

Can Food Allergy Be Prevented? The Current Evidence

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KEYWORDS

• Food allergy • Prevention • IgE • At-risk populations

The prevalence of IgE-mediated food allergy has increased in the last 2 decades, with approximately 3–6% of children in the developed world being affected^{1–6}; however, the increase in food allergy is best described for peanut allergy (PA).^{2,7,8} Although genetic factors are important in the development of food allergy,⁹ the increase in food allergy has occurred in a short period and is therefore unlikely to be the result of germline genetic changes alone. It seems plausible that 1 or more environmental exposure(s), or lack of exposure(s), may through epigenetic changes result in the interruption of the default immunologic state of tolerance to food. Strategies aimed at the prevention of food allergy are therefore required: primary prevention strategies seek to prevent the onset of IgE sensitization; secondary prevention seeks to interrupt the development of food allergy in IgE-sensitized children; and tertiary prevention seeks to reduce the expression of end-organ allergic disease in children with established food allergy.

This article highlights important conclusions of the many reviews in this field and adds to current evidence.

METHODOLOGICAL CHALLENGES

The fact that no single intervention, or combination of interventions, is able to repeatedly show a strong protective effect against food allergy reflects either on the interventions themselves or the study methods used to measure them. This section examines the methodological concerns that complicate the interpretation of these studies (summarized in **Table 1**).

A major limitation of many food allergy prevention studies lies in the study design; linked to this are the necessary ethical limitations that apply to allergy prevention, particularly when applied to the in-utero environment and in early childhood. For

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Pediatr Clin N Am 58 (2011) 481–509

doi:[10.1016/j.pcl.2011.02.002](https://doi.org/10.1016/j.pcl.2011.02.002)

pediatric.theclinics.com

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Table 1**Methodological issues known to complicate the interpretation of studies aimed at the prevention of food allergy**

Issue	Problem	Recommended Approach
Study design	Most studies in this field are observational studies	Randomized double-blind, placebo-controlled (RDBPC) trials reduce unmeasured and unknown sources of bias
Reverse causality	Early signs of suspected allergic disease (eg, eczema) may influence feeding patterns	Although challenging (and not always possible), trials should adopt RDBPC methodologies
Randomization	There are necessary ethical restraints that surround nutritional intervention studies in infancy	Breastfeeding should always be encouraged. Studies that wish to assess the effect of complementary feeding can then randomize breastfed children, from 4 months onwards and when exclusive breastfeeding no longer satisfies the infant
Blinding of dietary interventions	It may prove difficult to blind the dietary intervention/s	Some dietary interventions cannot be blinded
Determination of food allergy	Few studies make use of oral food challenges (OFCs) for the diagnosis of food allergy. The diagnosis of food allergy may therefore be inadequate both at study entry and exit. Too many studies rely on allergy testing (SPT and/or Sp-IgE) for the determination of food allergy	Aim to perform OFCs in all participants. For children who do not undergo OFCs, a priori diagnostic algorithms (which make use of the combination of history, examination, skin prick testing, and Sp-IgE) are required to reach a best possible diagnosis
Surrogate markers	IgE sensitization, eczema, asthma and rhinitis are often used as surrogate markers for food allergy	As above
Natural history of food allergy	Tolerance is anticipated for many, but not all, childhood food allergies	Account for natural remission rate of food allergy before assessing for a study effect
Nomenclature	There is insufficient consensus with respect to the terminology used for common allergic conditions, particularly in early childhood. Definitions of generic terms such as allergy or atopy are open to variability	Consensus with respect to the allergy nomenclature will facilitate research in this field
Determination of diet	The determination of food consumptions is usually by retrospective food frequency questionnaires (FFQs), which are prone to many forms of bias	Use should be made of prospective food diaries, which have been validated for context, language, and consistency

Dietary variables and measurement thereof	Few dietary analyses consider all variables; these include age of introduction, quantity ingested (individual and cumulative quantity), frequency of exposure, variability of allergens, and allergen processing and concomitant breastfeeding at time of commencing complementary feeds	Well-designed validated tools are required to accurately record all dietary variables
Definitions: weaning	Use of the term weaning is not consistent and indicates the introduction of solid foods only	WHO recommends that the term weaning should be replaced by the term complementary feeding, which incorporates any nutrient-containing food or liquid (other than breast milk) given to young children
Differing patterns of complementary feeding	Endless permutations make study effects difficult to compare (eg, many exclusively breastfed infants receive early top-up infant feeds with cow's milk formula)	Studies need to try to capture the following dietary variables: dose, timing, recurrence of exposure, variability of allergens, and allergen quality such as degree of processing
Outcome classifications	Many studies refer generically to allergy: allergic disease may encompass 1 or more of asthma, eczema, and hay fever. Definitions for each of these conditions are also open to great variability	A priori clinically validated definitions required
High-risk markers	Many studies are aimed at high-risk atopic populations; such populations are difficult to define	Studies should include entire study populations (ie, both low and high risk). At-risk populations should be defined a priori. Better at-risk markers are required
Separation of specific effects when interventions are combined	Multiple interventions are often studied at different time points. For example, probiotic administration may be administered to mother (during pregnancy and/or breastfeeding) and/or newborn infant. This strategy makes it difficult to determine the specific effect of each intervention at each time point	Preliminary proof-of-concept studies need to separate the effects of each intervention
Introduction of complementary feeds is associated with multiple variables	The early introduction of solid foods has been associated with cultural and socioeconomic factors as well as specific factors such as maternal age, formula feeding, and maternal smoking	Regression analysis should control for as many relevant confounders as possible, especially in observational studies. This strategy highlights the need for randomized controlled studies
Monitoring adherence	Monitoring of adherence to dietary interventions is difficult	Better tools for monitoring dietary adherence are required

example, strict ethical restrictions surround randomization of infants to anything but breast milk.

A second major limitation of studies in this field is the phenotypic description of food allergy. Few studies make use of food challenge diagnostic procedures; although tolerance is adequately determined by open food challenge, the gold standard for the determination of food allergy is the double-blind, placebo-controlled food challenge; these challenges are laborious and sometimes difficult to perform, particularly in young children. In addition, entry-level oral challenges cannot be performed in those children assigned to the avoidance arm of intervention studies, with the consequence that the true allergic phenotype of such infants at time of enrolment or exit from studies remains uncertain. This limitation is particularly problematic for the diagnosis of cow's milk allergy, which is a common, and frequently studied, childhood allergy.

The most frequently used surrogate marker for the determination of food allergy is the determination of IgE sensitization by skin prick test (SPT) results and/or serum specific IgE (sp-IgE) measurement. Although IgE-mediated food allergy requires a state of sensitization, most sensitized children are not food allergic. Many variables are also associated with the determination of sp-IgE and SPT, which further limit the use of this surrogate marker.

Eczema is also a commonly used surrogate, which itself has many limitations. Although eczema is strongly associated with food allergy, the 2 are not synonymous, as evidenced by studies that show an improvement in eczema but not in food allergy. Without proper study randomization it is often difficult to establish if studies that show protection against the development of eczema are showing the treatment thereof (ie, tertiary prevention, as opposed to primary prevention). Many studies do not adequately assess eczema severity; there is therefore a risk that beneficial effects are restricted to mild eczema, which runs a transient course, when compared with moderate to severe eczema. Similar limitations hold true for the use of asthma and rhinoconjunctivitis as food allergy surrogates.

Additional limitations of the surrogate markers used arise because of the inconsistencies in nomenclature used and difficulties in accurately diagnosing these conditions. For example, wheezing in infancy does not always mean that the child has asthma. Moreover, lung function is difficult to measure in infants.

There are many other limitations to studies in this field. For example, nutritional interventions are prone to both selection bias and reverse causality. Such bias may arise when atopic families (if aware of public health recommendations) are motivated to alter maternal and/or infant dietary practices. The effects of reverse causality are highlighted in various studies and for different allergic outcomes. For example, in the Avon Longitudinal Study of Parents and Children (ALSPAC) study,¹⁰ a history of an allergic reaction to peanut is associated with prolonged breastfeeding. However, when adjusted for infantile eczema by regression analysis, there was no effect of breastfeeding on the development of PA. This phenomenon is also true for asthma; Fussman and colleagues,¹¹ in a large ($n = 696$) international study, reported that reverse causation negates the finding that the consumption of cow's milk is associated with asthma, as shown by the finding that the presence of asthma in the months before assessment led to a reduction in further exposure to cow's milk. Likewise, Lowe and colleagues,¹² in a prospective birth cohort of 620 infants, reported that early symptoms of eczema prolong the duration of exclusive breastfeeding.

Childhood food allergies are dynamic, with the general trend being for resolution of many, but not all, food allergies during the first decade of life (a time course sometimes referred to as the food allergic march). Other atopic conditions such as childhood eczema and asthma also share unique natural histories. Study planning should

therefore take these natural histories into account when planning the introduction of interventions as well as when measuring potential outcomes.

The inclusion of a placebo in nutritional studies is not always practical, or safe. For example, in the LEAP (Learning Early about Allergy to Peanut) peanut intervention study¹³ a placebo snack is not used for safety reasons. If it were possible to create an equivalent peanut placebo, children consuming the placebo snack might be at risk of consuming peanut-containing foods (to which they might unknowingly be allergic). In addition to representing a major safety concern this action would nullify any immunologic consequence that may have resulted from the avoidance of peanut.

Study interventions should be safe for both mother and child. Safety concerns have nonetheless arisen in select studies. For example, dietary interventions have been noted to compromise fetal and maternal well-being,¹⁴ and probiotics have been shown to increase rates of sensitization and allergic outcomes in separate studies.¹⁵

Many interventions are introduced to both mother and child. This strategy complicates the understanding of specific study effects because it is unclear whether the immunologic effects were achieved prenatally or postnatally or whether effects should be attributed to a single or multiple factors.

The determination of dietary intake is usually performed by food frequency questionnaires (FFQs); FFQs are known to be subject to substantial forms of bias. Studies do not always make use of validated FFQs, a complex but important undertaking. FFQs do not always assess all relevant dietary variables, such as age of introduction, recurrence of exposure, quantity (single and cumulative) of exposure, variability of allergens eaten, and allergen processing. In addition, it is often difficult to disguise those questions that relate to the specific food/s of interest. Prospective food diaries are cumbersome because they demand detailed information and effort on the part of parents. It is particularly difficult to measure food allergen exposure that occurs via routes other than the oral route (eg, through an abraded skin barrier). For example, the nursing mother who ingests peanut butter is also likely to transfer this allergen to the infant through kiss and touch contact.^{16–19} In addition, it is often the nursing mother who determines consumption patterns within the household, which further increases (or decreases) the opportunity for environmental food allergen exposure to foods that the mother likes (or dislikes). A different problem arises if the intervention is one of avoidance, because the elimination of 1 or more foods from the diet is likely to affect the diet. Such changes may be anticipated and therefore measured, or unknown and missed.

Many studies in this field are aimed at at-risk children; however, at-risk populations are difficult to define. For example, approximately 10% of children without an allergic first-degree relative develop allergic disease, compared with 20% to 30% with single allergic heredity (parent or sibling) and 40% to 50% with double allergic heredity.^{20–22} In addition, the definition of the term atopy is inconsistent.

Observational study designs (ie, most studies in this field) are particularly vulnerable to bias from both unmeasured, and unknown, sources; study hypotheses would ideally be assessed using only randomized placebo-controlled, double-blind studies.

ONSET OF SENSITIZATION AND FOOD ALLERGY

It remains unclear when prevention strategies should be implemented. Prerequisites for the development of food allergy (particularly in genetically susceptible individuals) are believed to include allergen exposure, uptake, recognition, and processing. It is therefore important to determine whether sensitization occurs in-utero or afterwards. That in-utero sensitization to foods is possible is suggested by the early detection of

sp-IgE²³ and clinical presentation of IgE-mediated food allergies within the first few days of life²⁴ (but usually within the first years of life). This finding is also true for non-IgE-mediated food-induced immunologic reactions such as colitis induced by cow's milk protein,²⁵ eosinophilic esophagitis,²⁶ and colitis induced by food protein.²⁷

The fetal immune system is sufficiently mature and able to respond to both food allergens and aeroallergens. It has also been shown that food allergens and aeroallergens can pass transplacentally. The analysis of sp-IgE to foods in cord blood has been restricted to occasional studies. Two large birth cohort studies were unable to show measurable food sp-IgE in cord blood, even in those children who subsequently developed clinical or immunologic food sensitization.^{10,28}

Summary

There is no firm evidence to support the hypothesis that sensitization and allergy to foods commences in-utero.

MATERNAL DIET (DURING PREGNANCY AND/OR BREASTFEEDING) AND THE PREVENTION OF FOOD ALLERGY

This section examines the effect of maternal diet during pregnancy and/or lactation on the development of food allergy.

There are studies that assess the effects with respect to allergy prevention through maternal dietary avoidance of 1 or more common food allergens during pregnancy and/or lactation.^{29–31} Kramer and Kakuma³² in a Cochrane review assessed the evidence for allergy prevention through prescribing an antigen avoidance diet during lactation. Three trials were included involving 209 women; findings suggest a strong protective effect of maternal antigen avoidance on the incidence of atopic eczema during the child's first 12 to 18 months of life. The investigators note the methodological shortcomings in all 3 trials and argue for caution in applying these results; in particular, the high incidence of atopic eczema in the control groups is of concern and may be explained by non-blinding or de-blinding of the examining physicians. One trial reported that a restricted diet (egg and cow's milk) during pregnancy was associated with a small but statistically significant lower mean gestational weight gain and there were trends toward increased preterm delivery and lower birth weight. Given the uncertainty of these findings, and potential safety concerns, no allergy organizations recommend the avoidance of either egg or milk during pregnancy. The American Academy of Pediatrics³³ and the UK Government Department of Health³⁴ had previously suggested that at-risk families may wish to avoid peanut; these recommendations have been withdrawn, like in many organizations that offer similar, nonrestrictive, dietary recommendations for the prevention of allergy.^{23,35–37} Two large prospective birth cohort studies, one based on the Isle of Wight, UK³⁸ and the ALSPAC¹⁰ study, showed no effect of maternal peanut consumption in pregnancy or lactation on the development of immunologic or clinical reaction to peanuts on follow-up at 4 to 6 years of age. Likewise Fox and colleagues,¹⁹ in a questionnaire-based study, found no effect of maternal peanut consumption during pregnancy or lactation. More recently, 2 studies have suggested that peanut exposure during pregnancy and lactation may be associated with higher rates of PA; however, these studies made use of less rigorous methodologies.^{39,40}

There are studies that examine the role of dietary patterns on other allergic disease outcome. For example, the protective effects against childhood wheezing associated with a Mediterranean diet⁴¹ are largely a result of dietary effects in pregnancy.⁴² In the ALSPAC UK birth cohort,⁴³ health-conscious dietary patterns were positively

associated with eczema, total IgE, forced expiratory volume after 1 second, and forced expiratory flow, and negatively associated with early wheezing and asthma. The processed dietary pattern was positively associated with early wheezing and negatively associated with atopy and forced vital capacity; however, when controlling for confounders, these effects were substantially attenuated and became nonsignificant, suggesting that in this cohort dietary patterns in pregnancy did not predict asthma and related outcomes in the offspring.⁴³

Breast milk contains low concentrations of dietary proteins, which are present in maternal serum such as gliadin,⁴⁴ peanut, β -lactoglobulin, and ovalbumin.^{45,46} β -Lactoglobulin is found in the breast milk of as many as 95% of mothers consuming cow's milk during lactation.⁴⁷ Whether at-risk infants are protected by the many beneficial immunologic properties of breast milk or put at risk by this low-dose allergen exposure is an ongoing debate. No studies have modified maternal diet during lactation only. There are studies that modify the maternal diet during both pregnancy and lactation. Neither the study by Hattevig and colleagues⁴⁸ nor the study by Herrmann and colleagues⁴⁹ reported a protective role against infant food allergy through maternal dietary avoidance of cow's milk, egg, and fish during either pregnancy or both pregnancy and lactation. However, the study by Herrmann and colleagues⁴⁹ did note effects for eczema.

Summary

There is little evidence to suggest that manipulation of the maternal diet during pregnancy and/or breastfeeding has any protective effect on the development of food allergy; preventative effects are noted for eczema. Such strategies have been shown to potentially compromise the nutritional well-being of both mother and child.

COMPLEMENTARY INFANT FEEDING AND THE PREVENTION OF FOOD ALLERGY

This section examines the effect of complementary feeding on the development of food allergy. The World Health Organization (WHO) now recommends that the term weaning be replaced by the term complementary feeding, which incorporates any nutrient-containing food or liquid other than breast milk.

Exclusive Breastfeeding Versus Mixed Feeding/Complementary Feeding

Although there is universal consensus that breast milk remains unchallenged as the milk of choice for all infants, there is conflicting advice with respect to the age at which complementary feeding should occur. Whereas most allergy/gastrointestinal opinion leaders suggest that complementary feeding may occur (if the infant is ready) from 4 months of age onwards^{23,35–37} WHO recommends that complementary feeding should occur only after 6 months of age.⁵⁰

Breast milk provides a rich and favorable source of important immune-regulating substances such as immunoglobulins, lactoferrin, lysozymes, oligosaccharides, long-chain fatty acids, cytokines, nucleotides, hormones, antioxidants, and maternal immune cells. The importance of these factors was shown by Verhasselt and colleagues,⁵¹ who investigated whether the exposure of lactating mice to an airborne allergen affects asthma development in progeny; they found that airborne antigens were efficiently transferred from the mother to the neonate through milk and that tolerance induction did not require the transfer of immunoglobulins. Breastfeeding-induced tolerance relied on the presence of transforming growth factor β (TGF- β) during lactation, was mediated by regulatory CD4+ T lymphocytes, and depended on TGF- β signaling in T cells.⁵¹ Breast milk may affect other processes capable of directly

influencing allergic disease expression such as food antigen absorption and processing. It is frustrating therefore that breastfeeding rates remain below WHO targets.

Studies that support a protective effect of breastfeeding over cow's milk formulae date back to the 1930s, when Grulee and Sanford,⁵² in a large ($n \approx 20,000$) observational study, reported a protective effect with respect to the development of eczema in the first 12 to 48 months of life. A systematic review of 12 prospective studies (8183 infants) found that exclusive breastfeeding in the first months of life is associated with reduced rates of subsequent asthma (odds ratio [OR] 0.70; 95% confidence interval [CI] 0.60–0.81).⁵³ Many, but not all, of the observational studies that followed supported these early findings. Nonetheless, there is a consensus among reviews in the field that breastfeeding offers at least some protection against the development of allergy.^{53–55} For example, Muraro and colleagues⁵⁴ suggest an overall protective effect (for at-risk children) of exclusive breastfeeding during the first 3 months of life on atopic eczema, asthma, but not childhood allergic rhinitis. Although the protective effects are most consistent for eczema, the underlying immunologic mechanisms to explain this phenomenon remain unclear. In support of those previous studies that report a protective effect of breastfeeding over asthma is the observational study from Australia by Oddy and colleagues.⁵⁶ These investigators followed a large cohort ($n = 2602$) of children (enrolled before birth) and reported a protective effect for asthma (strict diagnostic criteria used) and atopy (positive reaction to common aeroallergens) at 6 years of age. After adjustment for sex, prematurity, and maternal smoking during pregnancy, they found that exclusive breastfeeding for less than 4 months was associated with an increased risk for current asthma (ie, there is a substantial reduction in risk of childhood allergy [asthma and atopy] at 6 years of age if infants are exclusively breastfed for at least the first 4 months of life); it may also be that the benefits of breastfeeding persist into the teenage years. Saarinen and Kajosaari,⁵⁷ in an observational community-based study, reported early (less eczema and food allergy at 1–3 years of age) and late (respiratory allergy at 17 years of age) effects in infants who were exclusively breastfed for 6 months compared with those who were breastfed for 3 months or less.

No studies report a clear benefit of breastfeeding over cow's milk formula on the development of food allergy; this is true even for premature infants (with an increased gut permeability and an immature gut immune system). Lucas and colleagues,⁵⁸ in a large ($n = 777$) randomized interventional study of premature infants, compared the effect of human milk, standard preterm formula, and nutrient-enriched preterm formula. At 18 months after term there was no difference in the incidence of allergic reactions between dietary groups. However, in the subgroup of infants with a family history of atopy, those infants who received preterm formula rather than human milk had a significantly greater risk of developing 1 or more atopic conditions (notably eczema) by 18 months. Furthermore, De Jong and colleagues⁵⁹ in a large ($n = 1693$) randomized intervention study (the BOKAAL study) found that early (first 3 days of life) high-dose exposure to cow's milk (as frequently occurs in nurseries) was not associated with an increase in allergic disease or symptoms. In addition, no increase between the groups was found in sensitization or allergy to cow's milk (up to 5 years of age).

There are observational studies that controversially report an increased risk for the development of allergic disorders in breastfed infants. Sears and colleagues⁶⁰ in a large ($n = 1037$ children) observational study followed children until 21 years of age. These investigators found that breastfeeding (for at least 4 weeks) does not protect against childhood atopy and asthma. Significantly more breastfed children were atopic to common aeroallergens at age 13 years than non-breastfed children. Breastfeeding also increased the likelihood of current asthma at age 9 years and at

age 21 years. Findings were similar when breastfeeding was considered over longer periods (8–12 weeks). However, there are many criticisms of this study; these include that data for breastfeeding were retrospectively gathered when infants were age 3 years; definitions for atopic heredity included parental atopy only, hence adjustments were not made for eczema or sibling atopy. The number of exclusively breastfed children in this study was low, with nonsignificant findings when considering the effects of exclusive breastfeeding only. Likewise, Bergmann and colleagues,⁶¹ in the large Multi-centre Allergy Study observational birth cohort ($n = 1314$ infants born in 1990), found that each month of breastfeeding increased the risk of developing atopic eczema in the first 7 years by approximately 3%. It was noted that breastfeeding persisted for longer if at least 1 parent had eczema, the mother was older, did not smoke in pregnancy, and the family had a high social status. Whereas many studies report the greatest benefit for the prevention of allergies lies with at-risk groups, this study suggests that breastfeeding does not prevent eczema in children with a genetic risk. However, multiple regression analysis cannot exclude reverse causation (ie, mothers may extend exclusive breastfeeding and duration of breastfeeding once infants develop eczema). Isolauri and colleagues⁶² observed that atopic eczema in exclusively breastfed infants improved when breastfeeding was stopped, which suggests that the protective effect may be caused by the reduction in allergic disease expression (tertiary prevention) rather than primary prevention. However, this finding cannot easily be assessed because this study did not include controls to confirm that this effect was caused by the cessation of breastfeeding. Hence, these studies suggest that prolonged breastfeeding could maintain eczema, at least in some infants, and that cessation of breastfeeding acts to treat the eczema as opposed to prevent it.

As detailed earlier, there are many potential mechanisms by which breastfeeding may reduce allergic outcomes. Alternatively, breastfeeding may serve as a surrogate for other important factors, the most obvious of which is the absence of complementary feeding (see definition in earlier discussion). Prospective birth cohorts that show a preventive effect of breastfeeding on allergy report prolonged breastfeeding (>4–6 months) and late introduction of solids (>4–6 months).⁵⁴ Most studies in this field consider weaning to be the introduction of solid foods only. However, the biophysical properties of allergens are complex and there is no reason to believe that the allergenic potential of liquid feeds is different from that of solid or semisolid feeds. For example, both cow's milk and hen's egg allergy (EA) are common childhood allergies despite being ingested as liquid and solid, respectively. It is therefore arbitrary to restrict the usage of the term weaning to solids. An infant who is breastfed while receiving cow's milk formula supplementation is no more or less weaned than a breastfed infant who is fed rice cereal mixed with expressed breast milk.

Kramer and Kakuma⁶³ performed a systematic review of the available evidence concerning the effects of exclusive breastfeeding for 6 months versus exclusive breastfeeding for 3 to 4 months followed by mixed breastfeeding (complementary liquid or solid foods with continued breastfeeding) to 6 months, on eczema, asthma, and other atopic outcomes. This extensive review covers 20 independent, observational studies. These investigators were unable to establish evidence for a significant reduction in the risk of atopic eczema, asthma, or other atopic outcomes amongst those infants who were exclusively breastfed for 6 months compared with those exclusively breastfed for only 3 to 4 months followed by mixed feeding.

Summary

Evidence suggests that exclusive breastfeeding offers some protection against eczema and asthma, but not food allergy, when compared with cow's milk protein

formulas. Observational studies that report an increase in allergic disease because of breastfeeding are prone to reverse causality. Studies in this area suffer from true randomization because of necessary ethical limitations.

Cow's Milk Hydrolysates and Other Milk Formulas

The Cochrane review by Osborn and Sinn⁶⁴ found no evidence to support feeding with a hydrolyzed formula for the prevention of allergy compared with exclusive breastfeeding. For high-risk infants who are unable to breastfeed there seems to be a consensus among reviews that the use of hydrolyzed milk formula offers at least some protection against allergic disease, and in particular eczema.⁵⁴ Although these findings are reflected in recent summary papers,^{65–67} in view of methodological concerns and inconsistency of findings, Osborn and Sinn⁶⁴ recommend for future research in this field that large, well-designed trials should be used, comparing formulas containing partially hydrolyzed whey or extensively hydrolyzed casein with cow's milk formulas. One such study is the German Infant Nutritional Interventional (GINI) Study.⁶⁸ This is a large ($n = 2252$) randomized multicenter study in which Von Berg and colleagues allocated at-risk infants to 1 of 4 milks (cow's milk formula, partially or extensively hydrolyzed whey formula, or extensively hydrolyzed casein formula). Overall, a significant reduction in the incidence of atopic dermatitis was achieved in this study using the hydrolyzed formula; the preventive effect of partially hydrolyzed whey formula and extensively hydrolyzed casein formula on allergic manifestations (defined as physician's diagnosis of atopic dermatitis, food allergy/intolerance, and allergic urticaria; asthma and rhinitis were added at the later time points) and atopic dermatitis found in the 2 previous analyses at age 1 year and until 3 years have been confirmed at age 6 years in both the intention-to-treat and the per-protocol analyses.⁶⁹ The results found with extensively hydrolyzed whey formula in this 6-year analysis are interesting; until 3 years, this formula showed only a small preventive effect that never reached significance, whereas at age 6 years it showed a preventive late-onset effect on atopic dermatitis and allergic manifestations in the per protocol population similar to that of the other 2 hydrolysates and a considerable, although not significant, effect on rhinitis. The GINI study is ongoing.

Although the clinical benefits reported by the GINI study⁶⁹ are convincing, it remains unclear whether dietary modification has prevented allergic disease. The challenge in interpreting these findings lies in the relationship between eczema and cow's milk allergy, because the preventative effect of select formula may simply show tertiary prevention (ie, eczema treatment, as opposed to the prevention of eczema). The GINI study was not able to clearly define the end point of food allergy by double-blind, placebo-controlled food challenge (because many parents declined). Thus, the reduction in eczema could be caused by a true preventative effect of infant dietary modification or alternatively it could reflect the beneficial effect of removing cow's milk protein from the diet of infants with eczema and milk allergy. It is difficult to separate these effects when the study intervention (modified formula) is introduced at, or before, the expected age of onset of eczema. In addition, the GINI study does not include the findings of the breastfed infants ($n = 945$) in the analysis (because this group differed significantly from the formula-fed group).

Soy Formula and Other Mammalian Milks and the Prevention of Allergy

Soy formulas have long been used as cow's milk formula alternatives. Osborn and Sinn,⁷⁰ in a recent Cochrane review, concluded that, on current evidence, the use of soy formulae could not be recommended for the prevention of allergy or food intolerance in infants at high risk. No study reported an increase in soy allergy. There is also

no evidence to support the use of other mammalian milks for the prevention of food allergy.

Summary

There is evidence that for high-risk infants who are unable to exclusively breastfeed the use of hydrolyzed infant formula may protect against the development of allergic disease, particularly eczema. It may be that protective effects better reflect tertiary prevention (ie, reduction of disease expression in infants with preexisting milk allergy) rather than true primary prevention. Overall, with 1 notable exception, the studies suggest a priority of an extensively hydrolyzed formula over a partially hydrolyzed formula.

Complementary Feeding (with Solid Foods)

Before 2001, WHO recommended that infants be exclusively breastfed for between 4 and 6 months, with the introduction of complementary foods thereafter. In 2001, after expert consultation and the systematic review by Kramer and Kakuma,⁶³ the recommended period of exclusive breastfeeding was extended to the first 6 months of life. Advice in this regard is conflicting, with other allergy organizations recommending exclusive breastfeeding for between 4 and 6 months. Since 1975, there has been a significant trend in developed countries for the later introduction of solid foods. For example, in the United Kingdom, the proportion of infants given solids by 8 weeks of age decreased from 49% in 1975 to 24% in 1980 and 1985 and 19% in 1990.³⁴ This decrease has coincided with a 3-fold increase in allergy in children. Reasons for differences in complementary feeding are complex and early weaning has been associated with cultural and socioeconomic factors, as well as specific factors such as maternal age, formula feeding, and maternal smoking. All of these factors need to be controlled for in study analyses.

A review of the evidence of the relationship between the early (defined as <4 months of age) introduction of solid foods to infants and the development of allergic disease was recently performed by Tarini and colleagues.⁷¹ Thirteen studies met their criteria for review, of which only one was controlled. Studies were not limited to at-risk study populations. These investigators conclude that there is insufficient evidence to suggest that, on its own, the early introduction of solids to infants is associated with an increased risk of asthma, food allergy, allergic rhinitis, or animal allergies. Tarini and colleagues note the consistent association between the persistence of eczema and the introduction of solid foods before age 4 months that is supported by long-term follow-up studies and the dose-dependent nature of the association.

Reverse causality has been proposed as an explanation for many of the study findings in this field. There are 2 studies that may be less severely affected by the effects of reverse causality. The first study by Fergusson and colleagues⁷² was performed in New Zealand in 1977 (ie, before the publication of WHO weaning recommendations); feeding practices would not therefore have been influenced by these recommendations. These investigators report a 2.9-times greater risk of chronic or recurrent eczema amongst children fed 4 or more solids before 4 months of age compared with those not fed solids before 4 months of age. This difference was still apparent at 10 years of age. However, individually, exposure to cow's milk, egg, cereals, vegetables, meat products, or fruit did not increase the risk for the development of atopic dermatitis.⁷² Zutavern and colleagues⁷³ studied a large population-based, multicenter cohort; they controlled for the effects of reverse causality and assessed the effect of early life diet on allergy outcomes. No measurements were made for sensitization to foods or food allergy. There was no evidence for a protective effect of late introduction of solids on the development of preschool wheezing, transient wheezing, atopy, or

eczema. On the contrary, there was a statistically significant increased risk of eczema in relation to late introduction of egg and milk. The late introduction of egg was also associated with a nonsignificant increased risk of preschool wheezing.

A common finding in these studies is that the introduction of 4 or more foods during the first 4 months of life may increase allergic outcomes but not increase risk for the development of food allergy. Whereas the influence of complementary feeding with solid foods during the fifth or sixth month of life is less clear, complementary feeding after the age of 6 months seems not to influence allergic outcomes. Why 4 or more, as opposed to 1, 2, or 3 foods, would confer an increased risk is unclear, but may simply reflect a greater opportunity for the food-allergic infant to encounter an allergen to which they are allergic. A later section covers in greater detail studies that relate to the early introduction of single common food allergens such as egg⁷⁴ and peanut.^{5,13}

Summary

Observational studies suggest that complementary feeding with 4 or more solid foods in the first 4 months of life may increase the risk of developing allergic disease (but not food allergy). There is no evidence that delaying the introduction of solid foods beyond 4 months of age is protective, and some evidence suggests that the delayed introduction of solids may promote allergies.

COMBINED MATERNAL AND INFANT DIETARY MEASURES AND THE PREVENTION OF FOOD ALLERGY

It seems intuitive that of all interventions aimed at the prevention of food allergy the combined approach should offer the greatest hope because it covers the many routes of allergen exposure at times of immune vulnerability and pliability. The past 2 decades have witnessed a trend to allergen avoidance, with early calls to support this⁷⁵; however, more recently many have questioned the wisdom of strict allergen modification in the diet of pregnant and breastfeeding women and the newborn diet.^{36,76–79}

Kramer and Kakuma,³² in a Cochrane review, assess the evidence for the prevention of allergic disease through maternal dietary antigen avoidance during pregnancy or lactation, or both. Their analysis finds that the prescription of an antigen avoidance diet to a high-risk woman during pregnancy is unlikely to substantially reduce her child's risk of atopic disease. These investigators warn against the potential dangerous nutritional consequences of overzealous and unsupervised dietary restrictions. However, they do acknowledge that the prescription of an antigen avoidance diet (to high-risk women) during lactation may reduce the child's risk of developing atopic eczema, but better trials are needed.

Of the existing studies in this field, 2 pioneering randomized studies adopt a multi-intervention approach (in both mother and child) with subsequent long-term blinded follow-up. Clinical assessments were robust in both these studies. Zeiger and Heller⁸⁰ report a significant reduction in milk sensitization and eczema before age 2 years but no differences for food allergy, atopic dermatitis, allergic rhinitis, asthma, any atopic disease, lung function, food or aeroallergen sensitization, or serum IgE level, at 7 years of age. The early dietary differences were almost entirely caused by cow's milk allergy, so it is not surprising that the early differences between the 2 groups were not sustained, and disappeared by 2 years of age. No difference in skin prick testing or sIgE was shown for the other food allergens tested, including peanut, which was the most common skin- test-positive food allergen at 7 years of age, indicating that the beneficial effect of the dietary interventions was mainly in reducing allergy to cow's milk.

Arshad and colleagues³⁸ also reported that allergic disease (asthma, atopy, rhinitis, eczema) could be reduced, at least for the first 8 years of life, by combined food and house dust mite allergen avoidance in infancy. These investigators recruited infants at high risk of atopy and randomized them to either a prophylactic ($n = 58$) or control ($n = 62$) group. Infants in the prophylactic group were either breastfed (with the mother on a low-allergen diet) or given an extensively hydrolyzed formula. The control group followed standard UK Department of Health advice. Repeated measurement analysis, adjusted for all relevant confounding variables, confirmed a preventive effect on asthma, atopic dermatitis, rhinitis, and atopy. The protective effects were primarily observed in the subgroup of children with persistent disease (symptoms at all visits) and in those with evidence of allergic sensitization. Study powering did not allow for the assessment of food allergy at 8 years of age, but earlier transient effects show some protection, at least for cow's milk allergy. The specific preventative contribution of the dietary and aeroallergen interventions is unclear.

Summary

There are randomized trials that adopt a multi-intervention approach (ie, dietary modification of both maternal diet during pregnancy and lactation and infant diet) that report a reduction in allergic disease. Although findings in 1 study were transient and no longer observed at 7 years of age, in a second study the effects in allergy reduction were still observed at 8 years of age. The effects with respect to a reduction in food allergy seem to predominantly apply to cow's milk allergy. Caution is required before the recommendation of such interventions because of the potential for nutritional compromise in both mother and child.

ROUTES OF SENSITIZATION, CROSS-SENSITIZATION, ORAL TOLERANCE INDUCTION, AND INTERVENTIONAL STUDIES IN THIS FIELD

Sensitization Through the Skin

Until recently, preventive strategies focused on oral exposure to foods. However, the oral route of exposure is not the only route because exposure to food allergens may occur through aerosolized allergen exposure (eg, fish and milk cooking vapors) or via the skin.^{16–18}

In animal models, the application of egg white^{81,82} and peanut⁸³ onto abraded skin has led to IgE sensitization. These observations support the occupational health findings in humans that sensitization may occur through contact with the skin, particularly through abraded skin.

The ALSPAC study¹⁰ followed a large cohort of children ($n = 13,971$) from birth. The results of this study show a positive association between PA and eczema, and an even greater association with an oozing or crusting skin rash. There was an increased use of preparations using peanut oil in children with PA; almost 91% of the children with PA had been exposed topically to creams containing *Arachis* oil in the first 6 months of life and more children with PA were exposed to significantly more preparations containing *Arachis* oil than were controls.

Although the ALSPAC study raised the possibility that exposure to low doses of peanut antigen through inflamed skin causes allergic sensitization, exposure to topical preparations may represent only 1 component of environmental exposure. For example, cutaneous contact may occur when a tolerant household member eats allergen-containing food and then touches or kisses someone naive to that allergen or when the infant touches a surface contaminated with peanut.^{16–18} After peanut butter has been consumed, there is residual detectable Ara h 1 on the hands or in saliva,

despite washing the hands or cleaning the teeth; there are thus many opportunities for an infant to experience cutaneous allergen exposure in households in which peanut-containing foods are consumed. That peanut is bioavailable after only skin contact is clear from studies showing that cutaneous exposure to peanut causes contact reactions in 33% of patients.⁸⁴ Fox and colleagues¹⁹ found that total weekly household peanut consumption during the first year of life is significantly higher for infants who developed PA than for those who did not. The median household peanut consumption is more than 10 times greater in these cases than in high-risk controls. These investigators reported a dose-response relationship between household peanut consumption and the risk of later PA that is unaffected by maternal peanut consumption during pregnancy and lactation. Furthermore, the household peanut consumption in the controls with EA is significantly lower than that of the low-risk controls. Children with EA are at high risk of developing PA, so these data suggest that reduced or absent levels of household peanut consumption may exert a protective effect.^{19,85}

Oral Tolerance Induction

There is a significant body of evidence with respect to oral tolerance induction in animal models in which a single oral dose of antigen was sufficient to induce tolerance, a phenomenon that has been reported for different antigens and in different experimental models.^{86–88} The data are consistent, uniformly showing that a single dose of oral protein administration effectively causes immunologic tolerance and prevents the expression of related clinical disease. Furthermore, oral tolerance to peanut in mice has been shown to be antigen-specific (ie, tolerizing doses of peanut did not promote tolerance to ovalbumin and vice versa).⁸⁶

In humans, 1 previous study showed a nonsignificant trend toward increased peanut consumption during pregnancy in mothers of children who developed PA.⁸⁵ Fox and colleagues¹⁹ showed a significant increase in maternal consumption of peanuts during pregnancy and lactation in mothers of children who develop PA; however, after adjusting for household peanut consumption, maternal consumption becomes insignificant. It seems the increased maternal consumption during pregnancy and lactation is merely a marker of high household peanut consumption: mothers in households with high peanut consumption are more likely to eat peanut because of its availability. However, this maternal consumption seems to be irrelevant.

Ecological data suggest that African, Asian, and Middle Eastern countries where peanuts are consumed throughout pregnancy and early childhood have low rates of PA compared with Western, industrialized societies such as the United Kingdom and United States, where PA is high despite peanut avoidance during pregnancy and infancy.^{1,5,89,90} Our cross-sectional data⁵ on the prevalence of PA and peanut consumption in the United Kingdom and Israel lends weight to the hypothesis that early and frequent oral exposure to peanut may facilitate the tolerance to peanut. Using a questionnaire-based study of 8600 schoolchildren, we found that the prevalence of PA is 10-fold higher in Jewish children in the United Kingdom compared with that seen in Jewish children in Israel (1.85% and 0.17%, respectively). These differences cannot be explained by differences in age, sex, ancestry, atopy, or socioeconomic class. After adjustment for atopy, other food allergies, age, and sex, the relative risk (RR) for PA in the United Kingdom remained high at 5.8 (95% CI 2.8–11.8), whereas the RRs for egg and milk allergy were low, at 1.3 (95% CI 0.9–1.9) and 1.8 (95% CI 1–3.1), respectively, suggesting an allergen-specific effect. The biggest difference in PA was observed in primary schools (in children aged 4–12 years), where the prevalence was 2.05% in the United Kingdom and 0.12% in Israel ($P<.001$). Even after adjustment, the RR for PA among UK primary schoolchildren

was 9.8 (95% CI 3.1–30.5). Even confining the analysis to the high-risk subgroup of children with a stringent diagnosis of eczema, the difference in PA between countries remained high (6.5% in the United Kingdom and 0.8% in Israel, $P = .024$). The most obvious difference in the diet of infants in both populations occurs in the introduction of peanut; Israeli infants are introduced to peanut during early weaning and continue to eat peanut more frequently and in higher amounts than UK infants, who avoid peanut, as per Department of Health recommendations. The difference between PA in United Kingdom and Israeli infants cannot be accounted for by differences in atopy, social class, ancestry, weaning, or methods of peanut processing in the 2 countries. These findings raise the question of whether early and frequent ingestion of high-dose peanut protein during infancy might prevent the development of PA through tolerance induction.

This study⁵ also found a greater prevalence of sesame allergy (SA) in the United Kingdom (0.79% vs 0.13% in Israel), with the latter being similar to that reported in Israel in 2002.⁹¹ The lower levels of SA in Israel could also be explained by higher consumption of sesame observed in Israeli infants. The differences in tree nut allergy between the 2 populations cannot be accounted for by differences in consumption of tree nut.

There are no interventional studies that examine the potential role of oral tolerance induction to foods in childhood. There is 1 adult human study showing that feeding keyhole limpet hemocyanin (KLH) results in immunologic tolerance to KLH antigen.⁹² Interventional studies under way that aim to further examine these associations using rigorous study designs. Examples include the National Institutes of Health/Immune Tolerance Network-sponsored interventional study (LEAP study)¹³ and the Enquiring About Tolerance (EAT) study.⁹³ The LEAP study seeks to compare 2 strategies for the prevention of PA in high-risk infants: participants were stratified into 2 groups based on SPT results for peanut: a first group with a wheal diameter of 0 mm (SPT-negative stratum, $n = 542$) and a second group with a wheal diameter of 1, 2, 3, or 4 mm (SPT-positive stratum, $n = 98$). Participants in each stratum were randomly assigned to receive a peanut-containing snack or to avoid peanut. Whereas half the infants carefully avoid peanut, the other half regularly eat peanut (6 g of peanut protein/wk). The prevalence of PA is compared at age 5 years (visit 60 months = V60) by oral challenge to peanut and is powered at 89% to detect the difference between a 9.04% rate in the avoidance group and a 2% rate in the consumption group within the negative stratum. Immunologic assays are performed to identify the mechanisms that underpin antigen-specific oral tolerance induction. Study findings are due in 2014.

The EAT study⁹³ is a randomized controlled trial testing the hypothesis that the introduction of 6 allergenic foods (cow's milk, egg, fish, wheat, sesame, and peanut) into the diet of infants from 3 months of age, alongside continued breastfeeding, results in a reduced prevalence of food allergies by 3 years of age. The study is recruiting from an unselected UK population over 2 years, with study results due in 2015.

There are observational studies to other foods that lend weight to the hypothesis of tolerance induction through early oral exposure. More than 20 years ago, Saarienen and Kajosaari⁵⁷ in a population-based observational study assessed the effect of fish and citrus consumption during the first year of life. These investigators found no difference in the cumulative incidence of fish and citrus allergy at 3 years of age between children with fish introduced early or late (after age 1 year). The reaction earlier in life of the children introduced to fish earlier suggests a delay in allergy presentation rather than protection from allergy. However, fish is not only a common food allergen but also a rich source of antiinflammatory omega-3 polyunsaturated fatty acids (PUFAs).

More recently, studies have assessed the influence between early introduction of, and allergy to, wheat and egg. Poole and colleagues⁹⁴ reported that delaying the initial exposure to cereal grains until after 6 months of age may increase the risk of developing IgE-mediated wheat allergy. Using a more stringent methodology, Koplin and colleagues recorded parental responses on infant feeding (73% response rate), and potential confounding factors, before SPT for egg white had been performed (to minimize bias in parental responses). Egg-sensitized infants were then offered an egg oral food challenge to definitively diagnose EA. Multiple logistic regression was used to investigate associations between diet and EA adjusted for possible confounding factors. Compared with the introduction at 4 to 6 months of age, introducing egg into the diet later was associated with higher risks of EA. At age 4 to 6 months, first exposure as cooked egg reduced the risk of EA compared with first exposure as egg in baked goods. Duration of breastfeeding and age at introduction of solids were not associated with EA.

There may be lessons to be learnt for the prevention of food allergy when assessing studies concerning celiac disease; although celiac disease is not an IgE-mediated allergy the disease processes are analogous in the sense that it is a gut disorder in genetically predisposed people in whom an immunologic response is raised to a commonly consumed food protein. In the last few years, epidemiologic studies have strongly suggested that the timing of the introduction of gluten, as well as the pattern of breastfeeding (ie, reduced prevalence if cereal grains introduced while still breastfed), may play an important role in the subsequent development of celiac disease.⁹⁵ An ongoing interventional study is examining this question further.⁹⁶

Summary

Recent observational and animal studies have raised the question whether sensitization to food antigens may occur via the cutaneous route. There is a body of literature (in animal models) that reports the effect of tolerance induction after early high-dose food allergen consumption. There are also observational data in humans to suggest that the early introduction of peanut, cereal grains, and egg is not associated with an increased prevalence of allergy to these foods and may possibly serve as a means of inducing oral tolerance to that protein; however, randomized interventional trials are needed to definitively answer these questions and to guide public health strategies. In the interim, international consensus does not support allergen avoidance as a strategy for the primary prevention of food allergy.

UNPASTEURIZED MILK AND THE USE OF PROBIOTICS AND PREBIOTICS

It is hypothesized that the increase in allergic disease may be caused by a relative lack of microbial stimulation of the infant gut immune system, often referred to as the hygiene hypothesis. Limited evidence for the hygiene hypothesis exists with respect to food allergy. A Norwegian birth cohort study showed that birth through a cesarean section was associated with a 7-fold increased risk of parental perceived reactions to eggs, fish, or nuts.⁹⁷ For infants whose mothers were allergic, there was also a 4-fold increased risk of confirmed EA in this study. A recent meta-analysis on the relationship between cesarean delivery and atopic outcome⁹⁸ found 6 studies that confirmed a mild effect of cesarean delivery increasing the risk of food allergy or food atopy (OR 1.32; 95% CI 1.12–0.55). One explanation is that early colonization of the infant by colonic microflora protects against the development of allergic disease. However, other explanations are possible: cesarean sections are more common in firstborns (therefore there may be a sibling effect); alternatively, the primary effect might be on reducing eczema rather than food allergy. Another possible explanation for the effect

of cesarean sections is that they are associated with high maternal age, which has been shown to be a possible risk factor for food allergy in a case-control study.⁹⁹

There are studies that investigate the role of other dietary or related immune-modulating factors associated with the anthropophosphic lifestyle and their effect on rates of allergic disease. For example, observations from rural environments suggest an inverse association between consumption of farm-produced dairy products and the prevalence of allergic disease. More specifically, Waser and colleagues¹⁰⁰ reported that the consumption of farm milk may offer protection against asthma and allergy. These associations are independent of farm-related coexposures, and other farm-produced products were not independently related to any allergy-related health outcome. Similarly, Perkin and Strachan¹⁰¹ reported that unpasteurized milk may be a modifiable influence on allergic sensitization in children. The effect was seen in all children, independent of farming status.

Other strategies have sought to alter the commensal gut flora either directly through the administration of living microorganisms (probiotics), or indirectly through the provision of nondigestible growth-enhancing substrates (prebiotics). One study assessed the effects of prebiotics on allergy prevention,¹⁰² in which 134 of 152 infants (68 in placebo, 66 in intervention group) completed the follow-up period; significant lower cumulative incidences for possible allergic outcomes such as atopic dermatitis, recurrent wheezing, and allergic urticaria in the intervention group compared with the placebo group were noted.¹⁰²

There are many studies that investigate the role of probiotics on the prevention and treatment of allergies; however, many variables are associated with such studies. For example, different probiotic strains have been studied, at different doses, and with different treatment regimens. Not all studies treat both mother (during pregnancy and/or breastfeeding) and child, and the viability of probiotic organisms is not always detailed. Hence, clinical trial results from 1 probiotic strain in 1 population cannot be automatically generalized to other strains or to different populations. There is also great variability with respect to patient groups recruited. A recent meta-analysis found evidence for the use of probiotics for the treatment of eczema, but the evidence regarding the role of probiotics for the prevention of eczema is described as weak.¹⁰³

Whether probiotic-induced microbiota changes (and associated clinical effects) persist after administration ceases remains unclear.

It has been shown that infant formulae that are fortified with prebiotics can bias the microbiota to more closely resemble that of breast milk (the so-called bifidogenic effect). The clinical correlates of these changes, at least with respect to allergy, remain unclear. Whether the many reviews in this field will yield different findings when more recent studies are included in the analyses of pooled data remains to be seen.

Summary

Observational studies suggest that the consumption of unpasteurized milk may reduce the prevalence of allergic sensitization and disease; however, there are safety concerns regarding consumption of unpasteurized milk and this cannot therefore be recommended for the prevention of food allergy. Study findings are inconsistent with respect to the use of prebiotics and probiotics for the prevention of allergy.

NUTRITIONAL SUPPLEMENTS

There are ecological observations that note geographic differences in allergy prevalence; such changes have been linked with regional dietary practices and/or environmental factors (eg, sunlight and its subsequent influence on metabolic factors). In

recent years, there has been a focus on the role of vitamins, antioxidants, and vegetables, as well as fatty acid intake, on the prevention or treatment of allergies.^{104,105}

Fatty Acids

Dietary lipids, especially n-3 and n-6 long-chain PUFAs (LCPUFA), regulate immune function, and may modify the adherence of microbes in the mucosal, thereby contributing to host-microbe interactions. Studies in this field report a positive effect with respect to the prevention of allergic outcomes (sensitization,¹⁰⁶ eczema,¹⁰⁷ and asthma¹⁰⁸). However, the outcomes are inconsistent.¹⁰⁹ For example, Dunstan and colleagues,¹¹⁰ in a small randomized controlled trial of omega-3 fatty acids administered prenatally in high dose to atopic women, reported a reduction in both hen's egg sensitization and severe eczema (at 1 year of age).¹¹¹ However, Peat and colleagues,¹¹² in a large randomized controlled trial (n = 616 children), reported only a positive allergy-preventive effect through fatty acid supplementation for the outcomes for dust mite sensitization and the atopic cough. However, the study intervention was of low dose and was introduced at only 36 weeks' gestation. In addition, many of the infants did not have direct dietary supplementation until 6 months post-natal age (ie, there was only limited perinatal intervention in this study). Oral food challenges were not performed. Kull and colleagues¹¹³ showed, after controlling for confounding factors (parental allergy and early onset eczema or wheeze), that regular fish (a rich source of omega-3 fatty acids) consumption during the first year of life was associated with a reduced risk for allergic sensitization to foods (by age 4 years). Oral food challenges were not performed. It is unclear whether such an effect could be explained by oral tolerance induction (as discussed earlier) to food proteins or whether omega-3 fatty acids could have a generic antiallergy effect. Negative study findings include those by Marks,¹¹⁴ who in a randomized, placebo-controlled trial found that a reduction in exposure to house dust mite allergens and modification of dietary fatty acids (in the first 5 years of life) did not reduce the risk of asthma or allergic disease at 5 years of age in at-risk children. These negative findings corroborate the negative results of previous studies trialing environmental modifications to reduce asthma in children.¹¹⁵ Despite these conflicting findings, many infant formulas are supplemented with LCPUFAs (such as arachidonic acid and docosahexaenoic acid). The ability of these fatty acids to exert immunologic effects has been shown¹¹⁶; however, the clinical benefits with respect to allergy outcomes require further investigation.

Vitamins

Dietary vitamins have potent immune-modulating effects.^{117,118} The most notable example of a clear epigenetic effect of a vitamin at risk of subsequent allergic disease is evident in a mouse model in which Hollingsworth and colleagues¹¹⁹ reported that folate (a dietary methyl donor) supplementation in pregnancy induces hypermethylation (silencing) of regulatory genes in lung tissue, leading to the development of allergic airway disease and associated allergic responses: this effect was also transmitted to subsequent generations. In humans, 1 study reported that folate supplements in pregnancy are associated with increased childhood wheezing¹²⁰; another found the opposite relationship.¹²¹ It has been possible to study the effect of vitamin supplementation in young children with respect to allergy outcomes, because many countries advocate routine vitamin supplementation during early childhood. Separate studies in Finland¹¹⁸ and the United States¹²² have observed an increased association between vitamin D supplementation in infancy and atopic disease. However, study outcomes were restricted to rhinitis in adulthood in the first study, and select subgroups in the second study: asthma (in black children) and food allergies (as defined by a medical

professional) in the exclusively formula-fed population. Kull and colleagues¹²³ in a large ($n = 4089$) prospective birth cohort investigated the association between the supplementation of vitamins A and D (administered in either a water-based or peanut-oil-based vehicle) during the first year of life, and the outcome of allergic disease up to 4 years of age. Children supplemented with vitamins A and D in the water-soluble vehicle during the first year of life had an almost 2-fold increased risk of asthma, food hypersensitivity (determined by parental questionnaire), and sensitization (to common food and airborne allergens) at age 4 years, when compared with those receiving vitamins in peanut oil. There are various possible explanations for these findings. Vitamin A and/or D may protect against the risk of developing allergy. The study findings then hinge on better absorption of vitamin A and D from the oil-based vehicle than from a water-based vehicle. Alternatively, vitamin A and/or D increase the risk for the development of allergy. The absorption of vitamin A and/or D then needs to be superior when the vitamins are administered in the water-based vehicle. Systemic uptake was not measured. The rates of allergy in the 2 study groups were not compared with children who had not received vitamin supplementation at all as only 2% of children in this cohort did not receive vitamin supplementation at all. It may also be that vitamin A and/or D has no effect on allergy outcomes and the effects observed are caused by the use of peanut oil. However, the fatty acids in peanut oil are strongly biased toward the proinflammatory omega-6 fatty acids in a ratio of omega-6/omega-3 fatty acids of 34:1. Were this effect to be significant, a higher rate of allergy would be expected in the group of children who received the oil-based supplement.

Vitamin D deficiency (VDD) has previously been linked with allergic disease; more specifically atopic dermatitis¹²⁴ and recurrent wheeze,^{124,125} In 2007, Camargo and colleagues¹²⁶ first implicated this deficiency as a potential risk factor for food allergy because of similar epidemiologic trends for UV-B exposure and VDD, and evidence of a striking north-south gradient in the prescription of epinephrine autoinjectors (used as a proxy for food allergy and/or anaphylaxis) in the United States. There are significant differences in UV-B exposure; levels of 25-hydroxyvitamin D (25 [OH]D) fluctuate with season (lowest in winter and highest in summer) and latitude (inversely with distance from the equator). The epinephrine autoinjector finding was recently replicated by Mullins and colleagues¹²⁷ and extended to hospitalizations for anaphylaxis in Australia; these investigators also reported similar findings using a different surrogate for food allergy, namely the use of hypoallergenic infant formulae.¹²⁸ Moreover, north-south differences in the United States have been reported for both emergency department visits and hospitalizations for food allergy.^{129,130} Several studies have described that food allergy is more commonly reported in children born in seasons of low UV-B intensity.^{131–133} Risk factors for VDD, such as obesity and race, have been associated with food allergen sensitization. For example, the prevalence of obesity (a risk factor for VDD¹³⁴ and associated with decreased bioavailability of vitamin D metabolites¹³⁵) has increased in children and adults in the past 20 years. Potentially further implicating VDD in the development of food allergy is the observation that obesity/overweight status in children between 2 and 5 years of age is a risk factor for food allergen sensitization relative to normal-weight peers.¹³⁶ In addition, characteristic racial variations in VDD (attributed to the effect of skin pigment on UV-B penetration essential for 25[OH]D synthesis) parallel food allergy and sensitization¹³⁷ because the prevalence of both conditions are highest among African Americans, followed by Hispanics and then non-Hispanic whites. The potential mechanisms for the hypothesized link between sunshine, vitamin D, and food allergy in children have been further analyzed in a review by Vassallo and Camargo.¹³⁸

More direct studies in this field need to proceed with caution, particularly during pregnancy, when fat-soluble vitamins A, D, and E have the potential to either increase or decrease disease or have other adverse effects.

Summary

Randomized controlled studies provide conflicting results with respect to LCPUFA supplementation for the prevention of allergy. Studies that show a positive effect do so for different allergic disease outcomes. Observational studies that examine the effect of vitamin A and D supplementation during the first year of life suggest an increased rate of sensitization and allergy at 4 years of age, but only when administered in water-soluble vehicles; it remains unclear why vitamin A and D supplementation in different vehicles exerts such different clinical effects. It may be that VDD, induced through decreased UV-B exposure, obesity, or factors related to ethnicity, is associated with increased food allergy or surrogates thereof; whether early life supplementation with vitamin D acts to prevent the development of allergy needs to be tested in safe randomized studies.

Antioxidants

Antioxidants such as vitamins C and E, β -carotene, zinc, and selenium are free-radical scavengers shown to decrease inflammatory processes. Recent dietary changes include decreasing intake of foods containing these compounds (eg, fresh fruit and vegetables). There are no interventional studies that assess the effect of antioxidant supplementation on the prevention of food allergy; however, ecological observations, suggest that the higher intake of fresh fruit and vegetables in certain European countries is associated with a decreased prevalence of food allergy.¹³⁹ In addition, there is preliminary evidence in children^{140,141} and adults^{142,143} to suggest that high antioxidant intake (in select subgroups) may influence respiratory diseases such as wheeze or hay fever.

Trace Elements

Low cord blood selenium and iron have been associated with a higher subsequent risk of persistent wheeze for the former and both wheeze and eczema for the latter.¹⁴⁴

Summary

Ecological observations, and preliminary studies, suggest that a higher intake of foods rich in antioxidants may confer protection against allergy outcomes. However, further randomized interventional studies are required.

NEW POTENTIAL STRATEGIES FOR THE PREVENTION OF FOOD ALLERGY

In addition to the studies detailed earlier, other approaches are being investigated to prevent the onset or progression of food allergy. Given that an abraded skin barrier such as that found in eczema may be an important route of food allergen sensitization, trials that adopt a rigorous approach to the treatment of infantile eczema are needed; Fukuie and colleagues,¹⁴⁵ using a retrospective methodology, recently explored the relationship between serum IgE levels and proactive treatment with corticosteroid creams in 45 patients with moderate to severe atopic dermatitis. In a 2-year period, 25 proactive and 20 reactive patients were followed; at baseline, their SCORAD (Scoring Atopic Dermatitis) scores were similar at 82.2 and 79.5 for proactive and reactive patients, respectively. Their serum IgE levels were 2442 and 2081 IU/mL, respectively. Serum IgE was significantly decreased in the proactive group at 24 months ($P < .01$). Moreover, the food-specific IgE levels for egg white and cow's milk

were significantly decreased in the proactive group ($P = .004$ and $P = .016$, respectively). Saprophytic mycobacteria such as *Mycobacterium vaccae* are potent type 1 immunostimulants and have also been trialed as candidates for the modulation of allergic disease. Studies into the alleviation of childhood eczema symptoms have proved disappointing.¹⁴⁶ A similar approach has also been trialed using intestinal helminthic infections. There is ongoing research into the use of novel immune-modifying agents such as vaccines and/or vaccine adjuvants. With respect to the use of adjuvants, CpG oligonucleotides might offer an alternative to conventional immunotherapy in preventing, and potentially reversing, Th2-biased immune deregulation (which leads to allergy).

SUMMARY

The natural history of food allergy suggests plasticity within the developing immune system as many common food allergies (such as egg and milk allergy) are outgrown. The switch from a state of allergy to tolerance may even occur during the first few years of life. Turcanu and colleagues¹⁴⁷ reported that the resolution of PA is accompanied by a reversal of the Th2-skewed to Th1-skewed, allergen-specific, immune response. These findings are encouraging because they raise the possibility that immune responses are susceptible to prevention strategies.

The conventional wisdom is that early exposure to allergenic food proteins during pregnancy, lactation, or infancy leads to food allergies, and that prevention strategies should aim to eliminate allergenic food proteins during these periods of immunologic vulnerability, especially in at-risk subgroups. There is some evidence to support the use of dietary interventions in at-risk pregnant and/or lactating women, but benefits are largely restricted to the outcome of mild atopic eczema and are not uniformly achieved. There is also a risk that these interventions may compromise maternal and fetal nutrition. Breastfeeding for at least the first 4 months of life offers some protection against allergic disease (eczema and asthma) but the protective effect of exclusive breastfeeding beyond 4 months of age is uncertain. For at-risk infants who are not exclusively breastfed, or who require supplementation of breastfeeding, the use of extensively hydrolyzed formula offers some protection against the development of allergy (eczema and possibly asthma). The findings of dietary interventions with products such as s LCPUFAs, antioxidants, prebiotics and probiotics, and vitamin supplementation, are unclear or inconsistent, with some having potential safety issues, and can therefore not be broadly recommended.

Future studies need to overcome the many methodological challenges detailed in this article. Better markers are required to identify at-risk populations, because not all children who develop food allergies are born to atopic families. With current advances in gene-environment interactions, future studies may be aimed at interventions of specifically defined groups of children, whose genotyping identifies them as being at risk.

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