

Role of diet in the development of immune tolerance in the context of allergic disease

Christina E. West^{a,b}, Diane J. Videky^a and Susan L. Prescott^a

^aSchool of Paediatrics and Child Health Research, University of Western Australia, Western Australia, Australia and ^bDepartment of Clinical Sciences, Pediatrics, Umeå University, Sweden

Correspondence to Professor Susan L. Prescott, School of Paediatrics and Child Health Research, University of Western Australia, Perth, Western Australia, PO Box D184, Princess Margaret Hospital, Perth, WA 6001, Australia
Tel: +61 8 9340 8171; fax: +61 8 9388 2097; e-mail: sprescott@meddent.uwa.edu.au

Current Opinion in Pediatrics 2010, 22:635–641

Purpose of review

Diet is arguably one of the most significant environmental exposures during early development. Here, we explore the effects of key perinatal dietary exposures on immune development and susceptibility to allergic disease.

Recent findings

Dietary changes are at the centre of the emerging epigenetic paradigms that underpin the rise in many modern diseases. There is growing evidence that exposures in pregnancy and the early postnatal period can modify gene expression and disease susceptibility. Specific nutrients, including antioxidants, oligosaccharides, polyunsaturated fatty acids, folate and other vitamins, have documented effects on immune function. Some have also been implicated in modified risk of allergic disease in observational studies. Intervention studies are largely limited to trials with polyunsaturated fatty acids and oligosaccharides, showing preliminary but yet unconfirmed benefits in allergy prevention. Avoidance of food allergens in pregnancy, lactation or infancy has provided no clear evidence in allergy prevention and is no longer recommended. Rather there is focus on their role in tolerance induction.

Summary

Modern dietary changes are clearly implicated in the rising propensity for inflammatory immune responses. These dietary changes, which appear to be providing less tolerogenic conditions during early immune programming, may provide important avenues for preventing disease.

Keywords

allergy prevention, antioxidants, complementary feeding, folate, polyunsaturated fatty acids

Curr Opin Pediatr 22:635–641
© 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins
1040-8703

Introduction

Dietary changes are among the many complex environmental changes implicated in the allergy epidemic. The recognized effects of many dietary nutrients on immune function make dietary change one of the logical candidates in the rise in immune disease [1–3]. Modern diets differ in many respects from more traditional diets, and as a result there have been changes in the levels and patterns of various dietary components. The complex interactions between specific nutrients and additional interactions with other modern environmental changes are a likely contributor to inconsistencies in the relationship between dietary factors and disease, particularly in observational studies.

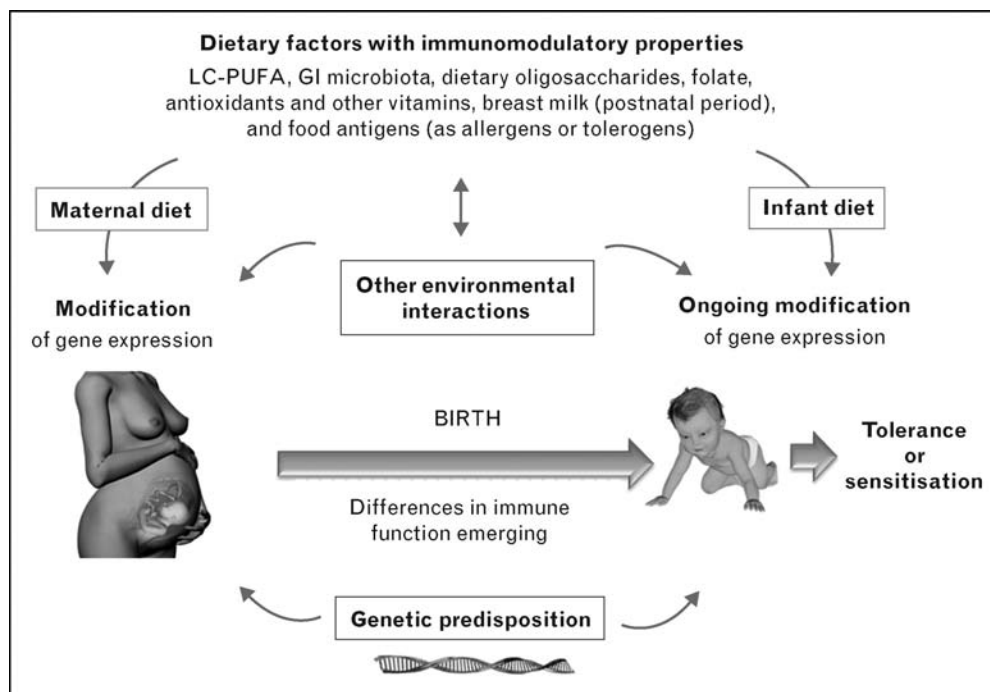
The critical influence of diet in pregnancy

There is mounting evidence that predisposing patterns of immune dysfunction are evident already at birth, and that

maternal diet [2] and other antenatal exposures [4••] can modify these neonatal immune responses. This, together with the rising rate of allergic disease in early infancy, provides clear evidence that the effects of modern environmental changes begin before birth. Emerging epigenetic paradigms provide novel mechanisms by which these early environmental changes lead to heritable changes in gene expression and disease propensity (reviewed in [5]). Notably, dietary change is one of the leading factors currently implicated in these ‘epigenetic modifications’. Although initially implicated in the rise of other modern diseases, there is now some evidence from animal models that maternal diet can have epigenetic effects on immune function and predisposition to an allergic phenotype [3]. This also suggests that pregnancy provides a significant window of opportunity for disease prevention.

Maternal diet can have critical effects on many aspects of developing structures and functions (Fig. 1). Although

Figure 1 Dietary influences play an important role in both the prenatal and the postnatal periods, with the potential to modify developing immune tolerance and disease risk



GI microbiota, gastrointestinal microbiota; LC-PUFA, Long-chain polyunsaturated fatty acids.

the culminating events in immune tolerance occur in the postnatal period, antenatal events may also influence susceptibility to immune dysregulation. A range of dietary nutrients have documented effects on immune function, as discussed individually below. At this stage, it is not clear how changes in intake of these dietary nutrients might be contributing to the differences in immune function of neonates who develop subsequent allergic disease, which include immaturity in effector T cell responses [6,7] regulatory T cells [8] and differences in innate immune function [9]. This remains an important avenue of future research.

The importance of the early postnatal diet and events in the gastrointestinal tract

In the early postnatal period, the gastrointestinal tract is the most important site for the development of immune tolerance. Immediately after birth, the infant gut is rapidly colonized by microorganisms, inducing the maturation of the associated mucosal network that comprises more than 70% of the total immune system. This process is shaped by interactions between host-related factors, mucosal barrier mechanisms, local immune activation, oral exposures including dietary factors and microorganisms. During this period, the infant gut is exposed to a range of new environmental antigens, mostly from commensal bacteria and dietary components. To prevent

inflammatory responses to these mainly harmless antigens, the gastrointestinal associated lymphoid tissue has evolved complex mechanisms to promote tolerance as a default response (reviewed in [10]).

With rising rates of allergic disease, it is also likely that the modern postnatal environment is not optimal for tolerance development, including colonization patterns and early dietary factors. Consequently, there is interest in understanding the role of specific factors in this process and how they may be modified to prevent allergic disease. There is speculation that dietary immunomodulatory factors (Fig. 1) can promote tolerogenic conditions in the gut, including polyunsaturated fatty acids (PUFA) for their effects on T cell ([2,11], and others) and dendritic cell function [12], vitamin A (retinoic acid) for promoting T regulatory (Treg) cell differentiation [13], and prebiotic oligosaccharides for their effects on both immune function and colonization [14,15,16]. Several of these have also been explored as postnatal interventions for allergy prevention and promotion of oral tolerance.

The role of specific dietary factors and dietary patterns

Assessing the effects of specific nutrients individually may be over-simplistic. Another approach is to examine the effects of changing composite patterns of specific

nutrient intakes [17[•]]. Some studies have suggested 'dietary patterns' such as the Mediterranean diet to be protective in the development of atopic disease [18–20], largely due to dietary effects in pregnancy [20]. Thus, as we also examine the literature on specific nutrients below, a more integrated approach will ultimately be required.

Effects of dietary polyunsaturated fatty acids

PUFA were one of the first dietary nutrients linked with the rise in allergic disease. Modern diets have shown a decline in the consumption of omega-3 (n-3) PUFA in favour of more proinflammatory omega-6 (n-6) PUFA, with possible effects on immune development and subsequent allergic disease. The potential protective role of n-3 PUFA in allergic disease was based on observational studies that found consumption of oily fish in childhood (higher n-3/n-6 ratio) to be associated with less wheeze and asthma ([21], and others). This was consistent with the recognized 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 [22[•]]).

Some more recent observational studies of n-3 PUFA in the postnatal diet have supported this hypothesis [23], but others have not [24], and postnatal intervention studies with fish oil have so far failed to reduce the development of allergic disease [25,26[•]]. Preliminary results from our ongoing 'Infant fish oil study' 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, N, personal communication).

As discussed earlier, with developmental programming arguably more critical *in utero*, there has been shifting interest to maternal PUFA status in pregnancy. Observational studies again suggest that maternal fish oil consumption in pregnancy may protect against allergic disease ([27], and others) although not unambiguously [28[•]]. So far, limited data from intervention studies suggest that benefits may be greater during pregnancy [2,29,30[•]]. Several large studies are underway to hopefully clarify this more definitively.

Role of antioxidants and vitamin D

Recent dietary changes include decreasing intakes of antioxidants (such as vitamin C, vitamin E, β -carotene, zinc and selenium). Lower intakes of antioxidant-rich foods have been associated with reduced pulmonary function and increased risk of wheeze (reviewed in [31[•]]). There is some evidence that antioxidant status in pregnancy may influence the susceptibility to allergic disease. Reduced maternal consumption of antioxidant-rich foods and vitamin E has been associated with

increased risk of developing childhood wheeze [32[•]], asthma, and sensitization [31[•]], whereas relationships between other antioxidants and allergic disease have been inconsistent [31[•]]. Antioxidant status can alter cell processes implicated in immune programming, including T cell regulation [33] and induction of interleukin-12 (IL-12) production by antigen presenting cells [34]. Theoretically, this could favour development of T helper 1 (Th1) and inhibit Th2 responses. Data on immunomodulatory effects by antioxidants in maternal diet during pregnancy are scarce. In one study, higher maternal vitamin E intake was associated with reduced cord blood mononuclear cell proliferative responses to allergens [1], suggesting effects on the developing immune system.

Another vitamin with immunomodulatory properties is vitamin D (reviewed in [35[•]]). Vitamin D intake during pregnancy has been associated with reduced early childhood wheeze [36], asthma and allergic rhinitis [37[•]], and eczema [36]. In contrast, others found a higher exposure to vitamin D early during development, either through maternal levels in pregnancy [38] or by infant supplementation [39], to increase the risk of allergic disease.

Although results are conflicting, it is likely that maternal antioxidant intake influences the fetal antioxidant status, with possible effects on tolerance induction and development of childhood allergy [1]. Ultimately, this needs to be confirmed in intervention studies. Such studies should be approached with vigilance due to concerns for adverse effects [40]. In the meantime, a healthy diet rather than specific vitamin supplementation should be advocated.

Fermentable dietary fibre and oligosaccharides

Dietary fibre and oligosaccharides have many recognized roles in gut health, particularly in promoting favourable colonization [14]; however, direct effects on the immune system have also been recognized [15[•],16[•]]. These undigested dietary components are fermented to produce short-chain fatty acids (SCFA) with newly discovered anti-inflammatory properties [41^{••}]. Declining intake of soluble dietary fibre in more refined modern diets may, therefore, be contributing to the epidemic of immune disease in several ways. Firstly, these changing dietary patterns lead to less favourable colonization patterns, which are already implicated in less tolerogenic properties [42,43]. Secondly, this is compounded by reduced substrate for production of anti-inflammatory SCFA. Thus, altered colonization together with declining intake of dietary fibre may also be implicated in the failure of immune tolerance and the rising propensity for both inflammatory and allergic diseases.

Earlier epidemiological studies suggested a protective link between dietary fibre and allergic conditions [44] and preliminary allergy prevention studies suggest an

allergy-protective effect of neonatal supplementation with 'prebiotic' oligosaccharides [45]. Studies in mice and humans suggest that these oligosaccharides have direct immunological effects [15[•],16[•]]. These findings provide a strong foundation to further explore dietary fibre and oligosaccharides in the promotion of oral tolerance.

Emerging relationships between dietary folate and allergic disease

Interest in the role of folate in immune development has intensified with the recent understanding that this dietary methyl donor can alter gene expression through epigenetic mechanisms. DNA methylation stably alters the gene expression patterns. This is fundamental to cell differentiation and governs all aspects of normal development. There is good evidence that immune development is under epigenetic control. Significantly, because epigenetic changes are transmitted with each cell division, patterns of early gene expression have lasting implications for subsequent development and disease risk (reviewed in [5]).

Recent animal models demonstrate that maternal supplementation with dietary methyl donors in pregnancy induces hypermethylation of key regulatory genes in lung tissue, with subsequent allergic airways disease in the offspring [3]. This has been followed by reports in humans [46[•],47[•]] linking folic acid supplementation during pregnancy with increased risk of asthma and respiratory disease in the infants. There have been links between folate status in the postnatal period and allergic disease, but, if anything, folate was protective [48[•]]. This could be evidence that the effects of this dietary exposure vary with developmental stage.

At this stage, it is premature to make any specific changes to the recommendations for using folate supplements in pregnancy. However, there has been an urgent call for further studies to address the role of folate in pregnancy.

Breast milk in the promotion of oral tolerance

The most important early nutritional source in the postnatal period is breast milk, which 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 [49]. Although the mechanisms need further investigation, the immunologic properties of these factors play a role in protection from infection and promotion of oral tolerance. Animal studies have shown that maternal milk is more tolerogenic through promoting regulatory T cells in the developing gut [50,51]. Tolerance has been shown to be mediated by CD4⁺ regulatory T cells and is dependent on transforming growth factor beta (TGF- β) being present in maternal

milk [50]. Although there is some evidence that continued breastfeeding during introduction of complementary foods may promote tolerance [52], it has been difficult to confirm any specific allergy-preventive effects. It remains important that breastfeeding is promoted for other nutritional and nonnutritional benefits to the mother and child. Because of the inherent difficulties in randomizing and double-blinding participants, it will remain difficult to definitively address the conflicting relationships reported between breastfeeding and allergic disease. Further study of the immunomodulatory properties of breast milk may reveal insights into the optimal development of a tolerogenic environment in the gut.

Role of dietary allergens in the development and prevention of allergic disease

There is little clear evidence that allergens are driving the allergy epidemic, and it appears more likely that this is due to other complex environmental changes. The first dietary interventions to prevent allergic disease were grounded in logical concepts that, if an allergen can be avoided completely, an allergic response to that allergen is unlikely. This approach has been unsuccessful, probably because complete avoidance is not possible, and sensitization may still occur through other less tolerogenic routes [53[•]]. With the recognition that specific oral tolerance is an antigen-driven process, there is now focus on earlier, regular exposure to allergenic foods to promote tolerance.

Most current recommendations reflect the lack of evidence that delaying the complementary feeding (beyond 6 months) or avoidance of specific 'allergenic' foods (such as cow's milk, eggs, peanuts, tree nuts and seafood) prevent allergic disease [54,55]. On the basis of this and growing evidence that avoidance of allergenic foods may even lead to an increase in food allergy [54], eczema ([56[•]], and others) and sensitization [57[•]], most expert bodies now recommend introduction of complementary foods from 4–6 months of age, with no specific delay in 'allergenic foods' [55,58–60]. There is still some evidence that starting complementary foods before 3–4 months of age may increase the risk of allergic disease ([54,61], and others) possibly because colonization is not yet well established and the gut is more permeable. In making recommendations, expert bodies have also called for more definitive studies. Several groups are conducting the first randomized controlled trials to directly investigate whether the early introduction of specific allergenic foods will induce tolerance and reduce allergic outcomes in children at risk of allergic disease. The results are anticipated to provide new insights into the role of early allergen exposure. Whatever the results, it remains important to consider the findings in the context of other modern environmental changes. Ideal approaches will be those promoting an optimal 'tolerogenic' microenvironment in the gut during the time of first allergen encounter, again highlighting the role of

colonization, breastfeeding and other dietary immunomodulators.

Genetic and environmental interactions: implications for future 'personalized' dietary interventions

The complexity of this field is further underpinned by genetic and environmental interactions, which may explain individual variability in response to dietary interventions and inconsistencies between studies. There are preliminary studies demonstrating functional polymorphisms in the metabolic pathways of several of the dietary factors that have been discussed earlier, including folate [62] and fatty acid metabolism [63], although more studies are needed to determine the significance of these. For example, variations in folate metabolism conferred by the MTHFR (C677T) genotype have been associated with allergic disease [62] and asthma [64[•]], although not unambiguously [65].

Although functional genetic polymorphisms are known to confer individual susceptibility to disease, they can also confer differences in the biological effects of an environmental exposure. Environmental changes that increase the risk of allergic disease in a subgroup of individuals (i.e. with a specific functional genetic polymorphism) may have no effects (or opposite effects) in other individuals. The implication for dietary interventions is that effectiveness may vary with specific genetic polymorphisms, leading to the realization that ideal intervention to prevent disease will need to be individualized according to genetic polymorphisms.

To complicate things yet further, the effect of genetic polymorphisms on disease risk can also vary with the level of a specific environmental exposure. Although not related to diet, a good example of this is seen with microbial exposure, where genetic polymorphisms confer different risk depending on whether children are raised in a 'low' versus a 'high' microbial burden environment [66]. Similar complex interactions with dietary nutrients could have implications for diet supplements. For example, increasing levels of specific nutrients could foreseeably create unanticipated or paradoxical relationships between genetic polymorphisms and disease risk. Although this may be largely theoretical, it highlights the need to regard interventions cautiously with consideration of these potentially complex interactions.

Conclusion

Diet is arguably one of the most important environmental exposures in early life. As a highly dynamic and metabolically active network, the immune system is dependent on dietary nutrients and highly sensitive to dietary

changes. There is accumulating evidence that changes in many dietary nutrients with urbanized diets may be contributing to the rising rates of immune disease. Although there are still many uncertainties and inconsistencies in the literature, these do not mean that dietary nutrients do not have important effects. Rather, this is more likely to reflect our inadequacy to study diet in ways that allow for the complexity of interactions. Future research strategies should attempt to account for complex interrelationships between dietary nutrients in addition to multifactorial genetic and environmental interactions. This may eventually lead to personalized early interventions that are adapted according to genetic predisposition. It remains highly likely that dietary strategies will play a major role in future strategies to prevent many diseases.

Acknowledgements

Christina West is supported by a fellowship from the Throne Holst foundation. Susan Prescott is supported by an NHMRC Practitioner Fellowship. We would like to acknowledge A/Professor Peter Smith for the graphics used in Fig. 1.

Professor Prescott has been a speaker at meetings sponsored by SHS/Nutricia and Nestlé. She has been a member of the independent Scientific Advisory Board of Nestlé Nutrition Institute Oceania, an expert panel on Cows Milk Allergy for Nutricia Australia, and expert panels for Mead Johnson and Fonterra. She has received travel assistance and speaker fees from these companies to present at or attend scientific meetings.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 683).

- 1 Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. *Clin Exp Allergy* 2002; 32:43–50.
- 2 Dunstan JA, Mori TA, Barden A, *et al.* Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. *J Allergy Clin Immunol* 2003; 112:1178–1184.
- 3 Hollingsworth JW, Maruoka S, Boon K, *et al.* In utero supplementation with methyl donors enhances allergic airway disease in mice. *J Clin Invest* 2008; 118:3462–3469.
- 4 Schaub B, Liu J, Hoppler S, *et al.* Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. *J Allergy Clin Immunol* 2009; 123:774.e5–782.e5.
- In this study, farm exposures during pregnancy increased the number and function of cord blood T regulatory cells associated with lower Th2 cytokine secretion and lymphocyte proliferation following innate exposure, suggesting 'a natural model of immunotherapy'.
- 5 Martino DJ, Prescott SL. Silent mysteries: epigenetic paradigms could hold the key to conquering the epidemic of allergy and immune disease. *Allergy* 2010; 65:7–15.
- 6 Prescott SL, Holt PG. Abnormalities in cord blood mononuclear cytokine production as a predictor of later atopic disease in childhood. *Clin Exp Allergy* 1998; 28:1313–1316.
- 7 Tang ML, Kemp AS, Thorburn J, Hill DJ. Reduced interferon-gamma secretion in neonates and subsequent atopy. *Lancet* 1994; 344:983–985.
- 8 Smith M, Tourigny MR, Noakes P, *et al.* Children with egg allergy have evidence of reduced neonatal CD4(+)CD25(+)CD127(lo/-) regulatory T cell function. *J Allergy Clin Immunol* 2008; 121:1460–1466; 6.e1–7.
- 9 Prescott SL, Noakes P, Chow BW, *et al.* Presymptomatic differences in Toll-like receptor function in infants who have allergy. *J Allergy Clin Immunol* 2008; 122:391–399; 9.e1–5.

- 10 Tsuji NM, Kosaka A. Oral tolerance: intestinal homeostasis and antigen-specific regulatory T cells. *Trends Immunol* 2008; 29:532–540.
 - 11 Field CJ, Van Aerde JE, Goruk S, Clandinin MT. Effect of feeding a formula supplemented with long-chain polyunsaturated fatty acids for 14 weeks improves the ex vivo response to a mitogen and reduces the response to a soy protein in infants at low risk for allergy. *J Pediatr Gastroenterol Nutr* 2010; 50:661–669.
 - 12 Weatherill AR, Lee JY, Zhao L, *et al.* Saturated and polyunsaturated fatty acids reciprocally modulate dendritic cell functions mediated through TLR4. *J Immunol* 2005; 174:5390–5397.
 - 13 Mucida D, Cheroutre H. TGFβ and retinoic acid intersect in immune-regulation. *Cell Adh Migr* 2007; 1:142–144.
 - 14 Scholtens PA, Alliet P, Raes M, *et al.* Fecal secretory immunoglobulin A is increased in healthy infants who receive a formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides. *J Nutr* 2008; 138:1141–1147.
 - 15 Schouten B, van Esch BC, Hofman GA, *et al.* Oligosaccharide-induced whey-specific CD25(+) regulatory T-cells are involved in the suppression of cow milk allergy in mice. *J Nutr* 2010; 140:835–841.
- In a murine model, oligosaccharides induced allergen-specific CD25(+) regulatory T cells, which are involved in the suppression of food allergy.
- 16 van Hoffen E, Ruiter B, Faber J, *et al.* A specific mixture of short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides induces a beneficial immunoglobulin profile in infants at high risk for allergy. *Allergy* 2009; 64:484–487.
- Infants at high risk of allergy supplemented with a mixture of short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides had a beneficial immunoglobulin profile and decreased cow's milk -specific IgG1 compared with a placebo group, suggestive of direct immunological effects of oligosaccharides.
- 17 Shaheen SO, Northstone K, Newson RB, *et al.* Dietary patterns in pregnancy • and respiratory and atopic outcomes in childhood. *Thorax* 2009; 64:411–417.
- In a UK birth cohort study, some dietary patterns were associated with allergic outcomes. However, none had any effect after allowing for other environmental confounders, stressing the need to interpret dietary effects in the wider context of the environment and other dietary factors.
- 18 Castro-Rodriguez JA, Garcia-Marcos L, Alfonseda Rojas JD, *et al.* Mediterranean diet as a protective factor for wheezing in preschool children. *J Pediatr* 2008; 152:823–828; 8.e1–2.
 - 19 Chatzi L, Apostolaki G, Bibakis I, *et al.* Protective effect of fruits, vegetables and the Mediterranean diet on asthma and allergies among children in Crete. *Thorax* 2007; 62:677–683.
 - 20 Chatzi L, Torrent M, Romieu I, *et al.* Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. *Thorax* 2008; 63:507–513.
 - 21 Hodge L, Salome CM, Peat JK, *et al.* Consumption of oily fish and childhood asthma risk. *Med J Aust* 1996; 164:137–140.
 - 22 Calder PC. Polyunsaturated fatty acids and inflammatory processes: new • twists in an old tale. *Biochimie* 2009; 91:791–795.
- This comprehensive review discusses the role of PUFA in inflammatory conditions.
- 23 Oddy WH, de Klerk NH, Kendall GE, *et al.* Ratio of omega-6 to omega-3 fatty acids and childhood asthma. *J Asthma* 2004; 41:319–326.
 - 24 Takemura Y, Sakurai Y, Honjo S, *et al.* The relationship between fish intake and the prevalence of asthma: the Tokorozawa childhood asthma and pollinosis study. *Prev Med* 2002; 34:221–225.
 - 25 Almqvist C, Garden F, Xuan W, *et al.* Omega-3 and omega-6 fatty acid exposure from early life does not affect atopy and asthma at age 5 years. *J Allergy Clin Immunol* 2007; 119:1438–1444.
 - 26 Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention • of allergic disease: systematic review and meta-analysis. *Allergy* 2009; 64:840–848.
- This meta-analysis demonstrated no benefits of PUFA in allergy prevention. However, the authors pooled the data from prenatal and postnatal intervention studies, which may not be ideal, given potential differences in the effects according to developmental stage.
- 27 Sausenthaler S, Koletzko S, Schaaf B, *et al.* Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. *Am J Clin Nutr* 2007; 85:530–537.
 - 28 Oien T, Storro O, Johnsen R. Do early intake of fish and fish oil protect against • eczema and doctor-diagnosed asthma at 2 years of age? A cohort study. *J Epidemiol Community Health* 2010; 64:124–129.
- In a report from the Prevention of Allergy among Children in Trondheim study cohort, there was no dose–response relationship between maternal fish intake and reported allergy at 2 years of age. However, there was a negative association between fish intake (at least once per week) at 1 year of age and parental reported eczema at 2 years of age.
- 29 Olsen SF, Osterdal ML, Salvig JD, *et al.* Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. *Am J Clin Nutr* 2008; 88:167–175.
 - 30 Furuhjelm C, Warstedt K, Larsson J, *et al.* Fish oil supplementation in • pregnancy and lactation may decrease the risk of infant allergy. *Acta Paediatr* 2009; 98:1461–1467.
- This study demonstrated a reduction in food allergy and IgE-associated eczema in infants whose mothers were supplemented with fish oil during pregnancy and lactation, compared with a placebo group. The effects of PUFA may vary according to developmental stage.
- 31 Allan K, Kelly FJ, Devereux G. Antioxidants and allergic disease: a case of too • little or too much? *Clin Exp Allergy* 2010; 40:370–380.
- In this review, the authors summarize the conflicting evidence of the role of antioxidants in allergic disease. There is still need for more studies to clarify their role in treatment and prevention of allergic disease.
- 32 Miyake Y, Sasaki S, Tanaka K, Hirota Y. Consumption of vegetables, fruit, and • antioxidants during pregnancy and wheeze and eczema in infants. *Allergy* 2010; 65:758–765.
- The results from a Japanese birth cohort study suggest protective effects of intake of antioxidant-rich foods, β-carotene and vitamin E during pregnancy on infant allergic outcomes.
- 33 Tan PH, Sagoo P, Chan C, *et al.* Inhibition of NF-kappa B and oxidative pathways in human dendritic cells by antioxidative vitamins generates regulatory T cells. *J Immunol* 2005; 174:7633–7644.
 - 34 Utsugi M, Dobashi K, Ishizuka T, *et al.* c-Jun N-terminal kinase negatively regulates lipopolysaccharide-induced IL-12 production in human macrophages: role of mitogen-activated protein kinase in glutathione redox regulation of IL-12 production. *J Immunol* 2003; 171:628–635.
 - 35 Lange NE, Litonjua A, Hawrylowicz CM, Weiss S. Vitamin D, the immune • system and asthma. *Expert Rev Clin Immunol* 2009; 5:693–702.
- In this review, the authors summarize data on the possible link between vitamin D status and asthma.
- 36 Miyake Y, Sasaki S, Tanaka K, Hirota Y. Dairy food, calcium, and vitamin D intake in pregnancy and wheeze and eczema in infants. *Eur Respir J* 2010; 35:1228–1234.
 - 37 Erkkola M, Kaila M, Nwaru BI, *et al.* Maternal vitamin D intake during pregnancy • is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy* 2009; 39:875–882.
- Results from the prospective Finnish Type 1 Diabetes Prediction and Prevention study suggest higher maternal vitamin D intake during pregnancy to be protective of childhood allergic outcomes. Future studies should investigate the effects of maternal dietary patterns on allergic outcomes, to assess whether the effects are attributed to vitamin D alone or to an overall healthier diet or lifestyle.
- 38 Gale CR, Robinson SM, Harvey NC, *et al.* Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr* 2008; 62:68–77.
 - 39 Bäck O, Blomquist HK, Hernell O, Stenberg B. Does vitamin D intake during infancy promote the development of atopic allergy? *Acta Derm Venereol* 2009; 89:28–32.
 - 40 Murr C, Schroecksnadel K, Winkler C, *et al.* Antioxidants may increase the probability of developing allergic diseases and asthma. *Med Hypotheses* 2005; 64:973–977.
 - 41 Maslowski KM, Vieira AT, Ng A, Kranich J, *et al.* Regulation of inflammatory • responses by gut microbiota and chemoattractant receptor GPR43. *Nature* 2009; 461:1282–1286.
- In this landmark study, SCFA were demonstrated to bind to molecules expressed by immune cells (GPR43) and directly suppress inflammation in the gut.
- 42 Sjögren YM, Jenmalm MC, Böttcher MF, *et al.* Altered early infant gut microbiota in children developing allergy up to 5 years of age. *Clin Exp Allergy* 2009; 39:518–526.
 - 43 Sjögren YM, Tomicic S, Lundberg A, *et al.* Influence of early gut microbiota on the maturation of childhood mucosal and systemic immune responses. *Clin Exp Allergy* 2009; 39:1842–1851.
 - 44 Hijazi N, Abalkhail B, Seaton A. Diet and childhood asthma in a society in transition: a study in urban and rural Saudi Arabia. *Thorax* 2000; 55:775–779.
 - 45 Arslanoglu S, Moro GE, Schmitt J, *et al.* Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. *J Nutr* 2008; 138:1091–1095.
 - 46 Håberg SE, London SJ, Stigum H, *et al.* Folic acid supplements in pregnancy • and early childhood respiratory health. *Arch Dis Child* 2009; 94:180–184.
- Results from the prospective Norwegian Mother and Child Cohort study demonstrated that folic acid supplementation in the first trimester was associated with a slightly increased risk of wheeze and lower respiratory tract infections until 18 months of age.

- 47 Whitrow MJ, Moore VM, Rumbold AR, Davies MJ. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. *Am J Epidemiol* 2009; 170:1486–1493.
In the prospective Australian Generation 1 Cohort Study, folic acid supplementation in late pregnancy increased the risk of asthma and persistent asthma in the child at 3.5 years, with a similar association at 5.5 years although not statistically significant.
- 48 Matsui EC, Matsui W. Higher serum folate levels are associated with a lower risk of atopy and wheeze. *J Allergy Clin Immunol* 2009; 123:1253–1259.
In this study, higher serum folate levels at 2 years of age were associated with lower IgE levels and reduced risk of atopy and wheeze.
- 49 Rautava S, Walker WA. Academy of Breastfeeding Medicine founder's lecture 2008: breastfeeding—an extrauterine link between mother and child. *Breastfeed Med* 2009; 4:3–10.
- 50 Verhasselt V, Milcent V, Cazareth J, *et al.* Breast milk-mediated transfer of an antigen induces tolerance and protection from allergic asthma. *Nat Med* 2008; 14:170–175.
- 51 Penttilä I. Effects of transforming growth factor-beta and formula feeding on systemic immune responses to dietary beta-lactoglobulin in allergy-prone rats. *Pediatr Res* 2006; 59:650–655.
- 52 Ivarsson A, Hernell O, Stenlund H, Persson LA. Breast-feeding protects against celiac disease. *Am J Clin Nutr* 2002; 75:914–921.
- 53 Fox AT, Sasieni P, du Toit G, *et al.* Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol* 2009; 123:417–423.
One of the explanations of the lack of effect of food allergen avoidance in allergy prevention is that sensitization may still occur through other less tolerogenic routes (such as the skin or respiratory tract) following low-level contaminating doses in the environment.
- 54 Tarini BA, Carroll AE, Sox CM, Christakis DA. Systematic review of the relationship between early introduction of solid foods to infants and the development of allergic disease. *Arch Pediatr Adolesc Med* 2006; 160:502–507.
- 55 Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008; 121:183–191.
- 56 Sariachvili M, Droste J, Dom S, *et al.* Early exposure to solid foods and the development of eczema in children up to 4 years of age. *Pediatr Allergy Immunol* 2010; 21:74–81.
The results from this case–control study do not support a delayed introduction of solid foods in the prevention of childhood eczema. Ongoing randomized controlled trials now investigate whether the early introduction of specific allergenic foods will induce tolerance and reduce allergic outcomes.
- 57 Nwaru BI, Erkkola M, Ahonen S, *et al.* Age at the introduction of solid foods during the first year and allergic sensitization at age 5 years. *Pediatrics* 2010; 125:50–59.
In the prospective Finnish Type 1 Diabetes Prediction and Prevention study, late introduction of solid foods was associated with increased risk of allergic sensitization to both food and inhalant allergens.
- 58 Agostoni C, Decsi T, Fewtrell M, *et al.* Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008; 46:99–110.
- 59 Høst A, Halken S, Muraro A, *et al.* Dietary prevention of allergic diseases in infants and small children. *Pediatr Allergy Immunol* 2008; 19:1–4.
- 60 Prescott SL, Smith P, Tang M, *et al.* The importance of early complementary feeding in the development of oral tolerance: concerns and controversies. *Pediatr Allergy Immunol* 2008; 19:375–380.
- 61 Zutavern A, Brockow I, Schaaf B, *et al.* Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. *Pediatrics* 2006; 117:401–411.
- 62 Husemoen LL, Toft U, Fenger M, *et al.* The association between atopy and factors influencing folate metabolism: is low folate status causally related to the development of atopy? *Int J Epidemiol* 2006; 35:954–961.
- 63 Rzehak P, Heinrich J, Klopp N, *et al.* Evidence for an association between genetic variants of the fatty acid desaturase 1 fatty acid desaturase 2 (FADS1 FADS2) gene cluster and the fatty acid composition of erythrocyte membranes. *Br J Nutr* 2009; 101:20–26.
- 64 Thuesen BH, Husemoen LL, Ovesen L, *et al.* Atopy, asthma, and lung function in relation to folate and vitamin B in adults. *Allergy* 2010. [Epub ahead of print]
In this large population-based prospective Danish study, low serum folate levels and the TT genotype of the MTHFR-C677T polymorphism were associated with increased prevalence of self-reported doctor-diagnosed asthma and attacks of shortness of breath, but not with objective measures of asthma or atopy.
- 65 Granell R, Heron J, Lewis S, *et al.* The association between mother and child MTHFR C677T polymorphisms, dietary folate intake and childhood atopy in a population-based, longitudinal birth cohort. *Clin Exp Allergy* 2008; 38:320–328.
- 66 Simpson A, John SL, Jury F, *et al.* Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. *Am J Respir Crit Care Med* 2006; 174:386–392.