

It's Not Mom's Fault

Prenatal and Early Life Exposures that Do and Do Not Contribute to Food Allergy Development



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KEYWORDS

• Food allergy • Food allergy prevention • Peanut allergy

KEY POINTS

- The most effective preventative strategy to date has been early allergenic solid introduction, in particular egg, peanut, and (potentially) cow's milk.
- There is insufficient evidence to support use of hydrolyzed formula as a means of allergy prevention.
- Early skin moisturization may be effective for eczema prevention in infancy (which by extension may have a role in food allergy prevention).
- Studies on vitamin D, omega 3, and probiotic supplementation; breastfeeding; early dietary diversity; and maternal peanut ingestion during pregnancy and breastfeeding are inconsistent.

INTRODUCTION

Food allergy is estimated to affect 2% to 10% of the population worldwide, and there has been an increase in food allergy prevalence over time.¹ Some food allergies, such as peanut allergy, are rarely outgrown.² In addition, food allergy has a very significant effect on quality of life.³ As a result, there has been an increasing focus on food allergy prevention.

There are several genetic risk factors associated with the development of food allergy, such as a family history of atopy, genetic polymorphisms, sex, and ethnicity.⁴

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However, it is also thought there are environmental factors that may contribute to food allergy development, thus opening the door for allergy prevention.

The goal of this article is to review prenatal and postnatal environmental exposures that may have a role in food allergy prevention and review the evidence that supports (or refutes) the use of such strategies.

COMBINED PRENATAL AND POSTNATAL EXPOSURES

Maternal Peanut Ingestion in Pregnancy and Breastfeeding

Evidence regarding peanut ingestion in pregnancy is conflicting and limited to observational studies. A systematic review on the influence of prenatal and early childhood peanut exposure in 2010 noted that the evidence was “heterogeneous” and “limited in quality” which “hindered the development of definitive conclusions.”⁵

Several retrospective studies have demonstrated an increased risk of peanut sensitization and/or allergy in childhood with increased maternal peanut ingestion. For example, a case control study of 403 infants with diagnosed peanut allergy compared with age-matched nonatopic controls found that maternal peanut consumption in pregnancy was significantly higher in the peanut allergic group (odds ratio [OR] 4.22, 95% CI 1.57–11.30).⁶ In contrast, a few studies have found no association between maternal peanut ingestion and risk of peanut allergy in childhood.⁷

Several recent observational studies have documented a decreased risk of peanut allergy with increased maternal peanut ingestion in pregnancy. For example, in contrast to previous retrospective studies, a large prospective national cohort study (Growing Up Today Study 2) of 10,907 mothers and their children documented a strong inverse association between compared peripregnancy peanut or tree nut consumption (≥ 5 times vs < 1 time per month) and physician-diagnosed peanut or tree nut allergy in childhood (OR 0.31, 95% CI 0.13–0.75).⁸

A recent secondary analysis of a nested cohort within the 1995 Canadian Asthma Primary Prevention Study also suggests that maternal peanut consumption while breastfeeding (in combination with early peanut ingestion in infancy) may reduce the risk of peanut allergy.⁹ Of 342 families within this cohort, the lowest incidence of peanut sensitization (1.7%) was observed among children whose mothers consumed peanuts while breastfeeding and introduced peanuts into the diets of their infants by 1 year of age. Incidence of peanut allergy was significantly higher ($P < .05$) if mothers avoided peanuts while breastfeeding, even if peanut was introduced directly into the infant diet by 1 year of age (17.6%).

There are several possible reasons for the discrepancies in the literature, which highlight the limitations of the studies to date. The older retrospective studies largely had an outcome of peanut sensitization, in contrast to the newer prospective studies with oral challenge-proven peanut allergy, and are limited by recall bias. Other factors (eg, atopic status; peanut consumption while breastfeeding; environmental exposure; and duration, frequency, and exposure level of antigen) may play a role.

Avoiding peanut consumption in pregnancy and breastfeeding is not without potential harms. A Cochrane Review on maternal dietary antigen avoidance during pregnancy, although not looking specifically at peanuts, found that antigen-avoidance diets were associated with a significantly lower mean gestational weight gain, nonsignificant higher risk of preterm birth, and a nonsignificant reduction in mean birth-weight, while also noting no significant reduction in atopic disease.¹⁰

Current guidelines do not recommend peanut avoidance in pregnancy or breastfeeding as a means of peanut allergy prevention.^{11,12} In the future, there may be a protective role for peanut consumption, although randomized studies are required.

Omega 3 Supplementation

Omega 3 supplementation has an antiinflammatory role through eicosapentaenoic acid, which has been postulated to have an effect on the risk of food allergy. However, studies to date have conflicting results. Some studies on omega 3 supplementation have looked specifically at supplementation in pregnancy, whereas others have looked at the antenatal and postnatal period as well.

For example, the Docosahexaenoic Acid to Optimize Mother Infant Outcome (DOMInO) study randomized 706 pregnant mothers to fish oil capsules from 21 weeks gestation until birth or to placebo (vegetable oil capsules) and found no significant difference in food allergy at 1 year of age between the omega-supplementation and control groups (absolute risk reduction 0.70, 95% CI 0.45–1.09, $P = .12$).¹³

A systematic review and meta-analysis of omega 3 and 6 oils for primary prevention of allergic disease found “no clear evidence of benefit” for reduced risk of allergic sensitization (risk ratio [RR] food allergy 0.51, 95% CI 0.10–2.55).¹⁴ In contrast, a more recent systematic review and meta-analysis on diet during pregnancy and risk of allergic disease found that, based on 6 studies, fish oil supplementation during pregnancy and lactation may reduce risk of egg sensitization (RR 0.69, 95% CI 0.53–0.90).¹⁰

At this time, based on conflicting evidence to date, there is no firm evidence that omega supplementation reduces the risk of food allergy.

Probiotics

The data on probiotic supplementation in pregnancy and lactation are not consistent and, to date, have not demonstrated a strong reduction in food allergy outcomes. For example, randomized trial of 1223 pregnant women to probiotics or placebo from 36 weeks gestation until birth noted no difference in atopic disease between the groups, although in the subset with caesarean-sections there was some protection against eczema noted.¹⁵

There have been some data suggesting that probiotic supplementation may have a role in prevention of eczema. For example, a randomized controlled trial of 1223 pregnant women supplemented with probiotics or placebo from 2 to 4 weeks before delivery until age 6 months in infancy found a significant reduction in eczema (OR 0.74, 95% CI 0.55–9.98, $P = .035$), although no effect on other atopic outcomes was observed.¹⁶ A meta-analysis and systematic review also noted that probiotic supplementation during pregnancy and lactation may reduce risk of eczema (RR 0.78, 95% CI 0.68–0.90).¹⁰

Limitations to the literature to date include varying intervals of probiotic supplementation, different microorganisms in the probiotics, and varying definitions of allergic outcomes (predominantly including a reliance on sensitization). At this time, as noted in a Cochrane review on the topic, there is “insufficient evidence” to recommend the addition of probiotics to infants to prevent allergic diseases or food allergy.¹⁷

POSTNATAL EXPOSURES

Early Moisturization

There is emerging evidence that eczema is due to skin barrier dysfunction and that food sensitization can occur through the skin.¹⁸ Mutations in the filaggrin (FLG) gene (involved in skin hydration and water retention) have been strongly linked with eczema and independently with food allergy as well.¹⁹ It is hypothesized that this association may explain the concept of transcutaneous sensitization to foods.⁷

In keeping with this hypothesis, recent randomized controlled trials of infants at high risk of eczema due to parental atopy found that regular emollient therapy for the first several months of life significantly reduced the incidence of eczema compared with no emollient use.^{20,21} One of these studies looked at rates of egg sensitization as a secondary outcome and found no significantly reduced rate.²¹ In contrast, a third randomized controlled trial of twice daily ceramide emollient application for the first 6 months of life found a trend toward reduced eczema and food sensitization at both 6 and 12 months of age.²² It has been shown that emollient use decreases skin pH and increases the proportion of *Streptococcus salivarius* long-term, which may be the cause of this protective effect.²³

At this time, more long-term evidence is needed for the outcome of food allergy, but there is some preliminary evidence for eczema prevention. Moreover, early regular emollient use is a noninvasive, inexpensive intervention and, as a result, may be considered, especially in higher risk infants.

Breastfeeding

The data on breastfeeding as a food allergy prevention strategy are mixed. Some studies demonstrate a reduced risk of food allergy with breastfeeding.²⁴ Some studies demonstrate no association between breastfeeding duration and food allergy. For example, the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) noted that among 335 children there was no significant association between duration of exclusive breastfeeding and development of sensitization in the first 6 years of life (OR 0.96, 95% CI 0.84–1.10 at 6 years of age).²⁵

The limitations to the literature on breastfeeding include entirely observational studies that have nonuniform breastfeeding durations and variable diagnostic criteria for food allergy (including often relying on food sensitization). Exclusive breastfeeding for the first 4 to 6 months of age is recommended for many other reasons, although current guidelines note no consistent benefit as a means of food allergy prevention.¹¹

Use of Hydrolyzed Formula

Guidelines have recommended the use of hydrolyzed formula in high-risk infants when mothers could not, or chose not, to breastfeed as a means of food allergy prevention.^{11,12} This was partially based on a Cochrane review that noted “limited evidence” that hydrolyzed formula compared with regular cow’s milk formula reduced the risk of infant and childhood allergy and cow’s milk allergy.^{26,27}

However, a recent meta-analysis of 37 studies (>19,000 participants) noted no evidence that partially or extensively hydrolyzed formulas reduced the risk of any allergic outcomes, including food allergy, and noted a high degree of bias in published studies.²⁸

In light of this recent meta-analysis, current evidence does not support the use of hydrolyzed formulas as a means of allergy prevention. Guidelines are beginning to reflect this emerging evidence.²⁹ These formulas are also potentially expensive and not well tolerated.

Early Introduction of Allergenic Solids

Both observational and randomized controlled trials published over the last decade have supported early introduction of allergenic solids, in particular, peanut, egg, and cow’s milk, as a means of food allergy prevention.

The first study to suggest a reduction in peanut allergy with early peanut introduction was a questionnaire-based survey in 2008 that found a higher rate of peanut allergy among 5171 Jewish schoolchildren in the United Kingdom compared with 5615

Jewish schoolchildren in Israel (1.85% vs 0.17%, $P < .001$).³⁰ This reduced prevalence was attributed to earlier and more frequent peanut ingestion in the first year of life in Israel compared with the United Kingdom. This study was followed by the Learning Early About Peanut (LEAP) study of 640 infants with either severe eczema and/or egg allergy that demonstrated that early peanut introduction between 4 to 11 months of age reduced the risk of peanut allergy by up to 81% compared with avoidance until 5 years of age.³¹ The LEAP study noted a preventative effect in both skin-test negative infants (13.7% vs 1.9%, $P < .001$) and skin-test positive infants (35.3% vs 10.6%, $P = .004$), supporting early peanut introduction as a means of both primary and secondary prevention.

The data on early egg introduction are more mixed. The HealthNuts observational study noted that among 2589 infants introduction of eggs at 4 to 6 months of age was associated with a lower prevalence of egg allergy compared with later introduction in both high-risk infants (adjusted OR [aOR] 1.6 for introduction at 10–12 months and 3.4 for introduction after 12 months) and lower risk infants (OR 3.3, 95% CI 1.1–1.9 at 10–12 months).³² In addition, the PETIT study out of Japan randomized 147 infants with eczema to introduction of heated (cooked) egg powder at 6 months of age or avoidance until 1 year and noted a significantly lower rate of egg allergy with earlier introduction (RR 0.222, 95% CI 0.081–0.607, $P = .0012$).³³ In fact, the study was so successful that it was halted prematurely.

In contrast, several randomized controlled trials examining early pasteurized raw egg introduction have either not shown a significant effect and/or have shown a high rate of adverse events. The Beating Egg Allergy Trial (BEAT) randomized 319 infants at high risk due to family history of atopic disease to pasteurized egg white at 4 months of age or placebo until 8 months of age and found a significant reduction in egg white sensitization at 1 year of age with early egg introduction (OR 0.46, 95% CI 0.22–0.95), although there was a nonsignificant trend in reduction of egg allergy and a high rate of reactions with early introduction.^{34–37} The Solids Timing for Allergy Research (STAR) trial randomized 86 infants with moderate-to-severe eczema to pasteurized raw egg introduction at either 4 months or avoidance until 8 months, with an outcome of egg allergy at 1 year of age. There was a nonsignificant trend toward lower rates of egg allergy in the early introduction group (33%) compared with the control group (51%); relative risk 0.65, 95% CI 0.38–1.11, $P = .11$), although a high rate of allergic reactions (31%) were noted upon early introduction. It has been postulated that the marked differences in study results may be attributed to the form of egg introduced because studies on early cooked egg introduction have found early ingestion to be protective, whereas studies on early raw egg introduction have either found no significant protective effect and/or a high rate of reactions.

A recent meta-analysis and systematic review of timing of allergenic food introduction and risk of allergic disease found that there was moderate-certainty evidence (5 trials, 1915 participants) that early egg introduction at 4 to 6 months of age was associated with reduced egg allergy (RR 0.56, 95% CI 0.36–0.87) and moderate-certainty evidence (2 trials, 1550 participants) that early peanut introduction at 4 to 11 months of age was associated with reduced peanut allergy (RR 0.29, 95% CI 0.11–0.74).³⁸

The studies on early cow's milk introduction have all been observational and supported the potential protective role of early cow's milk introduction. A prospective study of 13,019 infants noted that regular exposure to cow's milk formula starting within the first 14 days of life was associated with a lower risk of immunoglobulin (Ig)-E-mediated cow's milk allergy compared with later exposure (OR 19.3 for introduction after 14 days of age).^{39,40} A recent analysis of the HealthNuts longitudinal,

population-based study of 5276 infants noted that early exposure to cow's milk within the first 3 months of life was associated with a reduced risk of cow's milk allergy (aOR 0.31, 95% CI 0.10–0.91) at 1 year of age.⁴¹

There have not been many studies examining the effect of early introduction of other commonly allergenic foods such as wheat, finned fish, shellfish, tree nuts, sesame, or soy. The Enquiring About Tolerance (EAT) study is the only randomized controlled trial to examine early (3 vs 6 months) introduction of multiple allergenic solids (peanut, cow's milk, sesame, whitefish, wheat, cooked egg) in general population infants.⁴² In the intention-to-treat analysis, there was no significant difference in the rate of food allergy between the early and standard introduction groups (5.6% vs 7.1%, respectively, $P = .32$), although in the per-protocol analysis there was a significant reduction in food allergy overall with early introduction (2.4% vs 7.3%, $P = .01$). In the per-protocol analysis there was a 75% reduction in egg allergy (1.4% vs 5.5%, $P = .009$) and 100% reduction in peanut allergy (0% vs 2.5%, $P = .003$) with early introduction. Compliance was a significant issue in this study (42.8% overall).

There remain many ongoing questions about early feeding, including the duration that ingestion is required to ensure ongoing tolerance. The only study thus far to examine this is the LEAP-ON study, which examined whether avoidance of peanuts for 1 year after completion of the LEAP study would increase peanut allergy rates. It demonstrated that among 550 of the original LEAP study participants, 1 year of peanut avoidance resulted in no significant increase in the prevalence of peanut allergy among participants in the early introduction group ($P = .25$).^{43,44} The optimal dose of allergen that should be ingested remains unknown, although results from the EAT study have suggested that mean weekly consumption of 2 g a week of peanuts and eggs is effective at reducing the probability of egg or peanut allergy.⁴² It remains unknown how frequently these allergens should be ingested, and very few studies have been done in general population infants. A theoretic risk has also been raised that early introduction of allergenic foods may increase the risk of non-IgE-mediated food allergy such as food protein-induced enterocolitis syndrome (FPIES).

Since the release of the LEAP study results, the National Institute of Allergy and Infectious Diseases expert panel released addendum guidelines for the prevention of peanut allergy in the United States.⁴⁵ These addendum guidelines recommend that in high-risk infants (ie, those with severe eczema and/or egg allergy), peanuts should be introduced as early as age 4 to 6 months. Other international guidelines support the introduction of other allergenic foods such as cooked egg at around 6 months but not before 4 months of age.^{29,46}

In conclusion, in high-risk infants there is level 1 evidence for earlier introduction of allergenic foods, in particular to cooked eggs and peanuts. There are observational studies that support early cow's milk introduction. Ongoing exposure is as important as age of introduction. Extrapolation from the EAT and HealthNuts studies suggest that early exposure would be effective in general population infants as well. However, significant barriers exist, in particular when considering preemptive testing before introduction (eg, overinterpretation of positive skin prick tests or specific IgE blood tests, and poor availability of infant oral food challenges).^{47–49} There remain knowledge gaps about early introduction of some allergenic foods such as tree nuts.

Dietary Diversity

Several observational studies have suggested that increased dietary diversity may reduce the risk of food allergy. For example, in 2011, a longitudinal birth cohort of 594 infant–mother pairs in the United States noted that complementary food

introduction before age 4 months reduced the risk of peanut sensitization (aOR 0.2, $P = .007$) and perhaps egg sensitization (if egg-specific IgE ≥ 0.70 kU/L was used as a cutoff; aOR 0.5, $P = .022$) at age 2 years in children with parents with allergies or asthma.⁵⁰

There are criticisms that the data on dietary diversity lack biologic plausibility. In addition, the studies vary in their definition of food diversity and outcomes are largely sensitization instead of clinical allergy. No randomized controlled trials have been done.

Although the data are few and observational, and hence no firm conclusions can be made, this is another strategy that could be considered due to general lack of harm. However, care must be taken to ensure that inclusion of a long list of diverse nonallergenic foods does not delay the introduction of allergenic foods, which are higher priority for food allergy prevention.

Vitamin D

Studies have linked less geographic or sun exposure to vitamin D to the development of food allergy. Studies have noted that with increasing distance from the equator there is increased risk of food allergy-related hospitalizations and epinephrine autoinjector prescriptions.⁵¹ Vitamin D has been shown to have innate and adaptive immune functions, including suppression of type 2 T helper cell responses. Recent evidence suggests that polymorphisms that lower vitamin D-binding protein (which increases the biologic availability of vitamin D) attenuate the association between low vitamin D levels and food allergy, and provide some biologic plausibility for the role of vitamin D in the development of food allergy.⁵²

In 2013, data from the Australian HealthNuts study of 5276 infants noted that infants of Australian-born parents who had vitamin D insufficiency were significantly more likely to have challenge-proven peanut and/or egg allergy (aOR 11.51, 95% CI 2.01–65.79 and aOR 3.79, 95% CI 1.19–12.08, respectively) and to have multiple (vs single) food allergy, than those without vitamin D insufficiency.⁵³ However, a more recent case-cohort study of 1074 infants noted no association between vitamin D

Table 1
Exposures and their contribution to food allergy prevention

Exposure	Does Contribute	Does Not Contribute	Highest Level of Evidence	Quality of Evidence
Maternal peanut ingestion during pregnancy and breastfeeding	—	+	Observational	B
Omega 3 supplementation	—	++	RCT	C
Probiotics	—	+	RCT	C
Early moisturization	++		RCT	C
Breastfeeding	—	++	Observational	B
Hydrolyzed formula	—	+++	Observational	B
Early allergenic solid introduction	+++	—	RCT	A
Dietary diversity	—	+	Observational	B
Vitamin D supplementation	—	+	Observational	B

Quality of evidence: A, further research unlikely to change this recommendation; B, further research is likely to have an impact on the authors' confidence in this recommendation; C, further research is very likely to have an important impact on the authors' confidence in this estimate of effect.⁵⁶

Abbreviation: RCT, randomized controlled trial.

insufficiency at birth or 6 months of age and food allergy prevalence (predominantly egg allergy) at 1 year of age.⁵⁴

There are limitations to the literature to date, including variations in the definition of vitamin D insufficiency, known racial differences in vitamin D absorption, the role that atopy (or atopic risk) may play, and differences in vitamin D bioavailability from supplementation versus sun exposure. To date, no randomized studies have been completed and further data are needed. Studies are ongoing, including the VITALITY study, which is the first double-blind randomized controlled trial to examine whether vitamin D supplementation in breastfed infants could decrease the risk of challenge-proven food allergy.⁵⁵ Until such time, no formal recommendation about vitamin D supplementation can be made.

SUMMARY

To date, the most effective preventative strategy has been early allergenic solid introduction, in particular egg, peanut, and (potentially) cow's milk (**Table 1**). Early skin moisturization in infancy may be effective for eczema prevention (which theoretically could then prevent food allergy) and seems to be relatively easy to implement. The data on maternal peanut ingestion in pregnancy and breastfeeding are conflicting. Studies on vitamin D, omega 3 and probiotic supplementation, breastfeeding, and early dietary diversity are inconsistent. There is lack of evidence to support the use of hydrolyzed formulas as a means of allergy prevention. It is not known at this time whether breastfeeding has any role in food allergy prevention. Ongoing studies to further delineate possible environmental modifications in pregnancy, or early infancy, may help alleviate the ongoing burden of food allergy in children.

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