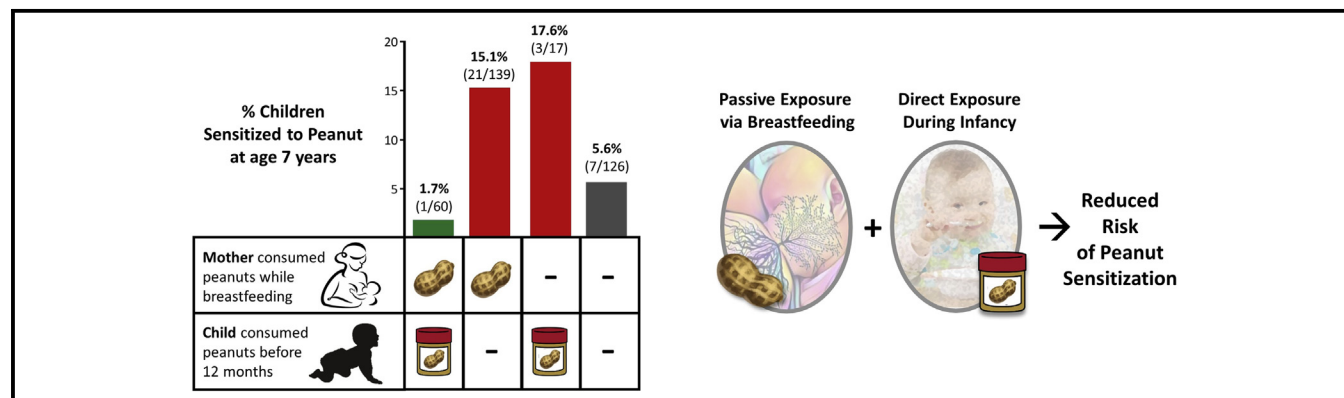


Reduced risk of peanut sensitization following exposure through breast-feeding and early peanut introduction

Tracy J. Pitt, MD,^a Allan B. Becker, MD,^{b,c} Moira Chan-Yeung, MD,^d Edmond S. Chan, MD,^e Wade T. A. Watson, MD,^f Rishma Chooniedass, MN,^{b,c} and Meghan B. Azad, PhD^{b,c}
 Toronto, Ontario, Winnipeg, Manitoba, Vancouver, British Columbia, and Halifax, Nova Scotia, Canada

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 breast-feeding 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 associated with the lowest risk of peanut sensitization, compared with all other combinations of maternal and infant peanut consumption. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

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

From ^athe Humber River Hospital, Toronto, Ontario; ^bthe Department of Pediatrics and Child Health, University of Manitoba, and ^cthe Developmental Origins of Chronic Diseases in Children Network (DEVOTION), Children's Hospital Research Institute of Manitoba, Winnipeg; ^dthe Department of Medicine, and ^ethe Division of Allergy and Immunology, Department of Pediatrics, University of British Columbia, Vancouver; and ^fthe Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia. The study was funded by the Canadian Institutes of Health Research and the Allergy, Genes and Environment (AllerGen) Network of Centres of Excellence. These entities had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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Corresponding author: Meghan B. Azad, PhD, Children's Hospital Research Institute of Manitoba, 501G—715 McDermot Avenue, Winnipeg R3E 3P4, Manitoba, Canada. E-mail: meghan.azad@umanitoba.ca.

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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

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.¹⁶ 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.

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.

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

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