



It is evident that a broad range of host and environmental factors interact during early development to influence patterns of immune response

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Strategies to Prevent or Reduce Allergic Disease

by Susan Prescott and Anna Nowak-Węgrzyn

Key insights

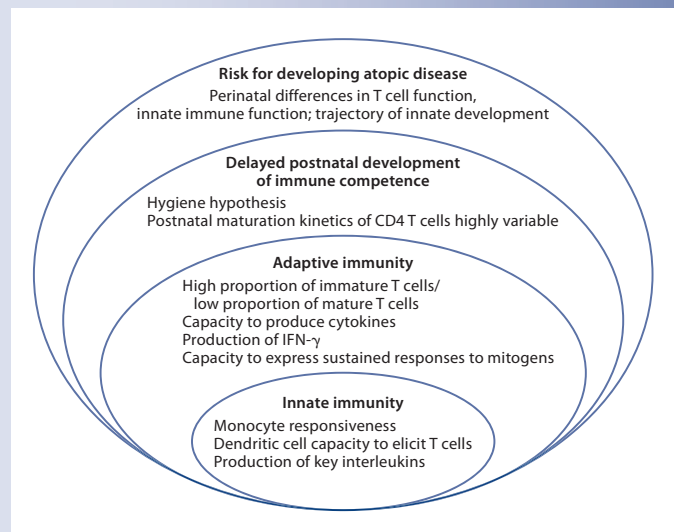
Studies suggest that certain 'western lifestyle' factors, modern dietary changes and environmental pressure are causally linked to many infant/childhood allergic diseases; however, guidelines remain limited. Prevention shifts to earlier introduction of antigens and supplementation to promote immune tolerance rather than the maintenance of overly hygienic conditions.

Current knowledge

The increasing prevalence of food allergens and differences in the disease profile require a better understanding of the triggers of immune responses, i.e. the environmental, genetic and/or epigenetic factors, so that effective prevention strategies can be derived. Little evidence supports the benefit of allergen avoidance, thus, the focus is on immunomodulatory prevention strategies. In allergy-prone children, clear differences in the early development of the immune system exist. Restoring microbial and dietary balance as well as understanding the roles of breastfeeding and hypoallergenic infant formula is the main strategy used today to reduce allergic disease and increase tolerance to allergenic foods.

Practical implications

Increasing rates of food allergy and eczema, plus the already substantial burden of asthma and respiratory allergic diseases, require a concerted long-term strategy to address these challenges. Supplementation, complementary foods and/or the early introduction of allergenic foods may play a modulatory role in allergic disease; trials are ongoing. When available, the data should support clearer recommendations.



The key components of the developing immune system and susceptibility to allergic disease (see text for details).

Recommended reading

West CE, Videky D, Prescott SL: Role of diet in the development of immune tolerance in the context of allergic disease. *Curr Opin Pediatr* 2010;22:635–641.

Strategies to Prevent or Reduce Allergic Disease

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Key Messages

- A number of factors associated with modern (westernised) lifestyle that may be causally linked with allergic disease have been identified, in an attempt to restore more favourable conditions for immune tolerance during early development.
- More hygienic conditions and disruption of microbial exposure have prompted strategies to restore this balance using probiotic and prebiotic supplements.
- Modern dietary changes linked with allergic diseases have prompted supplementation studies to assess the preventative merits of specific immunomodulatory dietary nutrients such as polyunsaturated fatty acids. Other nutrients such as antioxidants, folate and vitamin D are also currently under investigation.
- Current evidence-based guidelines for allergy prevention remain limited to avoidance of cigarette smoke, promotion of breastfeeding, the use of hydrolysed formula when breastfeeding is not possible in the first 6 months of life and introduction of solid foods between 4 and 6 months. Large, randomised clinical trials of early introduction of allergenic foods are ongoing.

Key Words

Allergy prevention · Breastfeeding · Dietary factors · Food allergens · Food allergy · Pollutants · Prebiotics · Pregnancy · Prenatal factors · Probiotics · Smoking

Abstract

The need for allergy prevention strategies has never been greater. Surging rates of food allergy and eczema are now adding to the already substantial burden of asthma and respiratory allergic diseases. The parallel rise in many other immune diseases suggests that the developing immune system is highly vulnerable to modern environmental changes. These strong environmental pressures may be one reason why simple allergen avoidance strategies have not been successful. Another more recent strategy to curtail the allergy epidemic has been to identify factors associated with modern lifestyle that may be causally linked with allergic disease, in an attempt to restore more favourable conditions for immune tolerance during early development. More hygienic conditions and disruption of microbial exposure have prompted strategies to restore this balance using probiotic and prebiotic supplements. Modern dietary changes linked with allergic diseases have prompted supplementation studies to assess the preventive merits of specific immunomodulatory dietary nutrients such as polyunsaturated fatty acids. Other nutrients such as antioxidants, folate, and vita-

min D are also currently under investigation. Modern environmental pollutants have also been associated with adverse effects on immune development and the risk of disease. While many of these avenues have provided some promise, they have not yet translated into specific recommendations. Current evidence-based guidelines for allergy prevention remain limited to avoidance of cigarette smoke, promotion of breastfeeding and the use of hydrolysed formula when breastfeeding is not possible. Allergen avoidance strategies have been largely removed from most guidelines. It is hoped that a number of ongoing studies will help provide clearer recommendations around the use of probiotics, prebiotics, specific dietary nutrients and the role of early introduction of allergenic foods for the promotion of tolerance. Despite the current uncertainties, prevention remains the best long-term strategy to reduce the growing burden of allergic disease.

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Introduction

The rise in allergic disease is fast becoming a major global health issue. While this was first evident in more developed countries of Australasia, Western Europe and North America where more than 40% of the population may be affected at some stage [1, 2], it is now also emerging in virtually all regions of the world undergoing industrial development and westernisation [3]. International trends provide some indication that environmental changes can affect immune function regardless of the genetic background. However, evidence that non-Caucasian races may be even more susceptible to allergic disease [4, 5] has alarming implications for the most populous areas of the world undergoing progressively urbanisation. Another disturbing development is the recent epidemic of food allergy in most westernised regions, most evident in preschool children [6–9]. While the ‘first wave’ of allergic disease (asthma and allergic rhinitis) gained momentum over 50 years ago, a ‘second wave’ of food allergy [10] has only emerged in the last 10–15 years [11]. This striking rise in food allergy has been most dramatic in the same countries that lead the respiratory epidemic, including the UK, Australia and the USA [6, 11, 12] where aeroallergen allergic disease has now reached a plateau or even

begun to decline [13]. Among food allergens, the most compelling evidence regarding increasing prevalence has accumulated for peanut allergy, which has been shown to triple over the past decade and is now affecting 1–2% of infants and young children in Australia, Canada, UK and the USA [8]. These temporal differences between different allergic conditions and apparent intergenerational differences in the profile of disease are still puzzling. Collectively, these observations highlight the critical importance of understanding the environmental drivers in order to design effective prevention strategies that might begin to reverse these alarming trends.

Environmental Targets for Prevention

The key to prevention is an understanding of the environmental factors driving the increasing prevalence of allergic disorders (fig. 1). Developing systems are especially vulnerable to the effects of adverse exposures, and the epidemic of allergy in early life is one of the clearest indicators that the early immune system is vulnerable to modern environmental changes. At this stage, the specific environmental factors driving this progressive vulnerability to disease have not been clearly defined, but

A better insight into disease pathogenesis and how immune development has become altered under modern environmental conditions will help identify the best candidates for effective prevention strategies.

most likely include progressively cleaner environments [14], more pro-inflammatory ‘western-style’ diets [15], environmental contaminants and pollutants [16–18], and maternal transmission of antigens during pregnancy or soon thereafter [19]. Many of these factors have been shown to modify early immune function even in pregnancy,

including maternal microbial exposure [20, 21], diet [22] and pollutants such as cigarette smoke [23]. Moreover, there is now evidence that these can modify early immune gene expression through potentially heritable epigenetic changes [18, 20, 24–27]. Therefore, these have been logical targets for disease prevention strategies.

Understanding Early Immune Development: An Important Prerequisite for Intervention Strategies

To target, optimise and predict the consequences of any intervention, it is important to have a clear understanding of early immune development. A better insight into disease pathogenesis and how immune development has be-

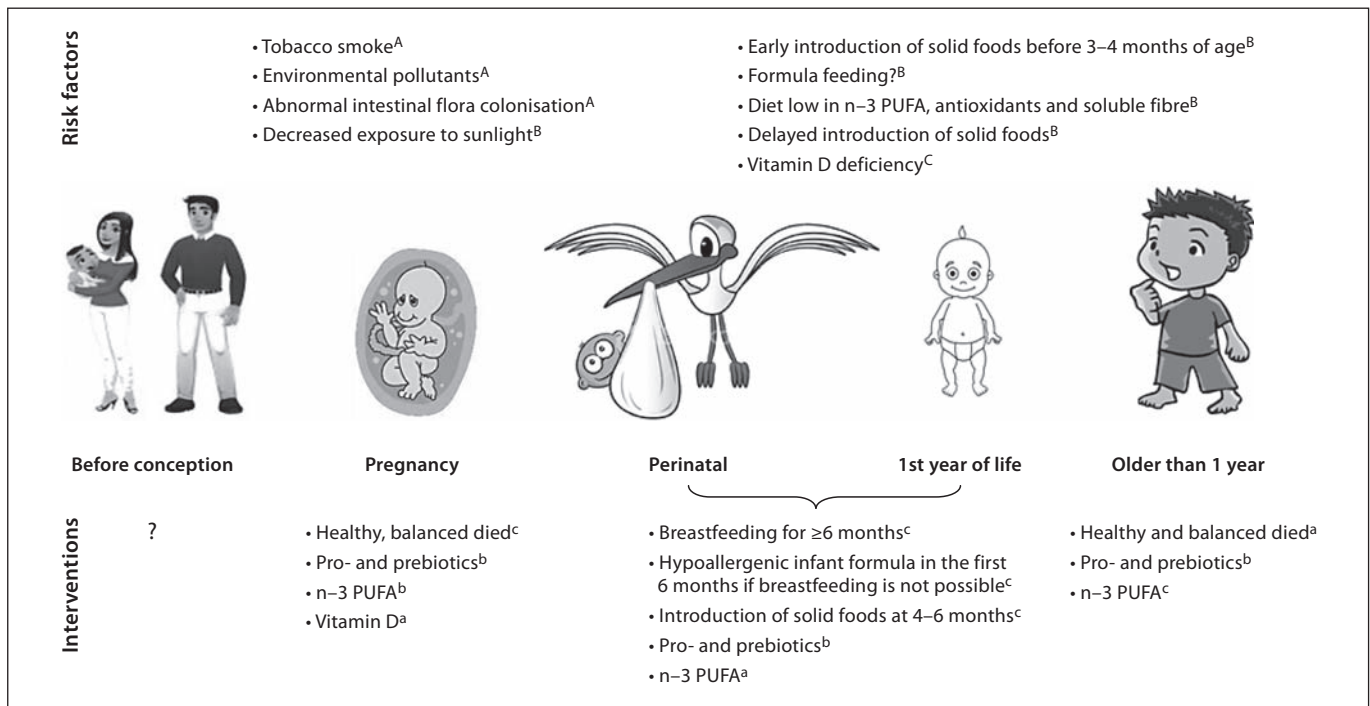


Fig. 1. Environmental modifiers in allergic disease: risk factors and preventive interventions that may alter development of food allergy and atopic disorder. Environmental pollutants = Traffic exhaust particles, polychlorinated biphenyl compounds, organochlorine pesticides, dioxins, phthalates, heavy metals. Strength of evidence for risk factors: ^A High: convincing body of evidence ex-

ists. ^B Moderate: limited evidence exists. ^C Low: needs more investigation. Strength of evidence for interventions: ^a Currently included in official guidelines. ^b Likely to be of benefit, based on growing evidence, but not yet part of recommended guidelines. ^c Requires more investigation.

come altered under modern environmental conditions will help identify the best candidates for effective prevention strategies. It may also lead to better early predictors of an allergic phenotype, which could lead to screening and more targeted early intervention. There are already a number of clear developmental differences documented in allergy-prone individuals (table 1). In the neonatal period, there is consistent evidence of pre-symptomatic differences in newborns that later develop allergic disease. Of these, immaturity of type 1 T-helper cell (Th1) function has been the most consistent observation [reviewed in ref. 28]. However, there is now preliminary evidence of attenuated T-

regulatory function [29, 30] and excessive innate inflammatory responses [31] compared with infants who remain non-allergic. These abnormalities appear to culminate in an increased propensity for uncontrolled Th2 immune responses in the post-natal period, which is associated with delayed Th1 maturation [31]. Because differences in immune function are evident at birth, there is intense interest in the prenatal factors that may be alternatively programming the developing immune system in pregnancy, particularly exposures that can disrupt normal gene activation or silencing patterns required for balanced neonatal immune responses [32, 33].

Rather, there is now increasing interest in the tolerogenic properties of allergens, and exploration of the potential preventive effects of much earlier exposure.

Pathways and Target Candidates for Prevention Strategies

Over the past decades, there has been a shift from allergen avoidance strategies towards more immunomodulatory approaches. This is because there has been little evidence that changes in allergen exposure played a significant role in the increase in allergic disease, and little

Table 1. Characteristics of the developing immune system and susceptibility to allergic disease [based on ref. 31, 116])

Adaptive immunity	Innate immunity	Delayed postnatal development of immune competence and risk for development of atopic disease
<ul style="list-style-type: none"> – High proportion of immature T cells (CD1+CD38+CD4+CD8+) – Low proportion of mature T cells CD25+CD69+ or CD154+ – In neonates: reduced capacity to express sustained responses to mitogens (due to greater susceptibility of immature T cells to apoptosis) – Reduced capacity for activation through T-cell receptors – Reduced expression of CD40 ligand by T cells – Reduced overall capacity to produce cytokines – Markedly diminished capacity of infant T cells to produce IFN-γ due to selective attenuation of IFN-γ gene expression in T cells in utero and in early postnatal life due to hypermethylation of CpG sites in the proximal promoter and reduced capacity to transcribe IFN-γ – Perinatal differences in T-cell function in children with allergic susceptibility 	<ul style="list-style-type: none"> – Neonatal monocytes are less responsive to LPS, dsRNA and bacterial lipopeptides that act through TLR2, TLR3 and TLR4 – Neonatal monocytes have reduced expression of the adapter protein MyD88 – Cord blood monocytes have impaired chemotaxis and capacity to produce TNF-α – Neonatal dendritic cells exhibit reduced antigen presentation – Neonatal dendritic cells lack the capacity to deliver polarising signals to T cells – The capacity to produce IL-12 and type I IFN is reduced at birth – Emerging differences in perinatal innate immune function in children who develop subsequent allergic disease 	<ul style="list-style-type: none"> – Maturation of the immune system is driven by contact with microbial stimuli not present within the fetal environment and is mediated through specific PRR, such as CD14 and TLR (hygiene hypothesis) – Kinetics of postnatal maturation of Th1 function of CD4 T cells are highly variable within the population – Evidence of delayed Th1 maturation in children with allergy – Emerging differences in the trajectory of innate immune development in children developing an allergic phenotype

PRR = Pathogen (microbial) recognition receptors.

evidence that avoidance approaches are effective. Rather, there is now increasing interest in the tolerogenic properties of allergens, and exploration of the potential preventive effects of much earlier exposure. Other immunomodulatory approaches focus on factors which may be causally implicated in the considerable changes in lifestyle, notably factors with both epidemiological associations with allergic disease and evidence of plausible immune mechanisms, including microbial exposure, environmental pollutants and complex dietary changes. Of considerable interest are emerging epigenetic paradigms which provide new perspectives on how these environmental factors may be producing heritable change in gene expression to increase the risk of allergic disease [20, 25, 33–36].

Prevention Strategies Aimed at Restoring Microbial Balance

As one of the leading candidates in the allergy epidemic, there has been a long-standing interest in the role of microbes as an essential stimulus for normal immune development in early life [37].

Although most of the focus has been on postnatal microbial effects, there is emerging evidence of intrauterine effects [20, 38], and new evidence that these may be conferred by epigenetic effects on gene expression [20] during critical periods of early development [36]. With increasing evidence that progressive westernisation and allergic disease are associated with disruption of the microbial ‘balance’, including altered early colonisation patterns [39, 40] and reduced diversity [41], it has been logical to attempt to restore a more optimal pattern of microflora [42]. So far, the main prevention strategies available to do this have been probiotic microbial supplements (in pregnancy and/or infancy) or prebiotic oligosaccharides (in infancy) to promote a favourable microflora in very early infancy [42]. Potential mechanisms of probiotic immunomodulation include increased synthesis of IgA and IL-10, suppression of TNF- α , inhibition of casein-induced T-cell activation and circulating soluble CD4, and toll-like receptor (TLR4) signalling [43].

Despite more than 19 randomised controlled trials (RCT; completed or in progress) to assess the effects of probiotics in allergy prevention, there are still no definitive benefits or recommendations [44]. The most recent

Table 2. The role of probiotic and prebiotics supplements in allergy prevention

Supplement	Comments
Probiotics	<ul style="list-style-type: none"> - In initial studies using <i>Lactobacillus</i> GG in a randomised human trial (159 mothers supplemented before delivery and infants supplemented for 6 months), analysis showed a 50% reduction in eczema at age 2 years; the protective effect persisted up to 7 years of age [117, 118]; the prevalent eczema was very low and not different from the probiotic-treated group - While there are a number of recognised effects of gut microflora on immune development, the mechanism of the clinical effect seen in this study is not clear; there was no effect on allergic sensitisation, or other allergic outcomes - Subsequent studies of the same strain in other populations have shown no effect [45] - The effects of probiotics are variable and appear to depend on the strain, the timing, method of administration, host and other environmental factors [reviewed in ref. 42] <p><i>Summary:</i> The revised Cochrane meta-analysis concludes that there is some evidence that a probiotic or a synbiotic containing <i>L. rhamnosus</i> may reduce the incidence of eczema in infants at high risk of allergic disease, but that there are no reproducible data for other probiotics; there is no evidence that any probiotic prevents other allergic conditions or sensitisation; they also advised caution based on methodological concerns with some of the included studies</p>
Prebiotics	<ul style="list-style-type: none"> - Initial studies using prebiotics in cow-milk-based formula showed reduced cumulative incidence of allergic outcomes in high-risk children including atopic dermatitis, recurrent wheezing and allergic urticaria in the treatment group compared with the placebo at 2 years; there were also reduced respiratory tract infections, fever episodes and antibiotic prescriptions reported [48] - Subsequent studies have also found a reduced risk of atopic dermatitis in children at low risk of allergic disease [50] - Mechanisms of effect are likely to include effects in promoting favourable colonisation with healthy commensal bacteria, as well as direct effects on the immune system [63, 64] <p><i>Summary:</i> There is encouraging evidence that prebiotics have a number of health-promoting effects, including immune effects, which may reduce the risk of allergic and infectious outcomes; the results of several large multicentre studies are awaited with interest as there are still relatively few studies to report on allergy outcomes</p>

meta-analysis [revised Cochrane review submitted; Sinn, pers. commun., July 2010) concludes that there is some evidence that a probiotic or a synbiotic containing *Lactobacillus rhamnosus* may reduce the incidence of eczema in infants at high risk of allergic disease, but that there is no reproducible evidence for other probiotics (table 2). Furthermore, the effects of *L. rhamnosus* are not seen in all studies [45]. There is also no evidence that any probiotics prevent other allergic conditions or sensitisation. They also advised caution based on methodological concerns with some of the included studies.

Wide variations in the methods, strains and protocols contribute to significant heterogeneity and further complicate the analysis and interpretation. The effects (or lack thereof) are likely to depend on the strain [46] or other

environmental and host factors that affect colonisation [43]. There is early promise in using prebiotics (non-digestible, fermentable oligosaccharides) to selectively stimulate the growth and activity of bacteria in the colon and improve host health. An initial study in high-allergy-risk infants indicated reduced cumulative incidences for possible allergic outcomes such as atopic dermatitis, recurrent wheezing and allergic urticaria compared with the placebo group [47, 48]. Another study has also reported reduced eczema in low-risk infants [49]. However, because of the paucity of

studies, at present, definitive recommendations cannot be made. Considerably more research is needed in this area to define optimal colonisation and then to understand how best to optimise it early in infancy.

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Table 3. The role of other specific nutritional supplements in allergy prevention

Supplement	Comments
n-3 PUFA (fish oil)	<ul style="list-style-type: none">- Epidemiological studies suggest dietary n-3 PUFA exposure in pregnancy [119, 120] and early childhood [54, 121] may protect against asthma and allergic disease- There are well-described immune effects of n-3 PUFA, including a range of anti-inflammatory properties [122]- RCT using fish oil in pregnancy demonstrate immunological effects [22] and some evidence of reduced allergic outcomes [61, 62, 123]- Postnatal interventions with fish oil have not shown consistent or long-term benefits [56, 57] <p><i>Summary:</i> The current findings suggest that any allergy-protective effects of increasing n-3 PUFA status are more likely to be greatest in pregnancy (i.e. earlier in development); the largest, most definitive RCT (n = 706 mothers of high-allergy-risk infants) recently found that fish oil in pregnancy was associated with a reduced risk of both eczema and egg sensitisation [123]; because of the differential effects of n-3 PUFA in the antenatal versus the postnatal period, future systematic reviews should examine these interventions separately</p>
Vitamin D	<ul style="list-style-type: none">- Based on recognized immunoregulatory effects and declining levels with more sedentary lifestyles, vitamin D has been proposed as a candidate factor in the rise in both 'autoimmune' and 'allergic' diseases [124]- Several authors have demonstrated a protective relationship between maternal vitamin D intake or status and asthma, wheezing or allergic rhinoconjunctivitis in children [125-127]; this is supported by studies showing a protective association between decreasing latitude (and by extension, likely higher vitamin D status through sunlight exposure) and allergic disease in both Australia and the US [73, 128, 129]- On the other hand, highlighting the conflicting literature, a contrary argument that relative vitamin D excess may increase the risk of allergic disease has also been proposed based on other observational [130-132] and immunological [133] studies <p><i>Summary:</i> There is a sound basis for further investigating the role of changing vitamin D status in the rising rates of immune disease; to address this more definitively, RCT are needed: several pregnancy trials are underway and the findings of these are awaited with great interest</p>

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Prevention Strategies Aimed at Restoring Dietary Balance

Modern diets differ in many respects from more traditional diets, and a number of the resulting changes in specific dietary components have been linked to the rise in allergic disease, including ω -3 polyunsaturated fatty acids (PUFA), antioxidants, soluble dietary fibre, folate and vitamin D [15]. Furthermore, there is some evidence that more traditional composite patterns of specific nutrient intakes during pregnancy such as those found in the Mediterranean diet protect against the development of allergy and may have some role in the prevention of sensitisation and asthma [50, 51]. Notably, a dietary change is one of the leading environmental mechanisms implicated in the 'epigenetic modifications' that may underpin the rise in many modern diseases, including allergic diseases [52, 53]. Animal models demonstrate that maternal diet can have epigenetic effects on immune function which predispose to an allergic phenotype [25]. This highlights that pregnancy provides an important

window of opportunity for disease prevention, and that diet may be a useful noninvasive strategy.

A range of dietary nutrients have documented effects on immune function [15]. Of these, PUFA have been the most extensively investigated in this context (table 3). Lower consumption of n-3 PUFA is a key characteristic of modern 'western' diets, which are typically rich in more pro-inflammatory n-6 PUFA. A role in the development of allergy and asthma was suggested by observations that low consumption of n-3 PUFA-rich foods (such as oily fish) was a risk factor for wheezing and asthma [54]. This raised interest in the use of fish oil as a preventative strategy to 'restore the balance' of n-3/n-6 PUFA to more traditional patterns. This approach was also supported by the recognised anti-inflammatory effects of n-3 PUFA and evidence that metabolic products of n-6 PUFA are more inflammatory than those of n-3 PUFA [reviewed in ref. 55]. However, postnatal intervention studies using fish oil have so far failed to reduce the development of allergic diseases [56-58]. Preliminary re-

sults from our ongoing ‘infant fish oil study’ also suggest no benefit of daily supplementation of fish oil from birth to 6 months on early allergic outcomes at 12 months compared with a placebo group [D’Vaz, pers. commun.]. Despite this, there has been continuing interest in the protective role of increasing maternal n-3 PUFA status in pregnancy, particularly as effects on early immune programming may be more significant in utero. Many observational studies support this [reviewed in ref. 59] with some exceptions [60], and limited data from intervention studies also suggest that benefits may be greater during pregnancy [22, 61, 62]. Several large studies are underway to hopefully clarify this more definitively.

While there has been long-standing interest in the role of other dietary factors that have changed with modern diets, few have been specifically investigated in intervention studies or RCT for allergy prevention. A key exception is soluble dietary fibre (prebiotics; as discussed above, table 2). In addition to promoting favourable colonisation, the short-chain fatty acids derived from fermentation of these products also have *direct* effects on the immune system [63, 64] with newly discovered anti-inflammatory properties [65]. This suggests that declining intake of soluble dietary fibre in more refined modern diets may be contributing directly to the epidemic of immune disease, and further explain the allergy-protective effect of prebiotics [47–49].

Other dietary factors that have been epidemiologically linked with allergic disease in observational studies include antioxidants such as vitamin C, vitamin E, β -carotene, zinc and selenium [reviewed in ref. 66], vitamin D [reviewed in ref. 67, 68] and folate [69, 70]. Vitamin D (table 3) has been attracting increasing attention due to the recent epidemiologic studies from Australia and the US that reported an association between the lower exposure to sunlight/UVB in the northern areas and anaphylaxis in children [71–73]. Birth during the winter months has been associated with a modest increase in food-induced anaphylaxis in children [74, 75]. Vassallo and Camargo [68] proposed a ‘multiple-hit’ model in which vitamin D deficiency in a developmentally critical period increases susceptibility to colonisation with abnormal intestinal microbial flora and gastrointestinal infections, contributing to abnormal intestinal barrier permeability and excess and inappropriate exposure of the immune system to dietary allergens.

To our knowledge, most of these dietary factors have not been examined in RCT to prevent allergic disease, although trials with vitamin D are in progress. Interest in many of these factors has been fuelled by evidence from animal or in vitro models demonstrating immune effects which either promote an allergic phenotype (i.e. folate [25]) or protect (i.e. vitamin D [67] and antioxidants [76]) against allergy. Furthermore, as many of these are implicated in recent dietary changes, they may be logical targets for interventions aimed at restoring ‘dietary balance’ for more favourable effects during immune development. Until more is known about the specific effects of these nutrients, it is premature to recommend any specific measures to prevent allergic disease, beyond a healthy balanced diet.

Prevention Strategies Aimed at Removing Toxins and Pollutants

Exposure to noxious agents during early development can have long-term effects on health outcomes. The best studies in the context of asthma and allergic disease focus on cigarette smoke and other respiratory pollutants such as diesel exhaust. Cigarette smoke has recognised adverse effects in pregnancy, including effects on fetal lung growth [77] and immune development [23], with increased risk of early-onset wheezing and reduced lung function in childhood [78, 79]. New studies indicate that children exposed to maternal tobacco smoke in utero may have epigenetic effects, modifying fetal gene

To our knowledge, most of these dietary factors have not been examined in RCT to prevent allergic disease, although trials with vitamin D are in progress.

expression (through aberrant DNA methylation) [34]. Similarly, high levels of maternal exposure to traffic exhaust particles have been associated with epigenetic effects (differences in gene methylation) and with the development of asthma symptoms in children [26]. Less is known about the effects of other pollutants, including heavy metals, such as nickel, cadmium, chromium and arsenic, which have been associated with epigenetic effects in rodent studies. Other modern products of industry and agriculture (polychlorinated biphenyl compounds, organochlorine pesticides, dioxins and phthalates) are highly lipid soluble and have been readily measured in breast milk, cord blood and placental tissue [80]. Interest in these contaminants stems from recognised immune effects [81], which may favour allergic Th2

responses [82]. Many of these and other contaminants have now been associated with epigenetic effects [reviewed in ref. 16], including effects on global DNA methylation patterns at the low-dose exposure found in the ambient environment [83]. Although the effects of many environmental contaminants are not well understood, it is logical to limit exposure where possible. Avoidance of cigarette smoke remains an absolute and unequivocal recommendation in pregnancy and childhood (and ultimately all ages) for improving many health outcomes.

Prevention Strategies Targeting Allergens: Avoidance or Exposure

The first, highly logical tactic to reduce the risk of allergic disease was to avoid allergens. Unfortunately, despite decades of research there is very little evidence that this approach (1) can be realistically achieved or (2) has any significant benefits. Rather, there is mounting evidence that this approach may have inadvertently contributed to an increased risk of allergic diseases [84, 85]. This appears to be true for both food allergens [84] and inhalant allergens [85].

Pregnancy and Lactation

There is conflicting evidence about the role of food allergen exposure during pregnancy and subsequent food allergy and atopic disease in the offspring. The interpretation of the data is confounded by differences in the study design and the interventions tested. A Cochrane review of 3 studies of maternal dietary avoidance of 1 or more common food allergen found a strong protective effect on the incidence of atopic eczema during the first 12–18 months of life. [10] In 2 recent studies of infants at high risk for peanut allergy, IgE sensitisation to peanuts in infants was positively correlated with the amount of peanuts consumed by mothers during the third trimester of pregnancy [5, 19]. In contrast, 2 prospective birth cohort studies (Isle of Wight, UK, and Avon Longitudinal Study of Parents and Children), as well as a questionnaire-based study, found no effect of maternal consumption during pregnancy or lactation on the development of allergy to peanuts [86–88]. In addition, in the mouse model of peanut allergy, maternal peanut exposure during pregnancy and lactation reduced the risk for peanut allergy in the offspring [89].

Because of these uncertainties, previous recommendations to delay the complementary feeding (until after 6 months of age) and to continue prolonged avoidance of

specific ‘allergenic’ foods have been dismantled. Strategies to avoid inhalant allergens in pregnancy and infancy are also not recommended.

Complementary Infant Feeding

While there is still some evidence that starting complementary foods before 3–4 months of age may increase the risk of allergic disease [90], most expert bodies now recommended introduction of complementary foods from 4–6 months of age, with no specific delay in ‘aller-

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genic foods’ [7, 91–94] (table 4). A review of 13 studies (only one was controlled) found a consistent association between the persistence of eczema and the introduction of solid foods before 4 months of age but not with an increased risk of asthma, food allergy, allergic rhinitis or animal allergies [84]. However, in a large, population-based, multicenter cohort, there was no evidence for a protective effect of late introduction of solid food on the development of pre-school wheezing, transient wheezing, atopy or eczema. Rather, there was actually a significantly increased risk of eczema with late introduction of egg and milk [95]. Delaying initial exposure to cereal grains until after 6 months was associated with increased risk of developing wheat allergy [96]. A number of recent reports suggested that early introduction of peanut, cow’s milk and egg into the infant diet was associated with decreased risk of allergy to these foods [97–99]. Countries in Asia, Africa and the Middle East have low rates of peanut allergy, and peanut consumption is unrestricted during pregnancy and early childhood. A questionnaire-based study found that prevalence of peanut allergy in the UK was 1.85%, and the prevalence in Israel was 0.17% ($p < 0.001$). Despite accounting for atopy, the adjusted risk ratio for peanut allergy between countries was 9.8 (95% confidence interval 3.1–30.5) in primary school children [97]. The only difference identified between the two populations was the timing of introduction of peanut, which in Israel occurs during early weaning. The median

Table 4. The role of infant feeding practices and allergy prevention

Practice	Comments
Breastfeeding and infant formula (role of hydrolysed formulas)	<ul style="list-style-type: none">– Breast milk contains many immunomodulatory factors with tolerogenic properties [104, 105]; although the allergy-protective effects of breast milk have been inconsistent the evidence is limited to observational studies for ethical reasons; breastfeeding has many benefits for mother and child– Early studies suggested that hydrolysed formulas have an allergy-preventive effect in randomised prospective studies of high-risk infants [61, 134–136]– More recently, a much larger RCT (GINI, n = 2,252 infants) [112, 114, 115] confirmed the allergy-protective effects of hydrolysed formulas; long-term follow-up at 6 years showed a reduced risk of allergic manifestations with both partially and extensively hydrolysed formulas [112] <p><i>Summary:</i> Breastfeeding is recommended whenever possible for the many benefits for mother and child. If breastfeeding is not possible, a hydrolysed formula (usually a partially hydrolysed formula) is recommended for infants at high risk of allergic disease (i.e. infants with parents or siblings who have a history of allergic disease)</p>
Complementary feeding practices (and allergen avoidance)	<ul style="list-style-type: none">– Early observational studies noted an association between early introduction of solid food (<3–4 months) and early eczema [137, 138]– This prompted combined dietary strategies in high-risk infants (maternal allergen avoidance in pregnancy and lactation, hydrolysed formula, delayed complementary feeding, prolonged avoidance of allergenic foods); initial reports suggested less food-associated atopic dermatitis, urticaria and/or gastrointestinal disease by 12 months [139]; some of these effects may have been due to hydrolysed formula rather than allergenic food avoidance; many of these restrictive practices were incorporated into recommendations for allergy prevention, although subsequent follow-up showed no long-term benefits [140]– Many subsequent studies have failed to show any consistent evidence that delaying the introduction of complementary solid foods beyond 6 months reduces the risk of allergy [reviewed in ref. 7, 91–94]– There have been some suggestions that delaying introduction of foods may actually increase (rather than decrease) allergy; however, at this stage, this is not proven <p><i>Summary:</i> Based on the currently available evidence, many experts across Europe, Australia and North America recommend introducing complementary solid foods from around 4–6 months, with no specific avoidance of allergenic foods [7, 91–94]. More research is needed to determine the optimal time to start complementary solid foods and a number of RCT are exploring the role of earlier introduction of allergenic foods to induce tolerance</p>

monthly consumption of peanut in Israeli infants aged 8–14 months was 7.1 g peanut protein, and it was 0 g in the UK ($p < 0.001$). The median number of times peanut is eaten per month was 8 in Israel and 0 in the UK ($p < 0.0001$). In addition to timing of the food introduction, the route of exposure to food allergens is likely relevant. Children with eczema who applied creams with peanut oils had increased risk of developing peanut allergy (odds ratio 6.8; 95% confidence interval 1.4–32.9) [87]. In animal models, exposure to food allergens (peanut or egg white) via the disrupted skin is associated with a Th2-skewed immune response characterised by IgE antibody production. In contrast, allergen ingestion (even a single dose) is sufficient for induction of oral tolerance in mice [100–102]. Since food allergens are present in household dust [103], cutaneous exposure to the environmental food

allergens in the absence of oral exposure may prime for pro-allergic immune response to foods.

Importantly, most expert bodies have also emphasised the need for more definitive studies, and the first RCT are currently underway to test the hypothesis that early, regular exposure to allergenic foods may actually promote tolerance [91]. It is hoped that these studies will further clarify the optimal time to introduce these foods in allergy-prone infants, although it is also anticipated that this may vary according to individual genetic and other environmental factors. The LEAP (Learning Early About Peanut Allergy; www.leapstudy.co.uk) study compares two approaches to peanut allergy prevention in 640 high-risk infants, aged 4–10 months, with atopic dermatitis and/or egg allergy. Children were randomised 1:1 to peanut avoidance until age 3 years or early peanut introduc-

tion with feeding of approximately 6 g peanut protein per week (an age-appropriate peanut snack 3 times per week). The proportion of each group that develops peanut allergy by 5 years of age will be used to determine which approach – avoidance or consumption – works best for preventing peanut allergy. The study will complete in 2013. The EAT (Enquiring About Tolerance; www.eatstudy.co.uk) study is an RCT testing whether the introduction of 6 allergenic foods (cow's milk, egg, fish, wheat, sesame and peanut) into the diet of unselected infants from 3 months of age together with continued breastfeeding results in reduced prevalence of food allergies by 3 years of age. The study results are expected in 2015. There are also at least 4 other double-blind RCT examining the early introduction of egg into the diet of children at high risk of allergic disease (including the STEP and the STAR trials in Australia).

Once again, this issue is likely to be a 'question of balance'. It is unlikely that changing allergen exposure is the underlying cause of the allergy epidemic. A rise in many immune diseases in the last 50 years (including a diverse range of autoimmune disorders) provides good evidence that the environmental effects of the immune system during this period have disrupted normal immune tolerance mechanisms. The first manifestations of allergic disease (eczema and food allergy) in early infancy suggest that environmental conditions before and during early allergen encounter are less optimal for promoting oral tolerance in a growing number of young infants. Therefore, the ideal approaches for preventing allergy will be to define and restore optimal conditions in pregnancy when the 'scene is set' for immune development, and to achieve a 'tolerogenic' microenvironment in the gut during the time of first allergen encounter.

The Role of Breastfeeding in Achieving Balanced Immune Responses

Animal models provide clear evidence of the tolerogenic properties of maternal milk [104, 105]. This appears to be mediated, at least in part, by tolerogenic cy-

Once again, this issue is likely to be a 'question of balance'. It is unlikely that changing allergen exposure is the underlying cause of the allergy epidemic.

tokines such as TGF- β [104], which promote regulatory T-cell populations in the newborn gut [105]. Although it is not clear how well these models translate to humans, breast milk also contains a large range of nutrients and growth factors with immunomodulatory properties, including immunoglobulins, lactoferrin, lysozymes, oligosaccharides, long-chain fatty acids, cytokines, nucleotides, hormones, antioxidants and maternal immune cells [106]. Although several studies have shown asso-

There is no doubt that breastfeeding should be strongly recommended for all the other nutritional and non-nutritional benefits to the mother and child.

ciations between the levels of these factors in breast milk and subsequent allergic disease [107, 108], the significance is not clear. Due to the intrinsic difficulties in randomising and double blinding participants, it will remain difficult to definitively address the inconsistent relationships reported between breastfeeding and allergic disease. There is some evidence that continued breastfeeding during the introduction of complementary foods is important for promoting tolerance in humans [109] as well as in animals [110]. Although specific allergy-preventive effects have not been confirmed, it seems logical to encourage continued breastfeeding as 'solid' foods are introduced. There is no doubt that breastfeeding should be strongly recommended for all the other nutritional and non-nutritional benefits to the mother and child. In the context of emerging evidence for the anti-inflammatory role of vitamin D, the protective effects of breastfeeding might be mitigated in the setting of vitamin D deficiency both in the mother and/or in the offspring.

Hypoallergenic Infant Formula

Although exclusive breastfeeding is recommended until complementary foods are introduced around 4–6 months, this is not always possible. There is some evidence that the use of hydrolysed formula may reduce the risk of infant and childhood allergies in infants at high risk of allergic disease [111–113] (table 4). Based on this, most expert bodies strongly recommend breastfeeding for as long as possible, but that if complementary infant

formula is required, infants with a history of allergic disease in parents or siblings may be placed on a hydrolysed formula (typically a partially hydrolysed formula) [7, 91]. GINI (German Infant Nutritional Interventional Study), a large multicenter study, randomised 2,252 at-risk infants to receive cow milk formula, partially or extensively hydrolysed whey formula or extensively hydrolysed casein formula [114]. The analysis excluded breastfed infants (n = 945), because they differed significantly from the formula-fed infants; overall, there was a significant reduction in the incidence of atopic dermatitis at 1, 3 and 6 years in children fed with hydrolysed formula [112, 115].

Soy-based formula and mammalian milks are not recommended for prevention of food allergy [31].

Conclusions

It is evident that a broad range of host and environmental factors interact during early development to influence patterns of immune response. While 'immune tolerance' is the default response to harmless foods and other environmental antigens, rising rates of allergic immune disease suggest that environmental conditions during this period are not optimal for tolerance induction. The ideal strategy to address this would be to restore more optimal conditions during this critical period. However, in the face of such rapid, complex and dramatic environmental changes this will be difficult. Identifying the causal factors and defining what is 'optimal' in the face of complex interactions has been so far problematic. It is also not clear if it will be even possible to restore traditional patterns, if we have already passed a critical 'tipping point'. So far, the most logical avenues to address this have been to examine environmental candidates with immunomodulatory effect that have undergone the most significant changes with 'modernisation'. While this has concentrated efforts on the change in microbial exposure, dietary patterns and environmental pollutants, the role of each of these is not clear enough to make specific recommendations, and there may be further unidentified factors. Current recommendations for allergy prevention remain limited (i.e. to avoidance of cigarette smoke, promotion of breastfeeding and use of hydrolysed formula when this is not possible), but future studies are likely to provide clearer recommendations around the use of probiotics, prebiotics and specific dietary nutrients. Uncer-

Identifying the causal factors and defining what is 'optimal' in the face of complex interactions has been so far problematic.

tainty around the role of early introduction of allergenic foods, and how this might vary according to allergic heredity or clinical phenotype (such as early eczema), will also be clarified by a series of

currently ongoing RCT. Until then, there is no basis for specific recommendations regarding these foods (either avoidance or deliberate early exposure). Despite the current uncertainties, prevention remains the best long-term strategy to reduce the growing burden of allergic disease.

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