Journal of Developmental Origins of Health and Disease

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Reduced peanut sensitization with maternal peanut consumption and early peanut introduction while breastfeeding

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Abstract

New guidelines for peanut allergy prevention in high-risk infants recommend introducing peanut during infancy but do not address breastfeeding or maternal peanut consumption. We assessed the independent and combined association of these factors with peanut sensitization in the general population CHILD birth cohort ($N = 2759$ mother–child dyads). Mothers reported peanut consumption during pregnancy, timing of first infant peanut consumption, and length of breastfeeding duration. Child peanut sensitization was determined by skin prick testing at 1, 3, and 5 years. Overall, 69% of mothers regularly consumed peanuts and 36% of infants were fed peanut in the first year (20% while breastfeeding and 16% after breastfeeding cessation). Infants who were introduced to peanut early (before 1 year) after breastfeeding cessation had a 66% reduced risk of sensitization at 5 years compared to those who were not (1.9% vs. 5.8% sensitization; aOR 0.34, 95% CI 0.14–0.68). This risk was further reduced if mothers introduced peanut early while breastfeeding and regularly consumed peanut themselves (0.3% sensitization; aOR 0.07, 0.01–0.25). In longitudinal analyses, these associations were driven by a higher odds of outgrowing early sensitization and a lower odds of late-onset sensitization. There was no apparent benefit (or harm) from maternal peanut consumption without breastfeeding. Taken together, these results suggest the combination of maternal peanut consumption and breastfeeding at the time of peanut introduction during infancy may help to decrease the risk of peanut sensitization. Mechanistic and clinical intervention studies are needed to confirm and understand this "triple exposure" hypothesis.

Introduction

Peanut allergy is the most common food allergy in children, causing substantial morbidity, mortality, and impaired quality of life.[1–4] As there is no cure for peanut allergy, it is critically important to develop effective primary prevention strategies.

Recently, the landmark Learning Early About Peanut (LEAP) trial[5] showed that early peanut introduction (commencing from 4 to 11 months) helped to prevent peanut allergy in high-risk children, prompting worldwide changes in infant feeding guidelines.[6,7] Consistent with LEAP, we observed that peanut introduction before 12 months was associated with a lower incidence of peanut sensitization at 12 months in the general population CHILD cohort.[8] However, neither report accounted for maternal peanut consumption nor breastfeeding at the time of peanut introduction. Current guidelines recommend no restriction of maternal peanut ingestion but stop short of recommending consumption due to insufficient evidence.[6,7,9–11]

The impact of breastfeeding on allergy development has been widely studied, with inconsistent results[12,13] – perhaps due to undocumented differences in maternal diet, breast milk composition, or complementary feeding practices. These are relevant to consider because maternal peanut ingestion could provide oral peanut exposure through lactation.[14–16] Also, given the immunomodulatory activity of breast milk cytokines, immunoglobulins, and other bioactives,[17,18] the timing of peanut introduction relative to breastfeeding cessation may be important. Indeed, a protective effect of breastfeeding while introducing cereals has been

Original Article

Cite this article: Azad MB, Dharma C, Simons E, Tran M, Reyna ME, Dai R, Becker AB, Marshall J, Mandhane PJ, Turvey SE, Moraes TJ, Lefebvre DL, Subbarao P, and Sears MR. (2021) Reduced peanut sensitization with maternal peanut consumption and early peanut introduction while breastfeeding. *Journal of Developmental Origins of Health and Disease* **12**: 811–818. doi: 10.1017/S2040174420001129

Received: 4 August 2020
Revised: 24 October 2020
Accepted: 28 October 2020
First published online: 9 December 2020

Keywords:
Breastfeeding; lactation; food allergy; developmental origins of health and disease; CHILD Cohort Study

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found for celiac disease,[19,20] and conflicting reports have suggested that breastfeeding while introducing cow's milk has a protective effect[21] or no effect[22] against cow's milk allergy. However, to our knowledge, no studies have examined this potential interaction in the context of peanut allergy or sensitization.

Our secondary analysis of the 1995 Canadian Asthma Primary Prevention Study (CAPPS) ($N = 342$)[23] suggests that, in high-risk children with immediate family history of asthma or two first-degree relatives with IgE-mediated allergic disease, early peanut introduction combined with breastfeeding and maternal peanut consumption is most effective for preventing sensitization. However, that study had insufficient power to examine the timing of peanut introduction relative to breastfeeding cessation, and findings could not necessarily be extrapolated to the general population. In the current study, using data from the general population CHILD birth cohort ($N = 2759$), we extend our previous work[8] to examine the role of breastfeeding and maternal peanut consumption in the development of peanut sensitization through 5 years of age.

Methods

Study population

Pregnant women were enrolled in the observational CHILD Cohort Study (www.childstudy.ca) between 2008 and 2012[24]. Notably, this period precedes the new recommendations for early peanut introduction.[6,7] This general population cohort was recruited from the general population in Vancouver, Edmonton, Manitoba (Winnipeg and Morden/Winkler), and Toronto; 3455 singleton infants born >35 weeks gestation were eligible at birth and commenced the study. For the current analyses, children in the vanguard cohort ($n = 191$) or missing data on breastfeeding, peanut introduction, or peanut sensitization ($n = 505$) were excluded, leaving 2759 for analysis (Fig. S1). This study was approved by the Human Research Ethics Board at McMaster University and ethics committees at the Hospital for Sick Children, and the Universities of Manitoba, Alberta, and British Columbia.

Breastfeeding and timing of peanut introduction

Breastfeeding and peanut introduction were determined from questionnaires at 3, 6, 12, 18, and 24 months.[8,25] Mothers reported when they stopped breastfeeding (infant's age in weeks or months) and first introduced peanut (not given, <3, 3–4, 5–6, >6–9, >9–12, or >12 months). To address the potential interaction between timing of peanut introduction and breastfeeding, children were classified into three mutually exclusive groups: "Introduced early with breastfeeding" (introduced peanut to the infant before 12 months and was breastfeeding at the time of introduction), "Introduced early without breastfeeding" (introduced peanut to the infant before 12 months but was not breastfeeding at the time of introduction), or "Avoided >12 months" (infant did not receive peanut before 12 months).

Because breastfeeding duration was reported with more precision (in continuous weeks or months) than peanut introduction (in time windows), it was not possible to determine whether peanut introduction occurred with or without breastfeeding if weaning occurred during the time window of peanut introduction ($n = 155$). We conservatively classified children as "Introduced early with breastfeeding" only if their breastfeeding duration matched or exceeded the upper range of the peanut introduction window. This definition ensures that children in this group were still breastfeeding when peanut was introduced, with possible misclassification in the "Introduced early without breastfeeding" group. In a sensitivity analysis, we took the opposite approach and required that breastfeeding duration matched or exceeded the lower range of the peanut introduction window.

Maternal peanut consumption

Maternal diet was reported by food frequency questionnaire (FFQ) during mid-pregnancy.[24] We assumed similar peanut intake during pregnancy and lactation, as reported by Frazier *et al.*[26] and observed in our own data (although the FFQ was not repeated, women were asked if they reduced or increased their intake of any specific foods during pregnancy, and only 2.5% reported modifying their peanut intake). Peanut consumption was determined from two questions asking about dietary intake of "peanuts and other nuts and seeds" and "peanut butter." Options for intake ranged from "never or <1 per month" to "2+ per day." For this analysis, we dichotomized consumption as "Regular" (at least once per week) versus "Never or infrequent" (all other groups). In a sensitivity analysis, we excluded mothers ($n = 330$) with unclear peanut intake (i.e., those who regularly consumed "peanuts and other nuts" but never consumed peanut butter).

Peanut sensitization and allergy

Sensitization was determined by forearm skin prick testing at ages 1, 3, and 5 years,[8] using a panel of inhalant and food antigens, including peanut (ALK Abello, Mississauga, ON, Canada) and Duotip-Test II devices (Lincoln Diagnostics Inc., Decatur, IL, USA). A positive skin test was defined as a mean wheal diameter ≥2 mm larger than the negative control (or ≥3 mm in a sensitivity analysis). In a sensitivity analysis, we evaluated probable clinical IgE-mediated peanut allergy at 3 years, defined as: sensitization to peanut, not consuming peanut at least once per month, and having a convincing history of signs or symptoms of an allergic reaction to peanut.[27] Sensitization trajectories were ascertained among children tested at all three ages ($N = 2185$), defined as: never sensitized, transient sensitization (sensitized at 1 and/or 3, but not 5 years), persistent sensitization (sensitized at 1 and/or 3, and 5 years), or late-onset sensitization (only at 5 years). Maternal atopy was defined as a positive skin test to peanut or any of 13 inhalant allergens.

Statistical analysis

Associations were evaluated using penalized logistic Firth regression because of the small number of sensitized children in some groups. Peanut sensitization was investigated cross-sectionally at each age and longitudinally in the form of sensitization trajectories. Crude and adjusted ORs are presented, with adjusted ratios controlling for maternal atopy and study center. These covariates were chosen as potential confounders because they were associated with infant feeding practices and peanut sensitization. We formally tested the interaction between breastfeeding and maternal peanut consumption and explored this interaction in stratified analyses. To address potential reverse causality, we performed a sensitivity analysis excluding infants with a parent-reported diagnosis of atopic dermatitis before 6 months. Analyses were performed using R software (v.3.5.3) and SAS software (v.9.4).

Results

Overall, 74% of mothers were White, 77% had a postsecondary education, and 58% were atopic (Table S1); 4.3% of mothers were

https://doi.org/10.1017/S2040174420001129 Published online by Cambridge University Press

Table 1. Exposure and outcome frequencies: timing of peanut introduction, breastfeeding, and peanut sensitization in the CHILD cohort ($N = 2759$)

	n (%)	*n* (%) breastfeeding at time of introduction
Timing of peanut introduction		
<6 months	48/2759 (1.7)	30 (62.5)
6–9 months	325/2759 (11.8)	212 (65.2)
9–12 months	619/2759 (22.4)	303 (48.9)
>12 months	1767/2759 (64.0)	–
Peanut exposure groups*		
Avoided >12 months	1767/2759 (64.0)	
Introduced without breastfeeding	447/2759 (16.2)	
Introduced with breastfeeding	545/2759 (19.8)	
Maternal peanut consumption		
Never or <1/month	221/2586 (8.5)	
Infrequent (1/month to <1/week)	577/2586 (22.3)	
Regular (at least 1/week)	1788/2586 (69.1)	
Child sensitization to peanut		
Peanut sensitization at each time point		
1 year	126/2708 (4.7)	
3 years	100/2460 (4.1)	
5 years	96/2328 (4.1)	
Trajectory groups**		
Never Sensitized	2047/2185 (93.7)	
Transient (early only)	57/2185 (2.6)	
Persistent (early and late)	48/2185 (2.1)	
Late Onset (late only)	33/2185 (1.5)	

Timing of peanut introduction was reported according to the time windows listed here. Breastfeeding cessation was reported more precisely, in weeks (before 3 months) or months (after 3 months).
*For 155 children, where breastfeeding cessation occurred within the time window of peanut introduction, we cannot be certain which occurred first. To be conservative, in the main analysis, we assumed these children were NOT breastfed at the time of peanut introduction. In a sensitivity analysis (Table S7), we assumed the opposite.
**Mutually exclusive, among children with skin test data at 1, 3, and 5 years; early = age 1 and/or 3 years, late = age 5 years.

sensitized to peanut and 2.3% reported a peanut allergy. The prevalence of peanut sensitization among children was 4.7% (126/2708) at 1 year, 4.1% (100/2460) at 3 years, and 4.1% (96/2328) at 5 years (Table 1).

Peanut introduction and breastfeeding

Nearly, all dyads (98%) initiated breastfeeding, and the median duration of any breastfeeding was 11 months. Introduction of peanut was rare before 6 months ($n = 48/2759$, 1.7%), and still relatively uncommon by 12 months ($n = 992/2759$, 36.0%) (Table 1). Of those who consumed peanut in the first year, about half (545/992, 54.9%) were breastfeeding at the time of peanut introduction. For subsequent analyses, infant peanut introduction was classified as: introduced early with breastfeeding ($n = 545$, 19.8%), introduced early without breastfeeding ($n = 447$, 16.2%), or avoided beyond 12 months, regardless of breastfeeding status ($n = 1767$, 64.0%).

Association of peanut introduction, breastfeeding, and peanut sensitization

As we have previously reported,[8] peanut introduction before 12 months was associated with a lower odds of peanut sensitization at 1 year. Here, we found that this protective association persisted at 3 and 5 years, especially among infants who were breastfed at the time of peanut introduction (Fig. 1 and Table S2). At 1 year, the prevalence of sensitization was 101/1734 (5.8%) among infants who avoided peanut beyond 12 months. Regardless of breastfeeding, sensitization was significantly less likely among infants consuming peanut, with 10/437 (2.3%) sensitized among those introduced to peanut early without breastfeeding (aOR 0.39; 95% CI 0.19–0.72), and 15/537 (2.8%) sensitized among those introduced to peanut early while breastfeeding (aOR 0.47; 95% CI 0.26–0.79). Over time, the prevalence of sensitization remained relatively constant in the avoidance group (5.8% at 1 year, 5.2% at 3 years, and 5.8% at 5 years) and was consistently lower among those who received peanut before 12 months without breastfeeding

https://doi.org/10.1017/S2040174420001129 Published online by Cambridge University Press

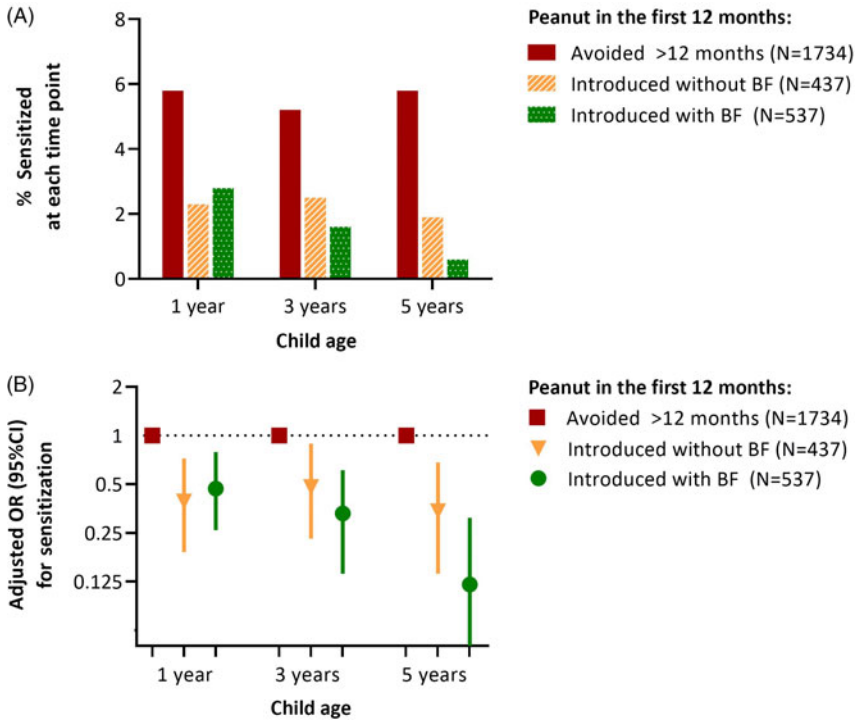


Fig. 1. (A) Frequency and (B) adjusted odds of peanut sensitization at 1, 3, and 5 years in the CHILD cohort, according to breastfeeding status and timing of peanut introduction. BF, breastfeeding (at the time of peanut introduction). Associations are adjusted for maternal atopy and study site. Sensitization was determined by skin prick testing; a mean wheal diameter ≥2 mm was considered positive. The numbers of children assessed at 1, 3, and 5 years were 2708, 2460, and 2328, respectively.

(2.3%, 2.5%, and 1.9%). Notably, beginning at 3 years and especially at 5 years, the prevalence of sensitization was further reduced among children who had been introduced to peanut while breastfeeding. In this group, there was a progressive decline in sensitization prevalence over time (2.8%, 1.6%, and 0.6%) such that by 5 years of age, the odds of peanut sensitization were 88% lower than in the avoidance group (aOR 0.12, 95% CI 0.03–0.31). These associations were essentially unchanged with adjustment for duration of breastfeeding or age at peanut introduction (Table S3). Peanut sensitization was not directly associated with various other measures of breastfeeding (Table S4). Together, these results indicate that the combination of early peanut introduction while breastfeeding is important in this context.

Trajectories of sensitization

Because the apparent effect of introducing peanut while breastfeeding seemed to strengthen over time, we explored different trajectories of peanut sensitization among children who were skin-tested at all three ages (1, 3, and 5 years; Table 1). Overall, 48 children (2.1%) were persistently sensitized at 1 and/or 3 years ("early") and 5 years ("late"). A similar proportion experienced late-onset sensitization ($n = 33$, 1.5%) or were transiently sensitized only at the early time point(s) ($n = 57$, 2.6%). Thus, among the 105 children who were sensitized early, about half (57/105, 54%) "outgrew" their sensitization and tested negative at 5 years of age. Although we had limited power to study these trajectories of peanut sensitization, we observed two interesting trends (Table 2). First, among infants who were sensitized early, those who avoided peanut in the first year were less likely to outgrow their sensitization by 5 years (36/83; 43% resolution) compared to those who received peanut before 12 months (21/22; 96% resolution; regardless of breastfeeding). Second, among infants who were not sensitized early, late-onset sensitization was most common among infants who avoided peanut for the first year (26/1299, 2.0%), less common in those fed peanut early without breastfeeding (5/345, 1.4%), and least common in those fed peanut early while breastfeeding (2/436, 0.5%).

Impact of maternal peanut consumption

Finally, we assessed maternal peanut consumption. About two-thirds (69%) of mothers reported regularly consuming peanut butter or "peanuts, other nuts or seeds" (Table 1). A possible interaction was detected between maternal peanut consumption and breastfeeding at the time of peanut introduction (p for interaction = 0.059), and stratified analyses showed that these exposures were most beneficial in combination (Fig. 2, Table S5). Among infants who did not receive peanut in the first year, the prevalence of sensitization at 5 years of age was similar whether or not their mothers consumed peanuts (5.9% and 5.6% sensitization with and without regular maternal peanut consumption, respectively). Maternal peanut consumption made only a modest difference among infants who received peanut early without breastfeeding (1.2% and 2.0% sensitization with and without maternal peanut consumption, respectively). However, among infants fed peanut early while breastfeeding, the prevalence of sensitization was substantially reduced with maternal peanut consumption (0.3% and 2.3% sensitization with and without maternal peanut consumption, respectively). Similarly, the enhanced protection from breastfeeding at the time of peanut introduction only occurred among mothers who regularly consumed peanuts (0.3% and 1.2% sensitization following early peanut introduction with and without breastfeeding); this enhanced benefit was not observed among mothers who never or rarely ate peanut (2.3% and 2.0% sensitization following early peanut introduction with and without breastfeeding) (Fig. 2).

Together, our findings suggest that early peanut introduction is beneficial regardless of maternal peanut consumption, and that breastfeeding provides additional benefit if the mother is regularly consuming peanut. Neither breastfeeding nor maternal peanut consumption were associated with peanut sensitization on their

https://doi.org/10.1017/S2040174420001129 Published online by Cambridge University Press

Table 2. Peanut sensitization trajectories from age 1 to 5 years according to timing of peanut introduction and breastfeeding ($N = 2185$)

Peanut sensitization	All children	Peanut introduction groups		
		Avoided >12 months	Introduced early without breastfeeding	Introduced early with breastfeeding
Overall trajectories*	2185	1382	355	448
Never sensitized	2047 (93.7)	1273 (92.1)	340 (95.8)	434 (96.9)
Transient sensitization (early only)	57 (2.6)	36 (2.6)	9 (2.5)	12 (2.7)
Persistent sensitization (early and late)	48 (2.1)	47 (3.4)	1 (0.3)	0 (0.0)
Late onset (late only)	33 (1.5)	26 (1.9)	5 (1.4)	2 (0.4)
Five-year outcome if sensitized early	105	83	10	12
Remained sensitized at 5 years ("Persistent")	57/105 (54.3)	47/83 (56.6)	1/10 (10.0)	0/12 (0.0)
No longer sensitized at 5 years ("Resolved")	48/105 (45.7)	36/83 (43.4)	9/10 (90.0)	12/12 (100.0)
Five-year outcome if NOT sensitized early	2080	1299	345	436
Developed sensitization by 5 years ("Late Onset")	33/2080 (1.6)	26/1299 (2.0)	5/345 (1.4)	2/436 (0.5)

Values are *n* (%) or *n*/*N* (%).
*Early = age 1 and/or 3 years; late = age 5 years.
$N = 2185$ children with skin test data for peanut at 1, 3, and 5 years.

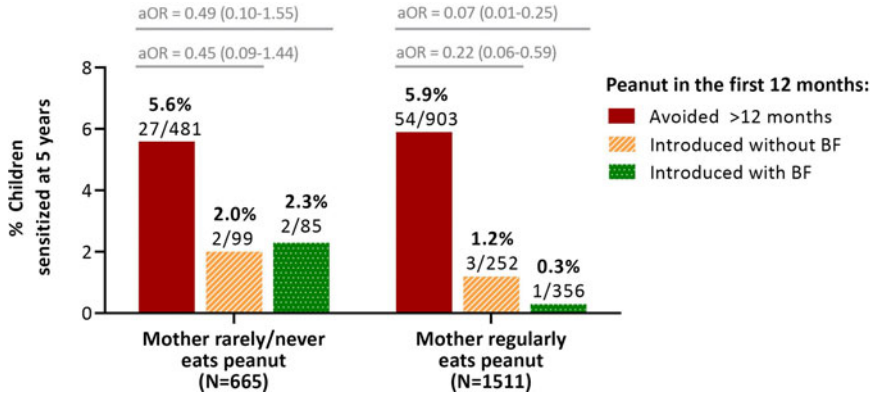


Fig. 2. Frequency of peanut sensitization at 5 years in the CHILD cohort, according to breastfeeding status and timing of introduction, stratified on frequency of maternal peanut consumption. BF, breastfeeding (at the time of peanut introduction). Adjusted for maternal atopy and study site. "Regularly" = at least once per week.

own (i.e., without accounting for each other and the timing of peanut introduction) (Table S4), emphasizing the importance of these three exposures in combination.

Sensitivity analyses

Results were similar in several sensitivity analyses using a less conservative definition to classify breastfeeding status at the time of peanut introduction, using an alternative cutoff (≥3 mm wheal) for sensitization, and excluding mothers with peanut allergy or infants with atopic dermatitis diagnosed before 6 months (Table S6). Results were also similar using probable peanut allergy as an alternative outcome to sensitization at 3 years (Table S2). Results for maternal peanut consumption were consistent after excluding mothers with unclear peanut consumption due to the questionnaire wording of "peanuts and other nuts" (Table S7).

Discussion

In the general population CHILD cohort, we found that peanut introduction before 12 months was associated with a 50%–70% lower risk of peanut sensitization throughout early childhood. At 1 year, this association appeared to be independent of breastfeeding. However, by 5 years, the risk was further reduced if the infant was breastfed at the time of early peanut introduction and the mother regularly consumed peanuts. Longitudinal analyses revealed that these associations were driven by higher odds of outgrowing early sensitization and lower odds of late-onset sensitization. Together, these findings highlight the value of longitudinal studies in evaluating trajectories of allergy development, and identify breastfeeding as an important focus for allergy prevention efforts.

Taken together and building on previous evidence, our results support a "triple exposure" hypothesis (Fig. 3): first, breastfeeding facilitates transmission of immunomodulatory factors in mother's milk (Exposure 1). If the mother is regularly consuming peanut, breastfeeding also provides oral exposure to peanut antigens or peanut immune complexes in breast milk, beginning at birth and throughout lactation (Exposure 2), which could "prime" the developing immune system for direct peanut oral exposure later in infancy. Peanut exposure may also occur in utero and/or through postnatal environmental exposures when the mother is

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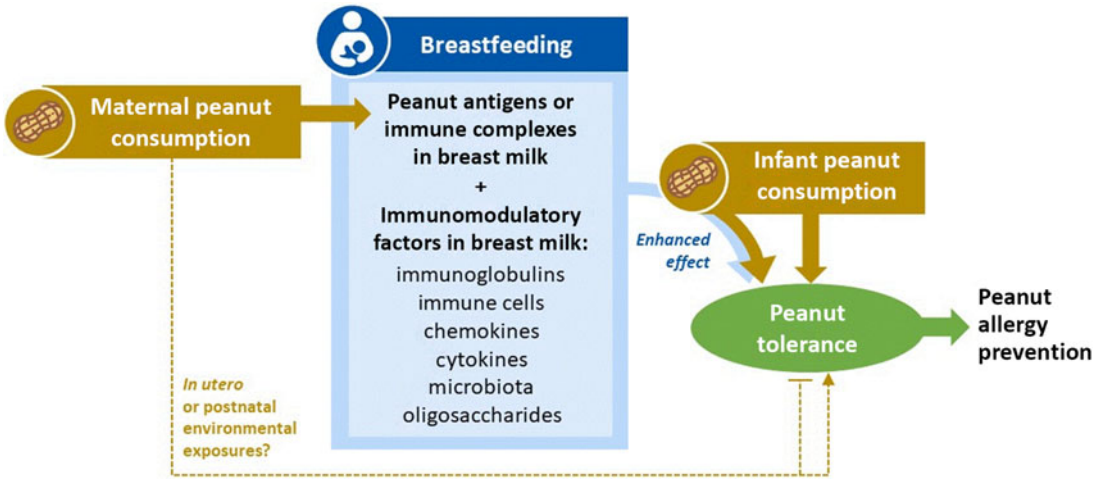


Fig. 3. Triple exposure hypothesis for the combined effects of maternal peanut consumption, breastfeeding, and infant peanut consumption in the prevention of peanut allergy. Breastfeeding (Exposure 1) facilitates exposure to immunomodulatory factors in mother's milk. If the mother is regularly consuming peanut (Exposure 2), breastfeeding further provides oral exposure to peanut antigens, beginning at birth and throughout lactation. Peanut exposure may also occur in utero and/or through postnatal environmental exposures when the mother is regularly consuming peanut, which could promote or prevent tolerance. Peanut introduction during infancy (Exposure 3) promotes peanut tolerance in all children, regardless of breastfeeding; however, this effect can be further enhanced through breastfeeding when the mother regularly consumes peanut. There is no direct effect of breastfeeding (1) in the absence of maternal peanut consumption (2) and early peanut introduction (3). All three exposures are required for optimal development of tolerance and prevention of peanut allergy. Further research is needed to refine and test this hypothesis.

regularly consuming peanut; these pathways were not studied in our analysis but warrant further investigation. Finally, peanut introduction during infancy (Exposure 3) promotes peanut tolerance regardless of breastfeeding; however, this effect is enhanced through breastfeeding when the mother regularly consumes peanut. We found no direct effect of breastfeeding in the absence of maternal peanut consumption and early peanut introduction, suggesting that all three exposures are required for optimal development of tolerance and prevention of peanut sensitization.

Our findings could help explain why previous studies have failed to demonstrate a clear impact of breastfeeding on food allergy development. In a systematic review, Lodge *et al.*[12] found no consistent evidence of this association; however, none of the included studies assessed the interaction of breastfeeding with maternal diet or timing of allergenic food introduction. Consistent with Lodge *et al.*, we found that breastfeeding was not directly associated with peanut sensitization when these factors were ignored. However, when we accounted for them, significant associations emerged: breastfeeding was associated with less peanut sensitization if the mother regularly consumed peanuts and introduced peanut to her infant before 12 months.

Further, our results may help explain the mixed evidence for maternal peanut consumption and peanut allergy in offspring. A case-control study by DesRoches *et al.* ($N = 403$ infants <18 months with or without peanut allergy diagnosis)[28] identified maternal peanut consumption as a risk factor for peanut allergy, and another study by Sicherer *et al.* ($N = 503$ high-risk infants aged 3–15 months)[29] found that maternal peanut consumption during pregnancy (although not during lactation) was associated with higher peanut IgE in offspring. However, these retrospective studies were limited by potential recall bias. By contrast, in the prospective general population GUTS2 cohort ($N = 8205$ children followed to age 13 years), Frazier *et al.* found that maternal peri-pregnancy peanut or tree nut consumption was protective against physician-diagnosed peanut or tree nut allergy,[26] although this was not replicated for peanut allergy by Lack *et al.* in the general population ALSPAC cohort ($N = 12{,}090$ children followed to age 38 months).[30] However, both cohorts were established in the early 1990s when peanut avoidance was common, and neither study assessed the potential interaction between maternal peanut consumption, breastfeeding, and the timing of peanut introduction to offspring. To our knowledge, ours is the first study to evaluate these exposures simultaneously, finding that all three are relevant in combination.

Our findings underscore the value of utilizing prospective, longitudinal cohorts to explore how breastfeeding impacts food sensitization and may contribute to food allergy prevention efforts. The importance of breastfeeding at the time of peanut introduction was not apparent at the 1-year assessment; this interaction emerged at 3 years and strengthened further by 5 years, suggesting a "programming" effect on the immune system that persists long after the period of exposure during infancy. A similar phenomenon was recently reported for egg allergy, where breastfed children had a lower risk of egg allergy at 2.5 years (but not at 1 year), if their mother's milk contained detectable levels of ovalbumin.[31] Further, while the overall proportion of sensitized children was relatively constant over time, trajectory analyses revealed that it was not uncommon for individual children to outgrow an early sensitization or develop sensitization later in childhood. Continued follow-up will be required to assess the clinical relevance of these early trajectories later in life, and further research is needed to explore underlying biological mechanisms.

It is important to note that while the optimal scenario appears to be "triple exposure" to maternal peanut consumption, breastfeeding, and early peanut introduction, there was no scenario in which early peanut introduction appeared "harmful." That is, even among mothers who did not consume peanut and infants who were not breastfed at the time of peanut introduction, early peanut introduction was associated with lower risk of sensitization. Thus, early peanut introduction (before 12 months) appears beneficial regardless of maternal diet or breastfeeding, but these benefits may be enhanced by breastfeeding and maternal peanut consumption. This implies that clinical recommendations for early peanut introduction need not depend on breastfeeding status or maternal

https://doi.org/10.1017/S2040174420001129 Published online by Cambridge University Press

diet but suggest that advising mothers to breastfeed and eat peanuts during this critical period could provide additional benefits beyond those provided by the current guidelines for early peanut introduction.

Strengths and limitations

The major strength of our study is the prospective design and repeated objective skin testing in a large general population birth cohort. A limitation of conducting this secondary analysis in a general population cohort is that we had relatively few cases of sensitization, limiting our statistical power in multivariable models to assess confounders. Further, 58% of the mothers in this study were atopic, which may have influenced both their breastfeeding practices and decisions around the timing of peanut introduction. Another important limitation is that we evaluated peanut sensitization rather than peanut allergy; however, it is well established that sensitization is a clinically important marker of immune dysregulation.[32–34] Since relatively few infants received peanut before 6 months of age, we could not assess the impact of introduction during this time window, and since nearly all dyads initiated breastfeeding, we could not study infants who were never breastfed. Finally, we did not document the frequency of infant peanut consumption, and we estimated maternal peanut consumption during lactation from a FFQ completed during pregnancy. However, we believe this approach was reasonable because only 2.5% of CHILD mothers reported modifying their peanut intake during pregnancy. We may have overestimated maternal peanut consumption because peanuts were not always distinguished from other nuts; however, our results were consistent in a sensitivity analysis excluding mothers where peanut intake was unclear. Finally, our study is observational and should be considered hypothesis-generating. Experimental studies are needed to test these hypotheses and inform clinical recommendations.

Conclusion

Our findings support current guidelines recommending early peanut introduction for allergy prevention and contribute new evidence that maternal peanut consumption and breastfeeding could further enhance this protective effect. Clinical and mechanistic studies are warranted to test this "triple exposure" hypothesis and characterize the underlying mechanisms. The results of such studies will have important implications for clinical practice, maternal and infant feeding recommendations, and the development of supplements or therapeutics for mothers who cannot safely consume peanut or infants who cannot be breastfed.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S2040174420001129

Acknowledgments. We are grateful to all the families who took part in this study, and the whole CHILD team, which includes interviewers, nurses, physicians, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, and receptionists. We also thank Michelle La and John Schellenberg (University of Manitoba) for assistance with the literature review and formatting.

Financial Support. The Canadian Institutes of Health Research (CIHR) and the Allergy, Genes and Environment Network of Centres of Excellence (AllerGen NCE) provided core support for the CHILD Study. This research was specifically funded by a CIHR Project Grant #156,155. This research was supported, in part, by the Canada Research Chairs program. MA holds the Tier 2 Canada Research Chair in Developmental Origins of Chronic Disease and is a CIFAR Fellow in the Humans and the Microbiome Program. SET holds the Tier 1 Canada Research Chair in Pediatric Precision Health.

Conflicts of Interest. The authors have no conflicts of interest relevant to this article to disclose.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation in Canada and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the Human Research Ethics Board at McMaster University and ethics committees at the Hospital for Sick Children, and the Universities of Manitoba, Alberta, and British Columbia.

Author contributions. Dr. Azad and Dr. Sears conceptualized and designed the study. Ms. Reyna, Mr. Dharma, and Ms. Dai carried out data analyses. Dr. Lefebvre managed the data. Dr. Becker, Dr. Mandhane, Dr. Turvey, Dr. Subbarao, and Dr. Sears designed the data collection instruments, and coordinated and supervised data collection. Dr. Simons conducted clinical data collection and contributed the peanut allergy outcome. Dr. Marshall and Mr. Tran contributed to the interpretation of results. Dr. Azad drafted the initial manuscript. All authors reviewed and revised the manuscript and approved the final manuscript as submitted. Dr. Azad agrees to be accountable for all aspects of the work.

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https://doi.org/10.1017/S2040174420001129 Published online by Cambridge University Press