Reduced risk of peanut sensitization following exposure through breast-feeding and early peanut introduction

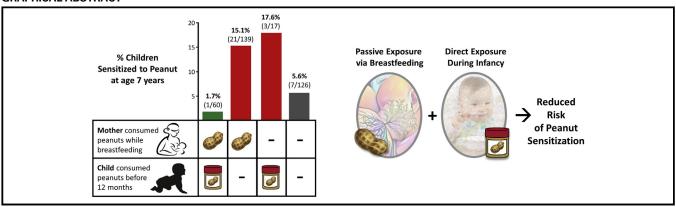


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GRAPHICAL ABSTRACT



Background: Recent trials have shown that avoiding peanuts during infancy increases the risk of peanut allergy; however, these studies did not address maternal peanut consumption. Objective: We sought to investigate the relationship between maternal peanut consumption while breast-feeding, timing of direct peanut introduction, and peanut sensitization at age 7 years.

Methods: Secondary analysis of a nested cohort within the 1995 Canadian Asthma Primary Prevention Study intervention study was performed. Breast-feeding and maternal and infant peanut consumption were captured by repeated questionnaires during infancy. Skin prick testing for peanut sensitization was performed at age 7 years.

Results: Overall, 58.2% of mothers consumed peanuts while breast-feeding and 22.5% directly introduced peanuts to their infant by 12 months. At 7 years, 9.4% of children were

sensitized to peanuts. The lowest incidence (1.7%) was observed among children whose mothers consumed peanuts while breastfeeding and directly introduced peanuts before 12 months. Incidence was significantly higher (P < .05) if mothers consumed peanuts while breast-feeding but delayed introducing peanuts to their infant beyond 12 months (15.1%), or if mothers avoided peanuts themselves but directly introduced peanuts by 12 months (17.6%). Interaction analyses controlling for study group and maternal atopy confirmed that maternal peanut consumption while breast-feeding and infant peanut consumption by 12 months were protective in combination, whereas either exposure in isolation was associated with an increased risk of sensitization (P interaction = .003). Conclusions: In this secondary analysis, maternal peanut consumption while breast-feeding paired with direct introduction of peanuts in the first year of life was

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associated with the lowest risk of peanut sensitization, compared with all other combinations of maternal and infant peanut consumption. (J Allergy Clin Immunol 2018;141:620-5.)

Key words: Breast-feeding, lactation, maternal peanut consumption, peanut allergy, peanut sensitization, timing of peanut introduction

The prevalence of food allergy has increased in recent decades, particularly in the United Kingdom and other industrialized nations.¹⁻⁵ Approximately 7% of Canadian children have a food allergy with peanut being among the most common.^{6,7} There are many theories regarding the cause of food allergy, including breaches in oral tolerance and alternative routes of exposure leading to sensitization.⁸⁻¹⁰ Recently, there has also been speculation that the timing of introduction to specific foods may be associated with the risk of sensitization. 11-14 Beginning in the 1990s, national pediatric and allergy societies recommended delaying the introduction of common highly allergenic foods, including peanuts, until 2 or 3 years of age. However, alongside these recommendations, the incidence and prevalence of food allergy continued to rise over the following decade, ¹⁵ casting doubt on delayed introduction as an effective strategy for allergy prevention. Recent studies suggest that early introduction to peanuts may in fact reduce the likelihood of developing peanut allergy. 11,16

In the Learning Early About Peanut allergy (LEAP) study, a randomized controlled trial in high-risk infants, early introduction of peanuts (between 4 and 11 months) significantly decreased the development of peanut allergy by 5 years of age. Similarly, in the randomized Enquiring About Tolerance (EAT) trial of early introduction to allergenic foods, ¹⁷ there was a significantly lower prevalence of peanut allergy among children adhering to the early introduction protocol, although differences were not significant in the intention-to-treat analysis. While infant feeding guidelines are already being revised in light of these new findings, ¹⁸ there are no data definitively showing risk or benefit from maternal peanut consumption while breast-feeding. Although not addressed in the LEAP and EAT trials, it is known that oral peanut exposure can occur through breast milk, 19,20 and this indirect exposure could potentially influence peanut sensitization.

In 1994, we initiated the randomized Canadian Asthma Primary Prevention Study (CAPPS). ^{21,22} One component of our multifaceted intervention was a recommendation to delay peanut introduction until at least 12 months of age, in accordance with the American Academy of Pediatrics guidelines at the time. ²³ We subsequently found a trend toward increased incidence of peanut sensitization in the intervention group, ²¹ although we did not evaluate the specific effects of maternal and infant peanut consumption because food allergy was not a primary focus of the CAPPS trial, where atopic sensitization was primarily measured for the purpose of classifying asthma phenotypes.

Motivated by the current debate and shifting recommendations regarding early introduction of allergenic foods, we took advantage of the unique CAPPS dataset to assess the relationship between maternal consumption of peanut while breast-feeding, timing of direct oral peanut introduction, and sensitization to peanuts at 7 years of age.

Abbreviations used

aOR: Adjusted odds ratio

CAPPS: Canadian Asthma Primary Prevention Study

EAT: Enquiring About Tolerance

LEAP: Learning Early About Peanut allergy

OR: Odds ratio

METHODS

Study design and population

We performed a secondary analysis of nested cohort data from CAPPS, which has been described in previous reports. 21,22 Briefly, 545 pregnant women were recruited in 1994 and 1995 from 2 major Canadian cities (Winnipeg and Vancouver). All children had an immediate family history of asthma or 2 first-degree relatives with IgE-mediated allergic disease. Women were randomized to a multifaceted intervention group, or to a control group receiving the usual care recommended by their physicians. Mothers in the control group received no specific instructions about dietary avoidance for themselves or their infant and were advised to follow recommendations from their primary care physician. Mothers in the intervention group were asked to avoid peanuts, nuts, fish, and eggs during their pregnancy and while breast-feeding. They were encouraged to breast-feed for at least 4 months and up to 12 months if possible. They were also advised to avoid introducing solid foods to their infants until after 6 months of age and to delay the introduction of allergenic foods (eg, milk, eggs, seafood, and peanuts) until at least 12 months. Compliance was monitored through frequent questionnaires documenting maternal and infant diet. Peanut sensitization was measured by skin prick testing at 7 years of age. In the current secondary analysis, we applied a nested cohort approach and specifically evaluated the association of maternal and infant peanut consumption with peanut sensitization, regardless of assigned study group. Statistical models were adjusted for study group to account for the randomized study design and other elements of the multifaceted intervention. Ethics committees at the University of British Columbia and the University of Manitoba approved the study, and participants provided written consent.

Main exposure: maternal and infant peanut consumption

The timing of peanut introduction was obtained from dietary questionnaires completed at 2 weeks and 4, 8, 12, 18, and 24 months of age. At each time point, mothers completed a table summarizing the consumption of specific foods, including peanuts, and any adverse reactions to these foods. This table included a row labeled "Age Introduced (months)." We determined the timing of peanut introduction from the earliest report of peanut introduction in the series of diet questionnaires. Mothers also reported on breast-feeding ("Are you breast-feeding?") and their own peanut intake ("During the past week have you had peanuts?") at each time point; these data were combined to estimate exposure to peanuts through breast milk. Mothers who responded "Yes" to both questions on any single questionnaire were considered to have consumed peanuts while breast-feeding.

Main outcome: peanut sensitization at age 7 years

Peanut sensitization was assessed by skin prick testing. Children were assessed by a pediatric allergist blinded to the group allocation and questionnaire results. Testing was performed via the prick Lancetter method (Bayer Inc, Mississauga, Ontario) and included common environmental and food (milk, egg, soy, and peanut) allergens, along with a positive (histamine) and negative (saline) controls. A mean wheal diameter of 3 mm or greater than what was elicited by the negative control was considered positive.

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Statistical analysis

For the current study, we excluded children with incomplete data for maternal or infant peanut consumption from birth through 24 months (n = 29), children who were never breast-fed (n = 24), and children who were lost to follow-up and not assessed at age 7 years (n = 150), leaving 342 of the original 545 enrolled children (62.7%) for analysis. These children did not differ systematically from the full cohort with respect to baseline demographic variables or maternal and infant peanut consumption (Table I). Bivariate screening of potential confounders was performed using chi-squared tests and t tests for categorical and continuous variables, respectively. Logistic regression was used to assess the relationships among maternal peanut consumption while breast-feeding, infant peanut consumption, and peanut sensitization at age 7, controlling for potential confounders. Results are presented as crude odds ratios (OR) and adjusted ORs (aOR) with 95% CI. To address the hypothesized interaction between maternal and infant peanut consumption, an interaction term was tested in the logistic regression model and ORs for each individual exposure (maternal or infant peanut consumption) were estimated while specifying the presence or absence of the other exposure. In addition, a 4-category variable was generated to classify children according to the 4 possible combinations of maternal peanut consumption while breast-feeding and introduction of peanuts to the infant before 12 months (+/+, +/-, -/+, -/-). This 4-category variable was used in a logistic regression model to estimate the aOR for peanut sensitization relative to children whose mothers consumed peanuts while breast-feeding and introduced peanuts to their infants before 12 months (ie, the double exposed "+/+" group). Statistical analysis was performed with SAS 9.4 (SAS Inc, Cary, NC).

RESULTS

Overall, only 77 of 342 families (23%) introduced peanuts to their infant by 12 months; 136 (40%) introduced peanuts between 13 and 24 months and 129 (38%) did not introduce peanuts before 24 months (Table II). Almost no families (<1%) introduced peanuts before 6 months of age. However, more than half of mothers (58%) reported consuming peanuts while breastfeeding. Mothers who avoided peanuts while breast-feeding were more likely to delay introducing peanuts to their infants (only 14% of peanut-avoiding mothers introduced peanuts before 12 months, compared with 30% of mothers who consumed peanuts while breast-feeding; P < .001). The majority of families in both study groups delayed peanut introduction beyond 12 months, as was the standard at the time; however, delayed introduction was significantly more likely and nearly universal in the intervention group (95%) compared to the control group (58%) (P < .0001) (Table II). Mothers in the intervention group were also significantly more likely to avoid peanuts while breast-feeding compared to mothers in the control group (55.8% vs 26.1%, P < .001) (Table II), despite breast-feeding significantly longer (median 8.7 vs 6.5 months; P = .01). There was no difference in maternal or infant peanut consumption according to study site, maternal education, infant birth order, or maternal food allergy (see Table E1 in this article's Online Repository at www.jacionline.org).

By 7 years of age, 32 of 342 children (9.4%) were sensitized to peanuts. The incidence of peanut sensitization was not significantly different between study groups, although we observed a trend toward higher rates in the intervention (n=21 of 181, 11.6%) versus the control group (n=11 of 161, 6.8%) (P=.13) (Table II). Independent of study group and maternal atopy, maternal and infant peanut consumption were significantly associated with peanut sensitization at 7 years of age (Fig 1). The lowest incidence of peanut sensitization (1.7%) was observed when mothers consumed peanuts while breast-feeding and

TABLE I. Baseline demographics and maternal and infant peanut consumption in the CAPPS cohort, comparing subjects included and excluded from the current analysis

	Excluded from current analysis n = 203	Included in current analysis* n = 342	P	
	n/n (%)	n/n (%)	value	
Study group				
Control	106/203 (52.2)	161/342 (47.1)	.25	
Intervention	97/203 (47.8)	181/342 (52.9)		
Study site				
Vancouver	100/203 (49.3)	171/342 (50.0)	.87	
Winnipeg	103/203 (50.7)	171/342 (50.0)		
Sex				
Female	95/183 (51.9)	162/342 (47.4)	.32	
Male	88/183 (48.1)	180/342 (52.6)		
Maternal atopy	, ,	, ,		
No	44/181 (24.3)	68/339 (20.1)	.26	
Yes	137/181 (75.7)	271/339 (79.9)		
Maternal food allergy				
No	122/181 (67.4)	225/339 (66.4)	.81	
Yes	59/181 (32.6)	114/339 (33.6)		
Maternal education	, ,	` ,		
No postsecondary	49/181 (27.1)	71/339 (20.9)	.11	
Postsecondary	132/181 (72.9)	268/339 (79.1)		
First born	` ′	` ′		
No	102/181 (56.4)	187/339 (55.2)	.79	
Yes	79/181 (43.6)	152/339 (44.8)		
Pets	, ,	` /		
No	119/178 (66.9)	221/342 (64.6)	.61	
Yes	59/178 (33.1)	121/342 (35.4)		
Breast-feeding duration		()		
<4 mo	28/130 (21.5)	62/342 (18.1)	.86	
4 to <8 mo	33/130 (25.4)	88/342 (25.7)		
8 to <12 mo	23/130 (17.7)	64/342 (18.7)		
≥ 12 mo	46/130 (35.4)	128/342 (37.4)		
Maternal peanut consu	, ,			
No	40/117 (34.2)	143/342 (41.8)	.16	
Yes	77/117 (65.8)	199/342 (58.2)		
Introduction of peanuts				
0-12 mo	51/160 (31.9)	77/342 (22.5)	.08	
13-24 mo	54/160 (33.8)	136/342 (39.8)		
Never before 24 mo		129/342 (37.7)		
Peanut sensitization at	, ,	-2.2 (2)		
No	48/53 (90.6)	310/342 (90.6)	.99	
Yes	5/53 (9.4)	32/342 (9.4)		

*Breast-fed children with complete data for maternal and infant peanut consumption and child peanut sensitization at age 7.

†Among those who initiated breast-feeding.

introduced peanuts to their infant's diet before 12 months. Compared with this group, the incidence of peanut sensitization was significantly higher (17.6%; P < .05) when mothers introduced peanuts to their infants before 12 months, but did not consume peanuts themselves while breast-feeding (aOR: 12.45, 95% CI: 1.18-131.30, adjusted for study group and maternal atopy). Peanut sensitization was also significantly higher (15.6%; P < .05) when mothers consumed peanuts while breast-feeding, but delayed introducing peanuts directly to their infant's diet until after 12 months (aOR: 8.30, 95% CI: 1.05-65.80). A formal interaction analysis confirmed that maternal peanut consumption while breast-feeding and direct introduction of peanut by 12 months were protective in combination, whereas

TABLE II. Maternal and infant peanut consumption and peanut sensitization at age 7 years in the CAPPS cohort

	Overall	Control	Intervention			
	n = 342	n = 161	n = 181	P value		
Maternal peanut consumption while breast-feeding	199 (58.2)	119 (73.9)	80 (44.2)	<.001		
Introduction of peanuts to infant						
<6 mo	1 (0.3)	1 (0.6)	0 (0.0)	<.0001		
6-9 mo	16 (4.7)	15 (9.3)	1 (0.6)			
10-12 mo	60 (17.5)	51 (31.7)	9 (5.0)			
13-17 mo	69 (20.2)	47 (29.2)	22 (12.2)			
18-24 mo	67 (19.6)	25 (15.5)	42 (23.2)			
Never before 24 mo	129 (37.7)	22 (13.7)	107 (59.1)			
Peanut sensitization at 7 years	32 (9.4)	11 (6.8)	21 (11.6)	.13		

Values are n (%). N = 342 breast-fed infants with complete data for maternal and infant peanut consumption, and child peanut sensitization at age 7. Comparisons by chi-squared test. Sensitization by skin prick test (mean wheal ≥ 3 mm).

either exposure in isolation was associated with an increased risk of peanut sensitization (*P* interaction = .003) (Table III).

DISCUSSION

This nested cohort study provides evidence that both the timing and route of peanut introduction may be associated with peanut sensitization. In our secondary analysis of the 1995 CAPPS study, we have identified a potentially novel interaction between maternal and infant peanut consumption, where early direct peanut introduction (before 12 months) was associated with protection against sensitization only if mothers consumed while breast-feeding, and maternal consumption during lactation was associated with an increased risk of peanut sensitization only if direct peanut introduction was delayed beyond 12 months. In our study population, the incidence of peanut sensitization by school age was substantially lower (1.7%) when mothers reported consuming peanuts while breast-feeding and introducing peanut directly to their infants in the first year of life, compared with any other combination of maternal and infant peanut consumption (6% to 18% sensitization). Moreover, our current results help to explain the previously reported trend toward increased peanut sensitization in the intervention arm of the CAPPS trial,²¹ suggesting this was likely due to maternal and infant peanut avoidance.

Our findings add to a growing body of evidence from observational studies²⁴⁻²⁶ and randomized trials^{16,17,27} showing that delaying the introduction of allergenic foods may increase the risk of allergy or sensitization. After observing a strong inverse association between peanut consumption in infancy and peanut allergy in childhood,¹¹ Du Toit et al¹⁶ conducted the randomized LEAP trial, which has confirmed that early introduction of peanut (between 4 and 11 months) decreases the risk of peanut allergy in high-risk children. Our current secondary analysis uniquely examined the potential role of maternal peanut consumption, which was not addressed in the LEAP trial, although we lacked information on the dose and frequency of maternal peanut intake, which limited our ability to quantify this exposure.

While not all studies find an association between maternal peanut consumption and peanut allergy in offspring, 8,28 some have found that mothers of children with peanut allergy are more likely to report consuming peanuts while pregnant or breast-feeding compared to mothers of children who do not have peanut allergy.²⁹ However, these retrospective studies are subject to recall bias because maternal diet was reported years later, after the child's allergy diagnosis. Recall bias was minimized in our study by repeatedly collecting maternal and infant dietary information during infancy, prior to the measurement of peanut sensitization at school age. Moreover, previous studies have not evaluated the potential interaction between maternal and infant peanut consumption. The associations noted in our secondary analysis suggest that maternal peanut consumption while breast-feeding may differentially influence peanut sensitization depending on the timing of direct peanut introduction, and vice versa, although further research is needed to formally test this hypothesis.

The lowest incidence of peanut sensitization in our study population was observed when both mother and infant consumed peanuts. Further research is warranted to determine whether this potential interaction extends to peanut allergy and applies equally in other settings and populations. While the LEAP trail focused on early peanut introduction without explicitly addressing maternal consumption, we suspect that most mothers randomized to early peanut introduction likely also consumed peanuts themselves, resulting in frequent "double exposure" among breast-fed infants in the intervention group. Given our current results, we recommend that peanut exposure through breast-feeding be considered in future research examining the timing of peanut introduction.

Although the underlying mechanisms require further investigation, our findings suggest that both maternal and infant peanut consumption may help prevent sensitization. When transmitted through breast-feeding, peanut antigens are delivered to the infant along with a plethora of bioactive factors including maternal immunoglobulins, cytokines, microbiota, and immune cells.³⁰ Packaged with these immunomodulatory factors, peanut antigens in breast milk may prime the infant immune system to develop tolerance when peanut is directly consumed a few months later. On the other hand, we speculate that exposure to peanut antigens in breast milk without peanut consumption during infancy may facilitate sensitization.

Strengths of this nested cohort study include the longitudinal follow-up from pregnancy through early childhood and frequent reporting of maternal and infant diet throughout infancy, which minimizes the risk of recall bias. This study also has important limitations, including incomplete dietary information and loss to follow-up, although no systematic differences were observed between children with and without complete data. The sample sizes were relatively small for some exposure groups, which reduced the precision of our effect estimates. While it would be ideal to evaluate narrower time windows of peanut introduction in the first year of life, this was not possible in our study because very few infants consumed peanuts before 10 months. We studied children considered to be at high genetic risk for allergic disease, thus our findings may not apply to the general population. Although peanut sensitization was objectively measured, we could not evaluate peanut allergy, as oral food challenges were not performed. While the timing of direct peanut introduction was specifically captured in our study, maternal peanut consumption

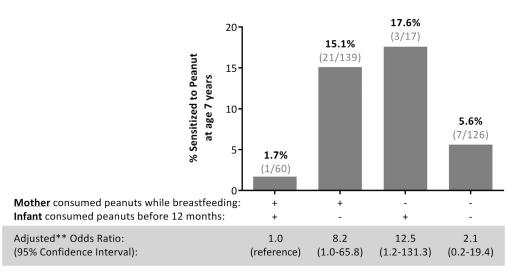


FIG 1. Peanut sensitization at age 7 years according to maternal and infant peanut consumption in the CAPPS cohort. Maternal and infant peanut consumption and breast-feeding were reported at age 2 weeks and 2, 4, 6, 8, 12, and 24 months. Peanut sensitization (≥3 mm mean wheal diameter) was measured by skin prick testing at age 7 years. **ORs from logistic regression adjusting for study group and maternal atopy, using a 4-category variable to classify maternal and infant peanut consumption.

TABLE III. Interactive association of maternal and infant peanut consumption with peanut sensitization at age 7 years in the CAPPS cohort

Peanut exposure	Adjusted OR (95% CI) for peanut sensitization at age 7*
Effect of maternal peanut consumption vs a	voidance while breast-feeding
With early peanut introduction to infant (<12 mo)	0.08 (0.01-0.85)
With delayed peanut introduction to infant (>12 mo)	3.94 (1.50-10.32)
Effect of early (≤12 mo) vs delayed (>12 mo)	introduction of peanuts to infant
If mother consumed peanuts while breast-feeding	0.12 (0.02-0.96)
If mother avoided peanuts while breast-feeding	5.91 (1.22-28.52)

P value for interaction between maternal and infant peanut consumption = .003. N = 339 breast-fed infants with complete data on maternal and infant peanut consumption, maternal atopy, and child peanut sensitization at age 7. *Mutually adjusted for maternal and infant peanut consumption, maternal atopy, and study group. The logistic regression model included an interaction term for maternal and infant peanut consumption; odds ratios for each individual exposure (maternal and infant peanut consumption) were estimated in this model while specifying the presence or absence of the other exposure.

while breast-feeding was not explicitly reported, and our estimate based on combined data for current breast-feeding and recent peanut consumption may have resulted in some exposure misclassification. Finally, we did not capture environmental peanut exposure or maternal peanut consumption during pregnancy, and we did not document the frequency or amount of maternal and infant peanut consumption. As a result, we could not address the relative importance of environmental and *in utero* exposure or regular versus infrequent peanut consumption.

It is also important to note that CAPPS was originally designed and implemented as a multifaceted intervention trial, which adds

a layer of complexity to the current nested cohort analysis. CAPPS was powered for asthma as the primary outcome; therefore, we may have been underpowered to detect differences in peanut sensitization between study groups, although this was not the primary goal of our current secondary analysis, which focused on associations between early peanut exposure and later peanut sensitization. We have adjusted for possible confounding by study group; however, residual confounding due to treatment contamination cannot be ruled out.

In summary, we found that introduction of peanut before 12 months of age was associated with a reduced risk of peanut sensitization by school age, particularly among children whose mothers consumed peanuts while breast-feeding. These results add to emerging evidence that early peanut consumption during infancy can reduce the risk of peanut sensitization later in childhood 16,17 and suggest this risk could be further reduced in breastfed infants by encouraging maternal consumption of peanuts during lactation. However, our secondary analysis has important limitations related to the study design, population, exposure, and outcome measurements. Thus, before drawing definitive conclusions or changing recommendations, further studies will be required to replicate our findings in other settings and contemporary populations, which have significantly different peanut consumption patterns compared to those of the 1995 CAPPS cohort. In addition, adequately powered and appropriately designed intervention trials will be required to establish whether the associations we have observed are causal and extend to peanut allergy, and to determine the optimal timing and combination of maternal and infant peanut consumption. Research is also needed to explore alternative strategies for mothers with peanut allergy and nonbreast-fed infants. Ultimately, in addition to determining the optimal timing for direct peanut introduction to infants, it will be important to consider breast-feeding and maternal peanut consumption as potential factors contributing to the development and prevention of peanut sensitization.

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Key messages

- In a high-risk birth cohort of breast-fed children, we provide evidence of an association between peanut introduction in the first year of life and a reduced risk of peanut sensitization by 7 years of age, but only if the mother consumed peanuts while breast-feeding.
- Our data suggest both passive peanut exposure through breast milk and peanut introduction in the first year of life may decrease the risk of peanut sensitization at age 7.

REFERENCES

- Rinaldi M, Harnack L, Oberg C, Schreiner P, St Sauver J, Travis LL. Peanut allergy diagnoses among children residing in Olmsted County, Minnesota. J Allergy Clin Immunol 2012;130:945-50.
- Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol 2011;127:668-76.
- Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of selfreported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol 2010;125:1322-6.
- Venter C, Hasan Arshad S, Grundy J, Pereira B, Bernie Clayton C, Voigt K, et al.
 Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. Allergy 2010:65:103-8
- same geographical location in the UK. Allergy 2010;65:103-8.

 5. Sampson HA. Update on food allergy. J Allergy Clin Immunol 2004;113:805-19.
- Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St Pierre Y, et al. Overall prevalence of self-reported food allergy in Canada. J Allergy Clin Immunol 2012:130:986-8.
- Ben-Shoshan M, Harrington DW, Soller L, Fragapane J, Joseph L, St Pierre Y, et al. A population based study on peanut, treenut, fish, shellfish and sesame allergy prevalence in Canada. J Allergy Clin Immunol 2010;125:1327-35.
- Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. J Allergy Clin Immunol 2009;123:417-23.
- Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2010; 125(suppl 2):S116-25.
- Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. N Engl J Med 2003;348:977-85.
- Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol 2008;122:984-91.
- Snijders BE, Thijs C, van Ree R, van den Brandt PA. Age at first introduction of cow milk products and other food products in relation to infant atopic

- manifestations in the first 2 years of life: the KOALA Birth Cohort Study. Pediatrics 2008:122:e115-22
- Sicherer SH, Wood RA, Stablein D, Lindblad R, Burks AW, Liu AH, et al. Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants. J Allergy Clin Immunol 2010;126:1191-7.
- 14. Zutavern A, Brockow I, Schaaf B, von Berg A, Diez U, Borte M, et al. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. Pediatrics 2006;117:401-11.
- Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics 2009;124:1549-55.
- Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015;372:803-13.
- Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med 2016;374: 1733-43.
- Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. Pediatrics 2015;33(1):103-6.
- Vadas P, Wai Y, Burks W, Perelman B. Detection of peanut allergens in breast milk of lactating women. JAMA 2001;285:1746-8.
- Bernard H, Ah-Leung S, Drumare MF, Feraudet-Tarisse C, Verhasselt V, Wai JM, et al. Peanut allergens are rapidly transferred in human breast milk and can prevent sensitization in mice. Allergy 2014;69:888-97.
- Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. J Allergy Clin Immunol 2005;116:49-55.
- Chan-Yeung M, Manfreda J, Dimich-Ward H, Ferguson A, Watson W, Becker A. A
 randomized controlled study on the effectiveness of a multifaceted intervention
 program in the primary prevention of asthma in high-risk infants. Arch Pediatr
 Adolesc Med 2000;154:657-63.
- American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. Pediatrics 2000;106:346-9.
- Joseph CL, Ownby DR, Havstad SL, Woodcroft KJ, Wegienka G, MacKechnie H, et al. Early complementary feeding and risk of food sensitization in a birth cohort. J Allergy Clin Immunol 2011;127:1203-10.
- 25. Zutavern A, Brockow I, Schaaf B, von Berg A, Diez U, Borte M, et al. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. Pediatrics 2008;121:e44-52.
- Tran MM, Lefebvre DL, Dai D, Dharma C, Subbarao P, Lou W, et al. Timing of food introduction and development of food sensitization in a prospective birth cohort. Pediatr Allergy Immunol 2017;28:471-7.
- Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, et al. Effect
 of avoidance on peanut allergy after early peanut consumption. N Engl J Med
 2016;374:1435-43.
- 28. Kemp AL, Ponsonby AL, Dwyer T, Cochrane JA, Pezic A, Jones G. Maternal antenatal peanut consumption and peanut and rye sensitization in the offspring at adolescence. Clin Exp Allergy 2011;41:224-31.
- DesRoches A, Infante-Rivard C, Paradis L, Paradis J, Haddad E. Peanut allergy: is maternal transmission of antigens during pregnancy and breastfeeding a risk factor? J Investig Allergol Clin Immunol 2010;20:289-94.
- Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. Pediatr Clin North Am 2013;60:49-74.

TABLE E1. Baseline demographics of study population and univariate associations with maternal peanut consumption, timing of peanut introduction during infancy, and peanut sensitization at age 7 years in the CAPPS cohort

Characteristic	Prevalence	Maternal peanut con- sumption while breast-feeding		Timing of peanut introduction to infant, n (%)			Peanut sensitization at age 7 years		
	n/N (%)	n (%)	P value	0-12 mo	13-24 mo	Never before 24 mo	P value	n (%)	P value
Overall	342 (100)	199 (58.2)		77 (22.5)	136 (39.8)	129 (37.7)		32 (9.4)	
Study group									
Control	161/342 (47.1)	119 (73.9)	<.001	67 (41.6)	72 (44.7)	22 (13.7)	<.001	11 (6.8)	.13
Intervention	181/342 (52.9)	80 (44.2)		10 (5.5)	64 (35.4)	107 (59.1)		21 (11.6)	
Study site									
Vancouver	171/342 (50.0)	101 (59.1)	.74	35 (20.5)	65 (38.0)	71 (41.5)	.33	12 (7.0)	.14
Winnipeg	171/342 (50.0)	98 (57.3)		42 (24.6)	71 (41.5)	58 (33.9)		20 (11.7)	
Sex									
Female	162/342 (47.4)	94 (58.0)	.95	36 (22.2)	64 (39.5)	62 (38.3)	.98	15 (9.3)	.95
Male	180/342 (52.6)	105 (58.3)		41 (22.8)	72 (40.0)	67 (37.2)		17 (9.4)	
Maternal atopy									
No	68/339 (20.1)	39 (57.4)	.80	15 (22.1)	35 (51.5)	18 (26.5)	.06	3 (4.4)	.13
Yes	271/339 (79.9)	160 (59.0)		61 (22.5)	101 (37.3)	109 (40.2)		28 (10.3)	
Maternal food allergy									
No	225/339 (66.4)	137 (60.9)	.25	54 (24.0)	93 (41.3)	78 (34.7)	.30	17 (7.6)	.15
Yes	114/339 (33.6)	62 (54.4)		22 (19.3)	43 (37.7)	49 (43.0)		14 (12.3)	
Maternal education									
No postsecondary	71/339 (20.9)	37 (52.1)	.20	13 (18.3)	26 (36.6)	32 (45.1)	.31	8 (11.3)	.49
Postsecondary	268/339 (79.1)	162 (60.4)		63 (23.5)	110 (41.0)	95 (35.4)		23 (8.6)	
First born									
No	187/339 (55.2)	114 (61.0)	.35	48 (25.7)	78 (41.7)	61 (32.6)	.09	19 (10.2)	.47
Yes	152/339 (44.8)	85 (55.9)		28 (18.4)	58 (38.2)	66 (43.4)		12 (7.9)	
Pets	`			. ,		` ′		` ′	
No	221/342 (64.6)	122 (55.2)	.13	44 (19.9)	85 (38.5)	92 (41.6)	.10	20 (9.0)	.79
Yes	121/342 (35.4)	77 (63.6)		33 (27.3)	51 (42.1)	37 (30.6)		12 (9.9)	

Comparisons by chi-squared test. N = 342 breast-fed infants with complete data for maternal and infant peanut consumption and child peanut sensitization at age 7.