 months was reported among children with no or mild atopic dermatitis in the first year of life (Methods section, available in this article's Online Repository at www.jaci-inpractice.org). The associations for peanut were further evaluated

for introduction at ages >9 to 12, >12 to 18, and >18 months compared with introduction ≤9 months.

The following covariables were assessed as possible confounders with contribution to sensitization or food allergy and association with delay in introduction: sex, moderate-to-severe atopic dermatitis, history of allergic reactions to foods in the first 6 to 12 months of life, number of older siblings, sibling food allergy, maternal and paternal atopic conditions, maternal education, socioeconomic status, maternal and paternal race, formula introduction, and study center. Covariables were initially removed by backward elimination if their maximum likelihood *P* value was greater than .1. Individual covariables were added back into the final model one at a time to see if their addition changed the ORs for the primary outcomes. Covariables were retained in any particular analysis when their inclusion led to a substantive (10% or greater) change in the ORs.

To account for the possible influence of knowing the 1-year-old SPT results on timing of peanut introduction for infants who were introduced to peanut after age 12 months, infants who were introduced to peanut after age 12 months were evaluated in a subanalysis. Children introduced to peanut after age 12 months but by 18 months were compared with children who had not yet introduced to peanut by age 18 months, stratified by peanut SPT result at age 1 year (wheal sizes of 0, >0 to 4, and >4 mm to parallel the LEAP Study gradations),⁵ and in sensitivity analysis, wheal sizes of 0 to <2, 2 to 8, and >8 mm to evaluate SPT below the 2 mm cut point for sensitization and sensitization below and above the 8 mm cut point for the 95% predictive level for peanut allergy.^{20,21} Once the level of peanut sensitization was known, most other covariables were unlikely to influence the timing of peanut introduction. Covariables such as older sibling food allergy were evaluated for possible confounding, and unadjusted ORs were reported for this subanalysis.

To examine the effects of possibly knowing 1-year-old SPT results among infants who were introduced to peanut just before age 12 months, infants introduced to peanut in the interval just before age 12 months and whose 1-year-old SPT was performed before their 1-year-old caregiver reports of peanut introduction were submitted were excluded in a sensitivity analysis. Sensitivity analyses were also conducted using sensitization cut points of 1 and 3 mm wheals. No attempt was made to adjust for multiple inference, but we report 95% CIs and describe results with *P* values less than .05 as statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Timing of highly allergenic food introduction (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org)

First introduction to peanut was rare before age 6 months (1.9%) and more common by age 12 months (45.1%) and 18 months (76.8%). Most children had been first introduced to egg by age 18 months (99%) and to non-formula cow's milk by age 12 months (99.9%). Of the 37% of children who were introduced to cow's milk formula, the vast majority were introduced by age 6 months.

Earlier timing of peanut introduction did not imply current consumption. Of the 1059 children who had been introduced to peanut by age 12 months, 10% were not eating peanut at least once per month at age 3 years, and of the 1817 children who had been introduced to peanut by age 18 months, 13% were not eating peanut at least once

TABLE I. Adjusted* associations (OR and 95% CI) between sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy to peanut, egg, and cow's milk at age 3 years and age of introduction of the specific food after age 12 months in the CHILD Cohort

Age of introduction (mo)	Sensitization	Possible IgE-mediated allergy	Probable clinical IgE-mediated allergy
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Peanut (>12 vs by 12)	2.38 (1.39, 4.07) [†] (N = 2437)	2.69 (1.42, 5.07) [‡] (N = 2426)	4.04 (1.66, 9.85) [‡] (N = 2384)
Egg (>12 vs by 12)	0.96 (0.49, 1.88) [‡] (N = 2511)	0.83 (0.092, 7.51) [§] (N = 2584)	1.16 (0.12, 11.2) [§] (N = 2485)
Cow's milk (non-formula + formula) (>12 vs by 12)	4.34 (1.73, 10.9) [†] (N = 2562)		

CHILD, Canadian Healthy Infant Longitudinal Development Study; CI, confidence interval; OR, odds ratio.

*Sex, moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, age of formula introduction, maternal and paternal histories of atopic conditions including asthma, rhinitis, and food allergy, reported sibling food allergies, number of older siblings, socioeconomic status, maternal education, maternal race, paternal race, and study site were evaluated for possible confounding. Covariables whose inclusion changed the adjusted odds ratio by >10% were retained in the models.

[†]Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, number of older siblings, and maternal race.

[‡]Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, and maternal race.

[§]Logistic regression adjusted for maternal race.

||The model would not run because too few children were present in one category.

TABLE II. Adjusted* associations (OR and 95% CI) between age of peanut introduction after age 12 months and peanut sensitization, possible IgE-mediated peanut allergy, and probable clinical IgE-mediated peanut allergy at age 3 years: comparison of the whole CHILD Cohort and subsets excluding high-risk children

Introduction after age 12 mo vs by age 12 mo	Sensitization	Possible IgE-mediated allergy	Probable clinical IgE-mediated allergy
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
All children	2.38 (1.39, 4.07) [†] (N = 2437)	2.69 (1.42, 5.07) [‡] (N = 2426)	4.04 (1.66, 9.85) [‡] (N = 2384)
Children without moderate-to-severe atopic dermatitis in the first year of life	2.69 (1.51, 4.78) [§] (N = 2378)	3.21 (1.58, 6.52) (N = 2367)	5.94 (2.05, 17.2) (N = 2330)
Children without moderate-to-severe atopic dermatitis in the first year of life or egg sensitization or reactions by age 1 y	2.58 (1.43, 4.67) [§] (N = 2355)	2.91 (1.43, 5.93) (N = 2344)	5.31 (1.83, 15.4) (N = 2309)

CHILD, Canadian Healthy Infant Longitudinal Development Study; CI, confidence interval; OR, odds ratio.

*Sex, moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, age of formula introduction, maternal and paternal histories of atopic conditions including asthma, rhinitis and food allergy, reported sibling food allergies, number of older siblings, socioeconomic status, maternal education, maternal race, paternal race, and study site were evaluated for possible confounding. Covariables whose inclusion changed the adjusted odds ratio by >10% were retained in the models.

[†]Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, number of older siblings, and maternal race.

[‡]Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, and maternal race.

[§]Logistic regression adjusted for history of allergic reactions to foods in the first 6-12 months of life, number of older siblings, and maternal race.

||Logistic regression adjusted for history of allergic reactions to foods in the first 6-12 months of life and maternal race.

per month at age 3 years. The reasons for eating or not eating peanut were not reported, but many of these children had no history of reported reactions or sensitization to peanut. In contrast, few children who had been introduced to egg or cow's milk by age 12 months were not consuming egg (1.3%) and cow's milk (0.16%), respectively, at least once per month at age 3 years.

Sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy at age 3 years

Of the 3455 CHILD participants (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org), 2669 children had available skin prick sensitization data to peanut, egg,

and cow's milk at age 3 years and 2434 had available information about consumption of and history of reactions to these highly allergenic foods. The frequencies of food sensitization (≥ 2 mm) at age 3 years were peanut (101, 3.80%), egg white (59, 2.21%), and cow's milk (30, 1.12%). The frequencies of possible IgE-mediated allergy because of sensitization plus no current consumption of the food to which the child was sensitized were peanut (71, 2.69%), egg (5, 0.19%), and cow's milk (2, 0.08%). The frequencies of probable clinical IgE-mediated allergy because of sensitization plus no current consumption plus history of any allergic reaction to the food to which the child was sensitized were peanut (46, 1.78%), egg (4, 0.16%), and cow's milk (2, 0.08%). Thus, the distinction between possible and probable

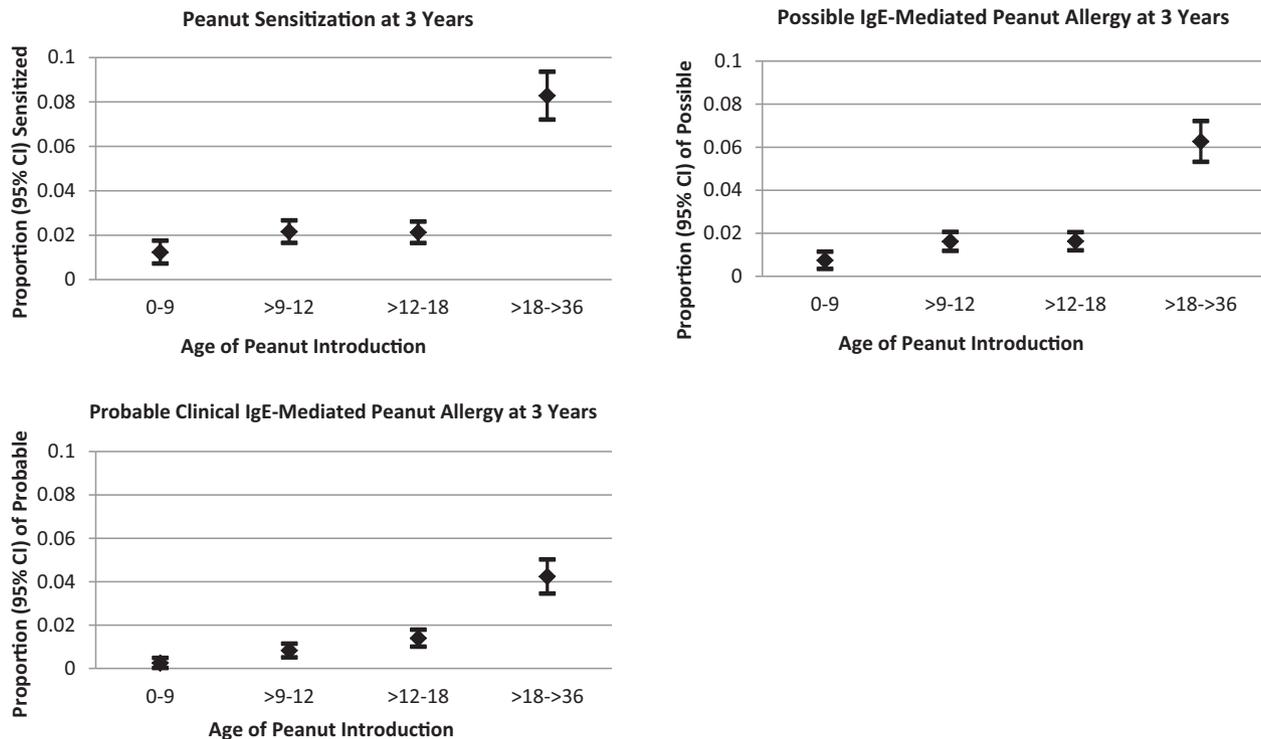


FIGURE 1. Proportion of Canadian Healthy Infant Longitudinal Development (CHILD) Study children sensitized to peanut and with possible IgE-mediated peanut allergy and probable clinical IgE-mediated peanut allergy at age 3 years versus age of peanut introduction. *CI*, Confidence interval.

clinical IgE-mediated allergy was most important for peanut, which had not yet been introduced into the diet of 25 of the 101 children with positive SPT to peanut at age 3 years.

Associations with age of peanut introduction

First dietary introduction of peanut after age 12 months was associated with over 2-fold increased odds of peanut sensitization and possible IgE-mediated allergy to peanut at age 3 years (Table I) and with 4-fold increased odds of probable clinical IgE-mediated peanut allergy (OR: 4.04, 95% CI: 1.66, 9.85). Associations were similar for dietary introduction after age 9 months (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). The associations between peanut introduction after age 12 months and sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy to peanut were slightly stronger when children with moderate-to-severe atopic dermatitis in the first year of life with or without egg sensitization and reactions were excluded (Table II). The 95% CIs overlapped for analyses using data from the whole cohort and subgroups excluding higher-risk children (Table II). Among the 97.3% of children with no or mild atopic dermatitis in the first year of life, the PAF of sensitization, possible allergy, and probable clinical IgE-mediated allergy to peanut associated with dietary peanut introduction delayed beyond 12 months were 48%, 53%, and 70%, respectively. Among the subset of children who regularly tolerated peanut at age 3 years, first introduction to peanut after age 12 months was not significantly associated with sensitization (OR: 1.88, 95% CI: 0.73, 4.87).

The proportion of children sensitized and with possible or probable clinical IgE-mediated allergy to peanut was substantially

higher for those who had not introduced peanut by age 18 months (Figure 1). Probable clinical allergy was present for 0.25%, 0.82%, 1.4%, and 4.3% introduced <9, >9 to 12, >12 to 18, and >18 months, respectively. Notably, none of the 52 infants introduced to peanut before 6 months was sensitized at age 3 years. Introduction to peanut from ages >9 to 12 and >12 to 18 months did not show statistically significant increased odds of sensitization, possible IgE-mediated allergy, or probable clinical IgE-mediated allergy to peanut at age 3 years compared with introduction ≤ 9 months, although the ORs approached 2 (Table III). Introduction to peanut after age 18 months showed at least 7-fold increased odds of sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy to peanut compared with peanut introduction ≤ 9 months (Table III).

Peanut SPT wheal sizes at age 1 year were similar for children introduced by age 12 months and from >12 to 18 months, but more children introduced after 18 months had a positive SPT to peanut at age 1 year (Table IV and Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Comparing only children who were introduced to peanut after age 1 year when their families knew their 1-year SPT results, introduction after age 18 months compared with introduction from >12 to 18 months was associated with significantly increased odds of sensitization at 3 years for children who were not sensitized at age 1 year (Table V and Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Children with wheal sizes >0 to 4 mm at age 1 year and introduction after 18 months had high but nonsignificant odds of sensitization at age 3 years compared with children introduced at >12 to 18 months (Table V). Timing of introduction did not

TABLE III. Associations* (OR and 95% CI) between age of introduction to peanut and peanut sensitization, possible IgE-mediated peanut allergy, and probable clinical IgE-mediated peanut allergy in the CHILd Cohort at age 3 years

Comparison vs ≤9 mo	Sensitization—no moderate-severe atopic dermatitis in the first year (N = 2389)		Sensitization—no moderate- severe atopic dermatitis in the first year or egg sensitization/ reaction at 1 y (N = 2365)		Possible allergy—no moderate-severe atopic dermatitis in the first year (N = 2378)		Possible allergy—no moderate- severe atopic dermatitis in the first year or egg sensitization/ reaction at 1 y (N = 2354)		Probable clinical allergy—all children (N = 2463)		Probable clinical allergy—no moderate- severe atopic dermatitis in the first year (N = 2341)	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
≤9 mo	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	
>9-12 mo	1.77 (0.64, 4.85)	1.31 (0.46, 3.74)	1.51 (0.48, 4.78)	2.20 (0.62, 7.85)	1.45 (0.38, 5.5)	2.20 (0.46, 10.4)	2.20 (0.46, 10.4)	3.32 (0.40, 27.7)	3.32 (0.40, 27.7)	14.6 (1.94, 110)		
>12-18 mo	1.74 (0.64, 4.75)	1.33 (0.47, 3.76)	1.53 (0.49, 4.79)	2.21 (0.63, 7.81)	1.70 (0.47, 6.23)	2.56 (0.56, 11.7)	2.56 (0.56, 11.7)	5.64 (0.73, 43.8)	5.64 (0.73, 43.8)	4.62 (0.58, 36.6)		
>18 mo	7.24 (2.85, 18.4)	6.48 (2.54, 16.6)	7.51 (2.65, 21.2)	8.95 (2.73, 29.3)	7.54 (2.27, 25.0)	10.1 (2.38, 42.9)	10.1 (2.38, 42.9)	17.7 (2.38, 132)	17.7 (2.38, 132)	17.7 (2.38, 132)		

CHILd, Canadian Healthy Infant Longitudinal Development Study; CI, confidence interval; OR, odds ratio.

*Sex, moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, age of formula introduction, maternal and paternal histories of atopic conditions including asthma, rhinitis and food allergy, reported sibling food allergies, number of older siblings, socioeconomic status, maternal education, maternal race, and study site were evaluated for possible confounding. Covariables whose inclusion changed the adjusted odds ratio by >10% were retained in the models. Unadjusted models are reported. Models evaluating children with probable clinical IgE-mediated peanut allergy who had no moderate-severe atopic dermatitis in the first year or egg sensitization/reactions at 1 year would not run because too few children were present in some categories.

seem important for children with the strongest sensitization (>4 mm) at age 1 year. Children with peanut wheal sizes of 2 to 8 mm, corresponding to sensitization below the 95% predictive level,^{22,23} at age 1 year also had higher odds of sensitization at age 3 years (Table E3, available in this article's Online Repository at www.jaci-inpractice.org), although the statistical significance was variable.

Associations with age of introduction to egg and cow's milk

First introduction of egg beyond ages 6, 9 (Table E1, available in this article's Online Repository at www.jaci-inpractice.org), or 12 (Table I) months was not associated with increased sensitization or possible or probable clinical IgE-mediated allergy to egg at age 3 years. First introduction to cow's milk (including cow's milk formula and non-formula cow's milk and milk products) after age 12 months was associated with an over 4-fold increased odds of sensitization to cow's milk at age 3 years (Table I). The association was stronger when first introduction of only non-formula cow's milk was considered (OR: 4.79, 95% CI: 1.82, 12.6) and weaker when first introduction to only cow's milk formula was considered (OR: 2.57, 95% CI: 0.92, 7.17), although all 95% CIs overlapped.

Covariables and sensitivity analyses

Extensive evaluation of the covariables did not suggest confounding of the associations between ages of introduction and sensitization, possible IgE-mediated allergy, or probable clinical IgE-mediated allergy, and adjustment did not alter the ORs significantly. The results of sensitivity analyses were similar after exclusion of the 5% of infants who were introduced to peanut in the interval immediately before age 12 months and whose 1-year-old SPT was performed before their 1-year-old caregiver report of food introduction was submitted (Table E4, available in this article's Online Repository at www.jaci-inpractice.org). Sensitivity analyses using sensitization cut points of 1- and 3-mm wheals likewise did not change the associations (Tables E5-E9, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This study in a general-population pregnancy cohort has demonstrated associations between introduction to peanut after age 12 months and sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy to peanut at age 3 years. Protective associations with introduction before age 9 months could not be clearly distinguished from the protective associations of introduction before age 12 months. None of the infants introduced to peanut before age 6 months were sensitized to peanut at 3 age years. Importantly, the associations persisted after exclusion of children at high risk of peanut allergy because of (1) moderate-to-severe atopic dermatitis in the first year of life and (2) moderate-to-severe atopic dermatitis in the first year of life and/or egg sensitization and reactions by age 1 year.

Of particular concern, children who were not introduced to peanut by age 18 months had an over 7-fold increased odds of sensitization and possible or probable clinical IgE-mediated allergy. Infants with the greatest delay until after 18 months likely made a large contribution to the increased odds of peanut sensitization and possible or probable IgE-mediated allergy with peanut introduction after age 12 months. Introduction from >9

TABLE IV. Age of introduction to peanut in the CHILD Cohort compared with peanut sensitization at age 1 year; the 1-year skin prick test cut points reflect the LEAP Study categories⁵

Peanut SPT at 1 y (mm)	Peanut introduced ≤12 mo (N = 1248)	Peanut introduced >12-18 mo (N = 872)	Peanut introduced >18 mo (N = 599)
0 (N = 2588)	1203 (96.4%)	843 (96.7%)	542 (90.5%)
>0-4 (N = 77)	34 (2.72%)	19 (2.18%)	24 (4.00%)
>4 (N = 54)	11 (0.88%)	10 (0.12%)	33 (5.50%)

CHILD, Canadian Healthy Infant Longitudinal Development Study; LEAP, Learning Early about Peanut; SPT, skin prick testing.

TABLE V. Comparison of CHILD Cohort children who had not been introduced to peanut by age 18 months with children introduced to peanut after 12 but by 18 months; all of these children would have had the presence or absence of peanut sensitization known at the time of peanut introduction; excluding children who were introduced to peanut before age 12 months: association between age of introduction to peanut and sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy to peanut at age 3 years with 1-year skin prick test cut points reflecting the LEAP study categories⁵

1-y peanut SPT (mm)	Sensitization—all children	Sensitization—no moderate-severe atopic dermatitis in the first year	Sensitization—no moderate-severe atopic dermatitis in the first year or egg sensitization/reaction at 1 y	Possible allergy—all children	Possible allergy—no moderate-severe atopic dermatitis in the first year	Possible allergy—no moderate-severe atopic dermatitis in the first year or egg sensitization/reaction at 1 y
Comparison >18 vs >12-18 mo	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
0	3.20 (1.28, 7.99) (N = 1246)	4.25 (1.51, 12.0) (N = 1201)	4.92 (1.58, 15.3) (N = 1193)	1.91 (0.58, 6.31) (N = 1241)	2.71 (0.65, 11.4) (N = 1196)	2.17 (0.48, 9.76) (N = 1188)
>0-4	5.38 (0.99, 29.3) (N = 39)	4.87 (0.87, 27.3) (N = 36)	4.33 (0.76, 24.6) (N = 35)	9.23 (1.01, 83.9) (N = 37)	8.17 (0.88, 76.2) (N = 34)	7.00 (0.74, 66.6) (N = 33)
>4	0.63 (0.062, 6.33) (N = 39)	0.57 (0.055, 5.88) (N = 29)	0.53 (0.051, 5.55) (N = 28)	0.57 (0.057, 5.78) (N = 33)	0.50 (0.048, 5.23) (N = 27)	0.47 (0.044, 4.90) (N = 26)

1-y peanut SPT (mm)	Probable allergy—all children	Probable allergy—no moderate-severe atopic dermatitis in the first year	Probable allergy—no moderate-severe atopic dermatitis in the first year or egg sensitization/reaction at 1 y
Comparison >18 vs >12-18 mo	OR (95% CI)	OR (95% CI)	OR (95% CI)
0	*	*	*
>0-4	7.64 (0.80, 73.1) (N = 32)	6.50 (0.65, 64.8) (N = 29)	5.20 (0.50, 54.1) (N = 28)
>4	0.53 (0.051, 5.55) (N = 28)	0.48 (0.044, 5.22) (N = 23)	0.44 (0.040, 4.82) (N = 22)

CHILD, Canadian Healthy Infant Longitudinal Development Study; CI, confidence interval; LEAP, Learning Early about Peanut; OR, odds ratio; SPT, skin prick testing.

*The models would not run because there were too few children in some categories.

to 12 and >12 to 18 months was associated with nonsignificant 1- to 2-fold increased odds of sensitization and possible or probable IgE-mediated allergy compared with introduction at or before 9 months. These analyses may have been underpowered to detect the smaller associations when timing of introduction was stratified into 4 age groups.

Once SPT to peanut was performed, the wheal size may have strongly influenced families' choices about introducing peanut for infants who had not already been introduced to peanut. The relatively large number of infants introduced to peanut after age 12 months in the CHILD cohort allowed evaluation of these infants stratified by their 1-year SPT results. Among infants introduced after age 12 months, introduction >18 months was associated with higher odds of sensitization

compared with infants introduced from >12 to 18 months, for infants who were not sensitized at age 1 year. The ORs for possible and probable clinical IgE-mediated allergy and for infants sensitized with wheals up to 4 or 8 mm were well above 1, but not statistically significant. The study may have been underpowered to evaluate these subgroups of children, given that the overall prevalence of peanut sensitization was only 3.8% at 3 years. The infants most strongly sensitized to peanut at 1 year may also have been so likely to remain sensitized and have probable clinical IgE-mediated peanut allergy at 3 years that the timing of introduction was less important for this group. These findings are consistent with the extremely high proportions of other allergic conditions demonstrated in highly sensitized children within the CHILD cohort.¹⁰

Introduction to peanut after age 12 months was associated with greater odds of peanut sensitization (OR: 2.38, 95% CI: 1.39-4.07) and possible and probable clinical IgE-mediated allergy at age 3 years compared with the increased odds of peanut sensitization in the CHILD cohort at age 1 year (OR: 1.76, 95% CI: 1.07-3.01) previously shown by Tran et al,¹ although the CIs overlapped. Overall, these results suggest greater importance of early peanut introduction for decreasing sensitization and possible or probable allergy to peanut by age 3 years compared with age 1 year.

Infants introduced to egg after ages 6, 9, or 12 months did not have increased odds of sensitization, possible IgE-mediated allergy, or probable clinical IgE-mediated allergy at age 3 years. In earlier CHILD Study analyses,¹ infants introduced to egg after age 12 months had increased odds of egg sensitization (OR: 1.89, 95% CI: 1.25-2.80) at age 1 year. Other studies have also shown variable benefit of early egg introduction for egg allergy prevention,^{4,24} although a meta-analysis has suggested an overall benefit of egg introduction within the first year of life.²⁵ Infants introduced to cow's milk after 12 months had increased odds of sensitization (OR: 4.34, 95% CI: 1.73-10.9) at age 3 years, comparable with the increased odds of sensitization previously shown at age 1 year (OR: 3.69, 95% CI: 1.37-9.08).¹ Too few infants had possible or probable clinical IgE-mediated cow's milk allergy to evaluate the associations statistically. Non-IgE-mediated allergies and intolerances to cow's milk may have been more common but were not included in this study, which focused on IgE-mediated sensitization and allergy.

This study is consistent with the hypothesis that early introduction of peanut is associated with decreased sensitization and probable clinical IgE-mediated allergy to peanut, one of the most prevalent and persistent food allergies in the United States²⁶⁻²⁸ and other countries.²⁹⁻³¹ At least 80% of children do not outgrow peanut allergy,³² compared with milk³³ and egg^{22,34} allergies, half of which are outgrown by ages 5 or 6 years. In a 2008-2009 telephone survey of Canadians,²³ 1.68% (95% CI: 1.14-2.23) of children had reported allergy to peanut with a convincing history of an IgE-mediated reaction, comparable with the proportion of children with probable clinical IgE-mediated peanut allergy identified in this study. The present study adds to the literature by demonstrating decreased odds of sensitization and possible or probable clinical IgE-mediated allergy to peanut with peanut introduction before age 12 months in infants at lower risk of peanut allergy. This study also documents a much higher odds of peanut allergy among infants who are not introduced to peanut by age 18 months compared with those introduced between 12 and 18 months, suggesting that early introduction should continue to be encouraged for infants over age 12 months.

Avoidance or later introduction of peanut^{18,19} has been associated with increased development of peanut allergy in some populations. Compared with primary school children living in Israel, where infants were introduced to peanut in the first year of life, Jewish primary school children in the United Kingdom, where infants were less likely to consume peanut, were 9.8 (95% CI: 3.1-30.5) times more likely to develop peanut allergy, strongly suggesting that earlier ingestion of peanut was protective against peanut allergy.¹⁹ These increased odds of peanut allergy development are comparable with the odds of sensitization and possible or probable clinical IgE-mediated allergy to peanut among the infants who had not been introduced to peanut by 18 months in the present study.

Perkin et al³ reported a randomized controlled trial in general-population breastfed infants evaluating the efficacy of preventing food allergy, diagnosed by double-blind, placebo-controlled oral food challenges, by age 3 years with early introduction to highly allergenic foods by age 3 months versus standard introduction after age 6 months. The relative risks of allergies were lower in the early-introduction group versus the standard-introduction group for peanut (51% lower, $P = .11$) and egg (31% lower, $P = .17$), although the differences were not significant in intention-to-treat analyses. Like the present study, this trial showed no detriment from early dietary introduction to peanut, egg, or cow's milk.

Atopic dermatitis is associated with food sensitization and allergy,⁸⁻¹⁰ especially for peanut,^{9,12} and may contribute to food allergy development.^{13,14} Sensitization to foods has also been associated with early onset (OR: 2.52, 95% CI: 1.11-5.74) and persistent (OR: 5.92, 95% CI: 2.23-15.7) atopic dermatitis, and sensitization to peanut has been most strongly associated with persistent atopic dermatitis (OR: 16.0, 95% CI: 5.00-51.3).¹² The associations between later peanut introduction and sensitization and possible or probable clinical IgE-mediated allergy to peanut found in this study persisted without significant attenuation after exclusion of higher-risk infants with moderate-to-severe atopic dermatitis in the first year of life, demonstrating that the associations were independent of the presence of infant atopic dermatitis and relevant to lower-risk infants at age 3 years. Moreover, this study showed a PAF of over 40% for peanut sensitization and 70% for probable clinical IgE-mediated peanut allergy among children with mild or no atopic dermatitis in the first year of life, which represented 97% of the study population. The high proportion of peanut allergy "attributable to" or associated with a delay in peanut introduction until after age 12 months in this population of children demonstrated that early dietary introduction of peanut may make a substantial contribution to reducing peanut allergy at the population level.

The LEAP randomized controlled trial of high-risk infants with severe eczema, egg allergy, or both showed less peanut allergy development by age 5 years among children who were eating peanut compared with those who were not, for both peanut nonsensitized (1.9% vs 13.7%, $P < .001$) and peanut sensitized (10.6% vs 35.3%, $P = .004$) children;⁵ the protective effect of early consumption persisted after 12 months of peanut avoidance.⁶ Early consumption of peanut did not protect against other allergic conditions.¹⁵ The LEAP Study focused on infants at the highest risk of peanut allergy. Design and recruitment for the present study occurred before publication of the LEAP Study,⁵ and less than half of the infants in this observational study were introduced to peanut before age 1 year, reflecting previous recommendations regarding delaying peanut introduction in early childhood. Examination of associations between timing of dietary peanut introduction and peanut sensitization and allergy in low-risk children who would not have been included in the LEAP study is an important contribution of the present study, particularly as there may be fewer children first introduced to peanut after age 12 months in future population cohorts.

Strengths of this study included the detailed, prospectively collected data regarding introduction, current consumption, sensitization, and reported allergic reactions to the highly allergenic foods, conditions such as atopic dermatitis, and relevant covariables in this cohort of children recruited before birth from the general population. The study was limited by dependence on

parental report of age of introduction and current consumption of highly allergenic foods and allergic reactions and by the absence of food challenges to confirm allergy, particularly to peanut, at age 3 years among children with possible or probable clinical IgE-mediated peanut allergy.

This study demonstrates that introducing peanut before age 12 months is associated with lower odds of sensitization and possible or probable clinical IgE-mediated peanut allergy in the general population of children by age 3 years. Importantly, the lower odds persisted after exclusion of children at high risk of peanut allergy because of moderate-to-severe atopic dermatitis with or without egg sensitization and reactions, confirming a protective association with early peanut introduction in low-risk infants. This study also showed a much higher risk of peanut allergy among infants without peanut in their diets by age 18 months, demonstrating that early introduction should continue to be encouraged after age 12 months.

This study showed no increased risk of sensitization or possible or probable clinical IgE-mediated allergy at age 3 years with earlier introduction of peanut, egg, or cow's milk for any infants. Although delaying the introduction of highly allergenic foods into children's diets is no longer recommended,³⁵ many parents continue to worry about introducing these foods. Our results support the current recommendations for early introduction of peanut, egg, and cow's milk in the first 12 months. In particular, encouragement of early introduction of peanut in the general population, including low-risk infants, may contribute to decreased odds of sensitization and possible or probable clinical IgE-mediated allergy to peanut.

Acknowledgments

The authors thank the CHILD Study participants and their families and the CHILD team members at each site; the dedication of these participants and team members made this study possible. The Allergy, Genes and Environment (AllerGen) Network of Centres of Excellence (NCE) and the Canadian Institutes of Health Research (CIHR) provided core funding for CHILD. This study was also funded by the Manitoba Medical Service Foundation, Children's Hospital Foundation, and University of Manitoba. ALK-Abello (Mississauga, ON, Canada) supplied all allergens for the study and Lincoln Diagnostics Inc. (Decatur, Ill) supplied the Duotip-Test II devices and skin testing kits.

ES collected clinical data at the Winnipeg site during this 3-year study period, designed and conducted the data analysis, and wrote and revised the manuscript. RB contributed to the statistical design and analysis and reviewed the manuscript. DLL and DD managed the CHILD Study data during this 3-year study period. SET was the Vancouver site lead during this 3-year study period, collected clinical data at the Vancouver site, and is the current Vancouver site lead. TJM collected clinical data at the Toronto site during this 3-year study period, reviewed the manuscript, and is the current Toronto site lead. PJM was the Edmonton site lead during this 3-year study period, collected clinical data at the Edmonton site, and is the current Edmonton site lead. MBA contributed to the development of the CHILD Study, reviewed the manuscript, and is a current Manitoba site lead. MRS was the overall CHILD Study Director during this 3-year study period and reviewed the manuscript. PS was the Toronto site lead during this 3-year study period, collected

clinical data at the Toronto site, reviewed the manuscript, and is the current CHILD Study Director. ABB was the Manitoba site lead during this 3-year study period, collected clinical data at the Manitoba site, reviewed the manuscript, and is a current Manitoba site lead. All authors contributed substantially to this study.

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ONLINE REPOSITORY**METHODS****Skin prick test measurements**

The mean wheal diameter for each allergen and the positive histamine and negative saline controls were determined by the mean of the maximum wheal length and the perpendicular diameter at the mid-point of the maximum length. The mean wheal diameter of the negative saline control was subtracted from the mean wheal diameter for each allergen. Sensitization was defined as a mean wheal diameter ≥ 2 mm larger than the saline control, regardless of the size of the positive histamine control wheal. Skin prick tests were considered valid if the histamine control wheal was ≥ 2 mm or if any allergen wheals were ≥ 2 mm. Skin prick testing was performed on the back at the Vancouver site and gave consistently larger histamine wheals; therefore, an adjustment factor of 0.82 was included for skin prick tests performed on the back, as previously reported.^{E1}

Population attributable fraction (PAF)

$PAF = (RR - 1)/RR * \text{proportion exposed among those with outcome} * 100\%$, where RR stands for relative risk estimated by the odds ratio (from Table II).

Stratified into children with and without moderate-severe atopic dermatitis in the first year of life

In stratified analysis—among children with no or mild atopic dermatitis in the first year of life:

Sensitization

$$\begin{aligned} PAF &= (RR - 1)/RR * \text{proportion introduced} > 12 \text{ mo among} \\ &\quad \text{infants sensitized to peanut} \\ &= (2.69 - 1)/2.69 * 0.7571 * 100\% \\ &= 48\% \end{aligned}$$

Possible allergy

$$\begin{aligned} PAF &= (RR - 1)/RR * \text{proportion introduced} > 12 \text{ mo among} \\ &\quad \text{infants with possible allergy to peanut} \\ &= (3.21 - 1)/3.21 * 0.7755 * 100\% \\ &= 53\% \end{aligned}$$

Probable clinical allergy

$$\begin{aligned} PAF &= (RR - 1)/RR * \text{proportion introduced} > 12 \text{ mo among} \\ &\quad \text{infants with probable allergy to peanut} \\ &= (5.94 - 1)/5.94 * 0.8438 * 100\% \\ &= 70\% \end{aligned}$$

In stratified analysis—among children with moderate-to-severe atopic dermatitis in the first year of life: the 95% CIs of these odds ratios include 1 and they were not used to calculate PAF.

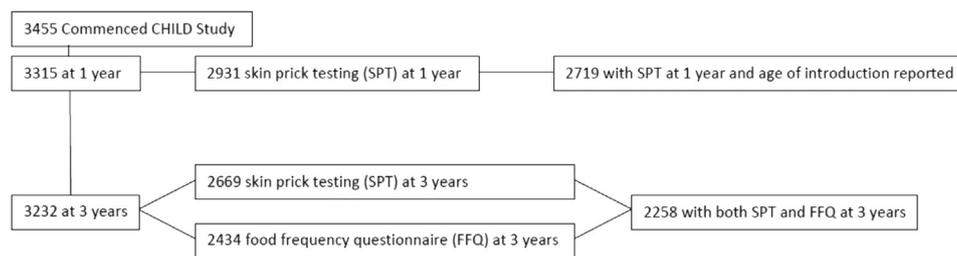


FIGURE E1. Canadian Healthy Infant Longitudinal Development (CHILD) Study Consort diagram of participation.

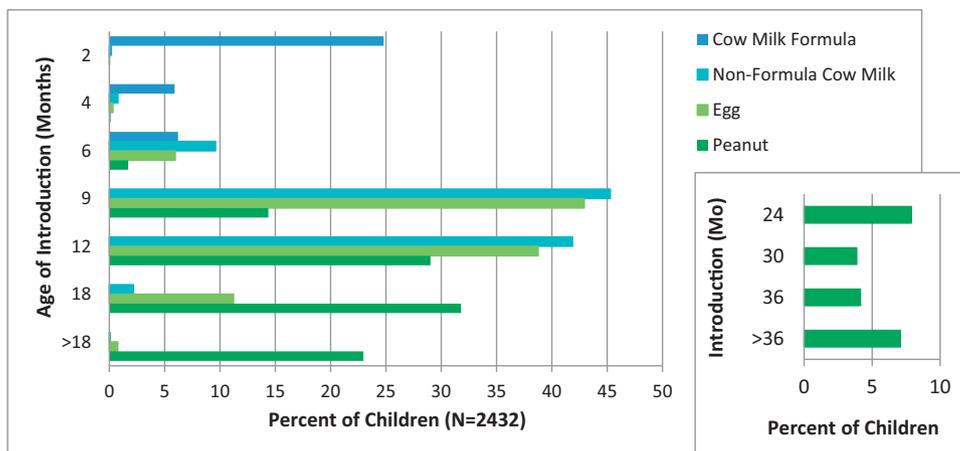


FIGURE E2. Canadian Healthy Infant Longitudinal Development (CHILD) Study Ages of introduction of cow’s milk formula, non-formula cow milk and milk products, egg, and peanut.

TABLE E1. Adjusted* associations (OR and 95% CI) between sensitization, possible IgE-mediated allergy and probable clinical IgE-mediated allergy to peanut, egg and cow’s milk at age 3 years and age of introduction of the specific food after age 12 months in the CHILD Cohort (expansion of Table I)

Age of introduction (mo)	Sensitization	Possible IgE-mediated allergy	Probable clinical IgE-mediated allergy
	Adjusted OR (95% CI) (N = 2437)	Adjusted OR (95% CI) (N = 2426)	Adjusted OR (95% CI) (N = 2384)
Peanut (>12 vs by 12)	2.38 (1.39, 4.07)†	2.69 (1.42, 5.07)‡	4.04 (1.66, 9.85)‡
Peanut (>9 vs by 9)	3.14 (1.13, 8.76)†	4.90 (1.18, 20.5)‡	§
Peanut (>6 vs by 6)	§	§	§
Egg (>12 vs by 12)	0.96 (0.49, 1.88)‡	0.83 (0.092, 7.51)	1.16 (0.12, 11.2)
Egg (>9 vs by 9)	1.27 (0.72, 2.24)‡	§	§
Egg (>6 vs by 6)	0.92 (0.28, 3.04)‡	§	§
Cow’s milk (non-formula + formula) (>12 vs by 12)	4.34 (1.73, 10.9)†	§	§
Cow’s milk (non-formula + formula) (>9 vs by 9)	1.77 (0.82, 3.82)†	§	§
Cow’s milk (non-formula + formula) (>6 vs by 6)	1.34 (0.61, 2.97)†	§	§

CHILD, Canadian Healthy Infant Longitudinal Development; CI, confidence interval; OR, odds ratio.

*Sex, moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, age of formula introduction, maternal and paternal histories of atopic conditions including asthma, rhinitis and food allergy, reported sibling food allergies, number of older siblings, socioeconomic status, maternal education, maternal race, paternal race, and study site were evaluated for possible confounding. Covariables whose inclusion changed the adjusted odds ratio by >10% were retained in the models.

†Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, number of older siblings, and maternal race.

‡Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, and maternal race.

§The model would not run because too few children were present in one category.

||Logistic regression adjusted for maternal race.

TABLE E2. Age of introduction to peanut compared with peanut sensitization at age 1 year in the CHILD Cohort; the 1-year skin prick testing cut points reflect nonsensitized and sensitized above and below the 95% predictive level^{E2,E3}

Peanut SPT at 1 y (mm)	N—peanut introduced ≤12 mo	N—peanut introduced >12-18 mo	N—peanut introduced >18 mo
0 to <2 (N = 2596)	1209	843	544
2 to 8 (N = 117)	38	28	51
>8 (N = 6)	1	1	4

CHILD, Canadian Healthy Infant Longitudinal Development; SPT, skin prick testing.

TABLE E3. Comparison of CHILD Cohort children who had not been introduced to peanut by age 18 months with children introduced to peanut after 12 but by 18 months; all of these children would have had the presence or absence of peanut sensitization known at the time of peanut introduction; excluding children who were introduced to peanut before age 12 months: association between age of introduction to peanut and sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy to peanut at age 3 years with 1-year skin prick test cut points reflecting nonsensitized and sensitized above and below the 95% predictive level^{E3,E4}

1-y peanut SPT (mm)	Sensitization—all children	Sensitization—no moderate-severe atopic dermatitis in the first year	Sensitization—no moderate-severe atopic dermatitis in the first year or egg sensitization/reaction at 1 y	Possible allergy—all children	Possible allergy—no moderate-severe atopic dermatitis in the first year	Possible allergy—no moderate-severe atopic dermatitis in the first year or egg sensitization/reaction at 1 y
Comparison >18 mo vs >12-18 mo	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
0 to <2	3.20 (1.28, 7.97) (N = 1247)	4.25 (1.51, 12.0) (N = 1201)	4.92 (1.58, 15.3) (N = 1193)	1.91 (0.58, 6.29) (N = 1242)	2.71 (0.65, 11.4) (N = 1196)	2.17 (0.48, 9.76) (N = 1188)
2 to 8	2.94 (1.06, 8.14) (N = 71)	2.47 (0.85, 7.19) (N = 63)	2.37 (0.81, 6.91) (N = 62)	3.06 (1.08, 8.71) (N = 67)	2.52 (0.83, 7.62) (N = 59)	2.40 (0.79, 7.27) (N = 58)
>8	*	*	*	*	*	*

1-y peanut SPT (mm)	Probable allergy—all children	Probable allergy—no moderate-severe atopic dermatitis in the first year	Probable allergy—no moderate-severe atopic dermatitis in the first year or egg sensitization/reaction at 1 y
Comparison >18 mo vs >12-18 mo	OR (95% CI)	OR (95% CI)	OR (95% CI)
0 to <2	*	*	*
2 to 8	2.86 (0.93, 8.75) (N = 57)	2.33 (0.71, 7.70) (N = 50)	2.18 (0.65, 7.25) (N = 49)
>8	*	*	*

CHILD, Canadian Healthy Infant Longitudinal Development; CI, confidence interval; OR, odds ratio; SPT, skin prick testing.

*Models would not run because of too few children in some categories.

TABLE E4. Sensitivity analyses (primary data in Table II) after removal of children who had their 1-year skin prick testing before their 1-year questionnaires were submitted and whose parents reported peanut introduction in the interval just before 12 months; adjusted* associations (OR and 95% CI) between age of peanut introduction after age 12 months and peanut sensitization, possible IgE-mediated peanut allergy, and probable clinical IgE-mediated clinical peanut allergy at age 3 years: comparison of the whole CHILD Cohort and subsets excluding high-risk children

Introduction after age 12 mo vs by age 12 mo	Sensitization	Possible IgE-mediated allergy	Probable clinical IgE-mediated allergy
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
All children	2.40 (1.37, 4.21) [†] (N = 2338)	2.69 (1.42, 5.07) [‡] (N = 2327)	5.51 (1.92, 15.8) [‡] (N = 2285)
Children without moderate-to-severe atopic dermatitis in the first year of life	2.59 (1.43, 4.67) [§] (N = 2282)	3.24 (1.55, 6.77) (N = 2271)	7.16 (2.15, 23.9) (N = 2234)
Children without moderate-to-severe atopic dermatitis in the first year of life or egg sensitization or reactions by age 1 y	2.50 (1.36, 4.59) [§] (N = 2261)	2.94 (1.40, 6.18) (N = 2250)	6.41 (1.92, 21.4) (N = 2215)

CHILD, Canadian Healthy Infant Longitudinal Development; CI, confidence interval; OR, odds ratio.

*Sex, moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, age of formula introduction, maternal and paternal histories of atopic conditions including asthma, rhinitis and food allergy, reported sibling food allergies, number of older siblings, socioeconomic status, maternal education, maternal race, paternal race, and study site were evaluated for possible confounding. Covariables whose inclusion changed the adjusted odds ratio by >10% were retained in the models.

[†]Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, number of older siblings, and maternal race.

[‡]Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, and maternal race.

[§]Logistic regression adjusted for history of allergic reactions to foods in the first 6-12 months of life, number of older siblings, and maternal race.

^{||}Logistic regression adjusted for history of allergic reactions to foods in the first 6-12 months of life and maternal race.

TABLE E5. Sensitivity analyses (primary data in Table I and Table E1) using 1 and 3 mm alternate cut points for positive skin prick tests to evaluate adjusted* associations (OR and 95% CI) between sensitization, possible IgE-mediated food allergy, or probable clinical IgE-mediated allergy to peanut, egg and cow's milk at age 3 years and age of introduction of that food after ages 12, 9 and 6 months in the CHILD Cohort

Introduction after age 12 mo vs before age 12 mo	Sensitization	Possible IgE-mediated allergy	Probable clinical IgE-mediated allergy
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Peanut (>12 vs by 12)			
2 mm cut point	2.38 (1.39, 4.07)†	2.69 (1.42, 5.07)‡	4.04 (1.66, 9.85)‡
1 mm cut point	2.32 (1.39, 3.87)†	2.82 (1.50, 5.31)‡	4.10 (1.68, 9.99)‡
3 mm cut point	2.40 (1.34, 4.31)†	2.86 (1.44, 5.67)‡	3.75 (1.53, 9.18)‡
Peanut (>9 vs by 9)			
2 mm cut point	3.14 (1.13, 8.76)†	4.90 (1.18, 20.5)‡	§
1 mm cut point	3.45 (1.24, 9.59)†	5.10 (1.22, 21.3)‡	§
3 mm cut point	2.62 (0.93, 7.35)†	4.31 (1.03, 18.1)‡	§
Peanut (>6 vs by 6)			
	§	§	§
Egg (>12 vs by 12)			
2 mm cut point	0.96 (0.49, 1.88)‡	0.83 (0.092, 7.51)	1.16 (0.12, 11.2)
1 mm cut point	1.05 (0.56, 1.98)‡	2.10 (0.50, 8.87)	1.76 (0.32, 9.69)
3 mm cut point	0.92 (0.40, 2.12)‡	1.16 (0.12, 11.2)	1.17 (0.12, 11.3)
Egg (>9 vs by 9)			
2 mm cut point	1.27 (0.72, 2.24)‡	§	§
1 mm cut point	1.12 (0.66, 1.92)‡	5.29 (0.65, 43.1)	3.73 (0.44, 32.0)
3 mm cut point	1.39 (0.69, 2.81)‡	§	§
Egg (>6 vs by 6)			
2 mm cut point	0.92 (0.28, 3.04)‡	§	§
1 mm cut point	1.02 (0.31, 3.36)‡	§	§
3 mm cut point	1.74 (0.23, 13.0)‡	§	§
Cow's milk (>12 vs by 12)			
2 mm cut point	4.34 (1.73, 10.9)†	§	§
1 mm cut point	3.48 (1.44, 8.44)†	§	§
3 mm cut point	9.43 (3.07, 28.9)†	§	§
Cow's milk (>9 vs by 9)			
2 mm cut point	1.77 (0.82, 3.82)†	§	§
1 mm cut point	1.50 (0.74, 3.06)†		
3 mm cut point	2.28 (0.80, 6.52)†		
Cow's milk (>6 vs by 6)			
2 mm cut point	1.34 (0.61, 2.97)†	§	§
1 mm cut point	1.00 (0.49, 2.02)†		
3 mm cut point	1.49 (0.50, 4.50)†		

CHILD, Canadian Healthy Infant Longitudinal Development; CI, confidence interval; OR, odds ratio.

*Sex, moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, age of formula introduction, maternal and paternal histories of atopic conditions including asthma, rhinitis and food allergy, reported sibling food allergies, number of older siblings, socioeconomic status, maternal education, maternal race, paternal race, and study site were evaluated for possible confounding. Covariables whose inclusion changed the adjusted odds ratio by >10% were retained in the models.

†Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, number of older siblings, and maternal race.

‡Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, and maternal race.

§The model would not run because too few children were present in one category.

||Logistic regression adjusted for maternal race.

TABLE E6. Sensitivity analyses (primary data in Table II) using 1 and 3 mm alternate cut points for positive skin tests to evaluate adjusted* associations (OR and 95% CI) between age of peanut introduction after age 12 months and peanut sensitization, possible IgE-mediated peanut allergy, and probable clinical IgE-mediated peanut allergy at age 3 years in the CHILd Cohort

Introduction after age 12 mo vs before age 12 mo	Sensitization	Possible IgE-mediated allergy	Probable clinical IgE-mediated allergy
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
All children			
2 mm cut point	2.38 (1.39, 4.07)†	2.69 (1.42, 5.07)‡	4.04 (1.66, 9.85)‡
1 mm cut point	2.32 (1.39, 3.87)†	2.82 (1.50, 5.31)‡	4.10 (1.68, 9.99)‡
3 mm cut point	2.40 (1.34, 4.31)†	2.86 (1.44, 5.67)‡	3.75 (1.53, 9.18)‡
Children without moderate-to-severe atopic dermatitis in the first year of life			
2 mm cut point	2.69 (1.51, 4.78)§	3.21 (1.58, 6.52)	5.94 (2.05, 17.2)
1 mm cut point	2.53 (1.47, 4.38)§	3.31 (1.63, 6.69)	5.94 (2.05, 17.2)
3 mm cut point	2.79 (1.48, 5.25)§	3.57 (1.64, 7.80)	5.47 (1.88, 15.9)
Children without moderate-to-severe atopic dermatitis in the first year of life or egg sensitization or reactions by age 1 y			
2 mm cut point	2.58 (1.43, 4.67)§	2.91 (1.43, 5.93)	5.31 (1.83, 15.4)
1 mm cut point	2.38 (1.35, 4.17)§	2.91 (1.43, 5.93)	5.31 (1.83, 15.4)
3 mm cut point	2.75 (1.43, 5.30)§	3.20 (1.46, 7.02)	4.87 (1.67, 14.2)

CHILd, Canadian Healthy Infant Longitudinal Development; CI, confidence interval; OR, odds ratio.

*Sex, moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, age of formula introduction, maternal and paternal histories of atopic conditions including asthma, rhinitis and food allergy, reported sibling food allergies, number of older siblings, socioeconomic status, maternal education, maternal race, paternal race and study site were evaluated for possible confounding. Covariables whose inclusion changed the adjusted odds ratio by >10% were retained in the models.

†Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, number of older siblings, and maternal race.

‡Logistic regression adjusted for moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, and maternal race.

§Logistic regression adjusted for history of allergic reactions to foods in the first 6-12 months of life, number of older siblings, and maternal race.

||Logistic regression adjusted for history of allergic reactions to foods in the first 6-12 months of life and maternal race.

TABLE E7. Sensitivity analyses (primary data in Table III) using 1 and 3 mm alternate cut points for positive skin prick tests to evaluate associations* between age of introduction to peanut and peanut sensitization, possible IgE-mediated peanut allergy, and probable clinical IgE-mediated peanut allergy at age 3 years in the CHILD Cohort

Comparison vs ≤9 mo	Sensitization—all children (N = 2517)	Sensitization—no atopic dermatitis in the first year (N = 2389)	Sensitization—no moderate-severe atopic dermatitis in the first year or egg sensitization/ reaction at 1 y (N = 2365)	Possible IgE-mediated allergy—all children (N = 2506)	Possible IgE-mediated allergy—no moderate-severe atopic dermatitis in the first year (N = 2378)	Possible allergy—no moderate-severe atopic dermatitis in the first year or egg sensitization/ reaction at 1 y (N = 2354)	Probable clinical IgE-mediated allergy—all children (N = 2463)	Probable clinical IgE-mediated allergy—no moderate-severe atopic dermatitis in the first year (N = 2341)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
≤9 mo	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
>9-12 mo								
2 mm cut point	1.77 (0.64, 4.85)	1.31 (0.46, 3.74)	1.51 (0.48, 4.78)	2.20 (0.62, 7.85)	1.45 (0.38, 5.50)	2.20 (0.46, 10.4)	3.32 (0.40, 27.7)	2.18 (0.24, 19.6)
1 mm cut point	1.99 (0.73, 5.40)	1.53 (0.55, 4.28)	1.79 (0.58, 5.53)	2.20 (0.62, 7.85)	1.45 (0.38, 5.50)	2.20 (0.46, 10.4)	3.32 (0.40, 27.7)	2.18 (0.24, 19.6)
3 mm cut point	1.43 (0.51, 4.04)	0.98 (0.33, 2.93)	1.09 (0.33, 3.66)	1.83 (0.50, 6.69)	1.08 (0.27, 4.36)	1.64 (0.33, 8.18)	3.32 (0.40, 27.6)	2.18 (0.24, 19.5)
>12-18 mo								
2 mm cut point	1.74 (0.64, 4.75)	1.33 (0.47, 3.76)	1.53 (0.49, 4.79)	2.21 (0.63, 7.81)	1.70 (0.47, 6.23)	2.56 (0.56, 11.7)	5.64 (0.73, 43.8)	4.62 (0.58, 36.6)
1 mm cut point	1.95 (0.72, 5.26)	1.44 (0.51, 4.02)	1.53 (0.49, 4.79)	2.56 (0.74, 8.90)	1.88 (0.52, 6.77)	2.56 (0.56, 11.7)	5.66 (0.73, 44.0)	4.62 (0.58, 36.6)
3 mm cut point	1.33 (0.47, 3.74)	0.92 (0.31, 2.75)	1.15 (0.35, 3.75)	1.87 (0.52, 6.73)	1.36 (0.36, 5.15)	2.04 (0.43, 9.65)	5.12 (0.65, 40.2)	4.10 (0.51, 32.9)
>18 mo								
2 mm cut point	7.24 (2.85, 18.4)	6.48 (2.54, 16.6)	7.51 (2.65, 21.2)	8.95 (2.73, 29.3)	7.54 (2.27, 25.0)	10.1 (2.38, 42.9)	17.7 (2.38, 132)	14.6 (1.94, 110)
1 mm cut point	7.57 (2.99, 19.2)	6.84 (2.68, 17.5)	7.95 (2.82, 22.4)	8.95 (2.73, 29.3)	7.54 (2.27, 25.0)	10.1 (2.38, 42.9)	17.7 (2.38, 132)	14.6 (1.94, 110)
3 mm cut point	6.57 (2.58, 16.7)	5.79 (2.25, 14.9)	6.64 (2.33, 18.9)	8.39 (2.56, 27.6)	6.96 (2.09, 23.2)	9.24 (2.17, 39.4)	16.9 (2.26, 126)	13.7 (1.82, 103)

CHILD, Canadian Healthy Infant Longitudinal Development; CI, confidence interval; OR, odds ratio.

*Sex, moderate-severe atopic dermatitis in the first year of life, history of allergic reactions to foods in the first 6-12 months of life, age of formula introduction, maternal and paternal histories of atopic conditions including asthma, rhinitis and food allergy, reported sibling food allergies, number of older siblings, socioeconomic status, maternal education, maternal race, paternal race, and study site were evaluated for possible confounding. Covariables whose inclusion changed the adjusted odds ratio by >10% were retained in the models. Unadjusted models are reported. Models evaluating children with probable clinical IgE-mediated peanut allergy who had no moderate-severe atopic dermatitis in the first year or egg sensitization at 1 year would not run because too few children were present in some categories.

TABLE E8. Sensitivity analyses in the CHILD Cohort (primary data in Table V) using 1 and 3 mm alternate cut points for positive skin prick tests to evaluate the association between age of introduction to peanut and sensitization, possible IgE-mediated allergy, and probable clinical IgE-mediated allergy to peanut at age 3 years with 1-year skin prick test cut points reflecting the LEAP Study categories^{E5} (comparison of children introduced to peanut after 18 months with children introduced to peanut after 12 but by 18 months; all of these children would have had the presence or absence of peanut sensitization known at the time of peanut introduction; excluding children who were introduced to peanut before age 12 months)

1-y peanut SPT (mm)	Sensitization —all children	Sensitization—no moderate-severe atopic dermatitis in the first year	Sensitization—no moderate-severe atopic dermatitis in the first year or egg sensitization/ reaction at 1 y	Possible IgE- mediated allergy— all children	Possible IgE- mediated allergy— no moderate- severe atopic dermatitis in the first year	Possible IgE- mediated allergy— no moderate- severe atopic dermatitis in the first year or egg sensitization/ reaction at 1 y
Comparison >18 mo vs >12-18 mo						
0	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
2 mm cut point	3.20 (1.28, 7.99)	4.25 (1.51, 12.0)	4.92 (1.58, 15.3)	1.91 (0.58, 6.31)	2.71 (0.65, 11.4)	2.17 (0.48, 9.76)
1 mm cut point	2.85 (1.25, 6.50)	4.10 (1.58, 10.6)	5.76 (1.89, 17.6)	1.36 (0.46, 4.08)	2.03 (0.54, 7.61)	2.17 (0.48, 9.76)
3 mm cut point	3.19 (1.19, 8.56)	4.48 (1.42, 14.2)	4.08 (1.27, 13.1)	1.91 (0.58, 6.29)	2.71 (0.64, 11.4)	2.17 (0.48, 9.74)
>0 to 4						
2 mm cut point	5.38 (0.99, 29.3)	4.87 (0.87, 27.3)	4.33 (0.76, 24.6)	9.23 (1.01, 83.9)	8.17 (0.88, 76.2)	7.00 (0.74, 66.6)
1 mm cut point	5.38 (0.99, 29.3)	4.87 (0.87, 27.3)	4.33 (0.76, 24.6)	9.23 (1.01, 83.9)	8.17 (0.88, 76.2)	7.00 (0.74, 66.6)
3 mm cut point	9.64 (1.08, 86.2)	8.62 (0.94, 78.7)	7.54 (0.81, 69.9)	7.50 (0.82, 68.9)	6.46 (0.68, 61.2)	5.39 (0.55, 52.4)
>4						
2 mm cut point	0.63 (0.062, 6.33)	0.57 (0.055, 5.88)	0.53 (0.051, 5.55)	0.57 (0.057, 5.78)	0.50 (0.048, 5.23)	0.47 (0.044, 4.90)
1 mm cut point	0.63 (0.062, 6.33)	0.57 (0.055, 5.88)	0.53 (0.051, 5.55)	0.57 (0.057, 5.78)	0.50 (0.048, 5.23)	0.47 (0.044, 4.90)
3 mm cut point	2.10 (0.39, 11.4)	2.00 (0.34, 11.7)	1.88 (0.32, 11.0)	1.90 (0.35, 10.4)	1.75 (0.30, 10.3)	1.63 (0.27, 9.66)
Comparison >18 mo vs >12-18 mo						
0						
>0 to 4						
2 mm cut point		Probable clinical IgE-mediated allergy— all children		Probable clinical IgE-mediated allergy— no moderate-severe atopic dermatitis in the first year		Probable clinical IgE-mediated allergy— no moderate-severe atopic dermatitis in the first year or egg sensitization/ reaction at 1 y
1 mm cut point		OR (95% CI)		OR (95% CI)		OR (95% CI)
3 mm cut point		7.64 (0.80, 73.1)		6.50 (0.65, 64.8)		5.20 (0.50, 54.1)
>4						
2 mm cut point		0.53 (0.051, 5.55)		0.48 (0.044, 5.22)		0.44 (0.040, 4.82)
1 mm cut point		0.53 (0.051, 5.55)		0.48 (0.044, 5.22)		0.44 (0.040, 4.82)
3 mm cut point		1.07 (0.16, 7.06)		1.00 (0.14, 7.10)		0.92 (0.13, 6.56)

CHILD, Canadian Healthy Infant Longitudinal Development; CI, confidence interval; LEAP, Learning Early about Peanut; OR, odds ratio; SPT, skin prick testing.

*The models would not run because there were too few children in some categories.

TABLE E9. Sensitivity analyses in the CHILD Cohort (primary data in Table E3) using 1 and 3 mm alternate cut points for positive skin prick tests to evaluate association between age of introduction to peanut and sensitization, possible IgE-mediated allergy and probable clinical IgE-mediated allergy to peanut at age 3 years with 1-year skin prick test cut points reflecting nonsensitized and sensitization above and below the 95% predictive level^{E3,E4} (comparison of children introduced to peanut after 18 months with children introduced to peanut after 12 but by 18 months; all of these children would have had the presence or absence of peanut sensitization known at the time of peanut introduction; excluding children who were introduced to peanut before age 12 months)

1-y peanut SPT (mm)	Sensitization— all children	Sensitization—no moderate-severe atopic dermatitis in the first year	Sensitization—no moderate-severe atopic dermatitis in the first year or egg sensitization/ reactions at 1 y	Possible IgE- mediated allergy— all children	Possible IgE- mediated allergy— no moderate- severe atopic dermatitis in the first year	Possible IgE- mediated allergy— no moderate- severe atopic dermatitis in the first year or egg sensitization/ reactions at 1 y
Comparison >18 mo vs >12-18 mo	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
0 to <2						
2 mm cut point	3.20 (1.28, 7.97)	4.25 (1.51, 12.0)	4.92 (1.58, 15.3)	1.91 (0.58, 6.29)	2.71 (0.65, 11.4)	2.17 (0.48, 9.76)
1 mm cut point	2.85 (1.25, 6.49)	4.10 (1.58, 10.6)	5.76 (1.89, 17.6)	1.36 (0.46, 4.07)	2.03 (0.54, 7.61)	2.17 (0.48, 9.76)
3 mm cut point	3.19 (1.19, 8.55)	4.48 (1.42, 14.2)	4.08 (1.27, 13.1)	1.91 (0.58, 6.28)	2.71 (0.64, 11.4)	2.17 (0.48, 9.74)
2 to 8						
2 mm cut point	2.94 (1.06, 8.14)	2.47 (0.85, 7.19)	2.37 (0.81, 6.91)	3.06 (1.08, 8.71)	2.52 (0.83, 7.62)	2.40 (0.79, 7.27)
1 mm cut point	2.94 (1.06, 8.14)	2.47 (0.85, 7.19)	2.37 (0.81, 6.91)	3.06 (1.08, 8.71)	2.52 (0.83, 7.62)	2.40 (0.79, 7.27)
3 mm cut point	4.42 (1.48, 13.2)	3.94 (1.22, 12.7)	3.76 (1.16, 12.2)	3.79 (1.26, 11.4)	3.22 (0.98, 10.6)	3.04 (0.92, 10.0)
>8	*	*	*	*	*	*

1-y peanut SPT (mm)	Probable clinical IgE- mediated allergy—all children	Probable clinical IgE- mediated allergy—no moderate-severe atopic dermatitis in the first year	Probable clinical IgE- mediated allergy—no moderate-severe atopic dermatitis in the first year or egg sensitization/ reactions at 1 y
Comparison >18 mo vs >12-18 mo	OR (95% CI)	OR (95% CI)	OR (95% CI)
0 to <2	*	*	*
2-8			
2 mm cut point	2.86 (0.93, 8.75)	2.33 (0.71, 7.70)	2.18 (0.65, 7.25)
1 mm cut point	2.86 (0.93, 8.75)	2.33 (0.71, 7.70)	2.18 (0.65, 7.25)
3 mm cut point	3.17 (1.00, 10.0)	2.63 (0.76, 9.08)	2.44 (0.70, 8.50)
>8 mm	*	*	*

CHILD, Canadian Healthy Infant Longitudinal Development; CI, confidence interval; OR, odds ratio; SPT, skin prick testing.

*The models would not run because there were too few children in some categories.

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