

# Food allergy and atopic eczema

Allison Worth and Aziz Sheikh

Allergy & Respiratory Research Group, Centre for Population Health Sciences: General Practice Section, The University of Edinburgh, Edinburgh, Scotland, UK

Correspondence to Professor Aziz Sheikh, Allergy & Respiratory Research Group, Centre for Population Health Sciences: General Practice Section, The University of Edinburgh, Doorway 3, Medical School, Teviot Place, Edinburgh EH8 9AG, UK  
Tel: +44 131 651 4151; fax: +44 131 650 9119;  
e-mail: aziz.sheikh@ed.ac.uk

**Current Opinion in Allergy and Clinical Immunology** 2010, 10:000–000

## Purpose of review

To review recent developments on the inter-relationship between food allergy and atopic eczema, with a particular focus on understanding the role of filaggrin gene defects.

## Recent findings

Filaggrin gene defects have recently been identified as a major risk factor for the development of atopic eczema. These skin barrier defects increase the risk of early onset, severe and persistent forms of atopic eczema. They also increase the risk of allergic sensitization, and asthma and allergic rhinitis in those with co-existent eczema. These skin barrier defects are also likely to increase the risk of food allergy.

## Summary

Atopic dermatitis and food allergy are frequently herald conditions for other manifestations of 'the allergic march'. They commonly co-exist, particularly in those with early onset, severe and persistent atopic eczema. Filaggrin gene defects substantially increase the risk of atopic eczema. The increased skin permeability may increase the risk of sensitization to food and other allergens, this pointing to the possible role of cutaneous allergen avoidance in early life to prevent the onset of atopic eczema and food allergy. Emerging evidence also indicates that oral exposure to potentially allergenic foods may be important for inducing immunological tolerance.

## Keywords

atopic eczema, dermatitis, eczema, filaggrin gene defects, food allergy

Curr Opin Allergy Clin Immunol 10:000–000  
© 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins  
1528-4050

## Introduction

Allergic diseases are now very common conditions globally, with recent data suggesting that these now affect up to 50% of the pediatric population at some point in their lives [1]. Allergic conditions frequently co-exist, with the first manifestations of an allergic tendency typically appearing in early life. A number of disease trajectories for this so-called 'allergic march' have been described, but a consistent finding from these epidemiological investigations is that food allergy and atopic eczema are amongst the earliest manifestations of allergic disease [2,3].

The association between atopic eczema and food allergy has long been recognized as a complex subject with sometimes contrasting perspectives among clinicians, patients and families [4•]. Contributing to this lack of agreement is the fact that food allergy appears to be an important factor in only a subset of children (and a much smaller subset of adults) with atopic eczema, that non-IgE-mediated mechanisms are sometimes implicated in the atopic eczema flare-ups associated with ingestion of the foods in question, and that food allergy appears to

have little or no role in children with nonatopic eczema [5,6•,7].

There has, in the last few years, been renewed interest in the inter-relationship between atopic eczema and food allergy. The identification of the loss-of-function mutations in the gene encoding filaggrin (FLG) as a possible causal mechanism for the development of atopic eczema [8] has triggered this interest. These gene defects result in increased permeability of the skin to proteins, this possibly representing a key mechanism through which they are associated with increased risk of allergic sensitization. Cutaneous exposure to food allergens in those with FLG gene defects may thus represent an important route for the development of food allergy in such predisposed individuals.

The article aims to review evidence on the inter-relationship between food allergy and atopic eczema, with a particular focus on new insights emerging on the important role of genetic skin barrier defects. In this article, we use the term food allergy to refer to IgE-mediated reactions, and atopic eczema to refer to the subset of

those with eczema (synonym dermatitis) in whom sensitization is either proven or likely [9].

## Epidemiology

The prevalence of food allergy and atopic eczema has increased in recent decades – particularly in the Western world – where these conditions are now common [10–12]. Both conditions most commonly first manifest in early childhood, this together with familial clustering, pointing to the importance of genetic factors [13]. There are, however, very significant international variations in the prevalence of eczema, with estimates ranging from approximately 2% of children in China and Iran to prevalence rates in Western Europe, Australia and the US that are in the region of 15–20% [14,15], this pointing to the additional importance of environmental factors in its cause. The international epidemiology of food allergy is less well characterized, but the limited data available also point to substantial international variations in risk [16]; further support for the importance of environmental factors also comes from within country secular disease trends, which have demonstrated substantial increases in food allergy over a short time-span [17], so this cannot be explained by genetic drift.

Allergic diseases frequently co-exist, this having been demonstrated in a range of epidemiological studies and by a wealth of clinical experience [3]. The co-prevalence of atopic eczema and food allergy has been estimated at 35–40% of children, this largely being based on estimates derived from specialist settings in which those with early onset, more severe and persistent forms of atopic eczema are generally managed [4<sup>•</sup>,7]. For example, a recent international cohort study of 2222 infants aged 11.5–22.5 months with atopic eczema found that 64% of those in whom the condition developed before 3 months of age had high-risk IgE-mediated food sensitivity to egg and/or cow's milk and/or peanut [18]. In the children in whom the atopic eczema developed before 12 months of age, the frequency of high-risk IgE-mediated food sensitivity increased with increasing disease severity. These effects were, however, lost in children whose eczema developed after 12 months of age. The actual population-based prevalence of food allergy in patients with the typical relatively mild dryness of skin managed in primary care settings is likely to be substantially lower than this.

Another key point that needs to be borne in mind when interpreting these data is that both atopic eczema and food allergy are, in the majority of individuals, transitory conditions that improve with increasing age [19]. Food allergy is thus only a consideration in a very small minority of adult patients with atopic eczema [5].

## The emerging role of filaggrin

Loss-of-function mutations in the gene encoding FLG have recently been identified as a strong genetic risk factor for atopic eczema and eczema-associated allergic airway disease [8,20]. This original finding has triggered a flurry of genetic epidemiological studies such that these results have now been replicated in a number of populations internationally. These studies are discussed briefly below, but are reviewed in detail elsewhere [21<sup>••</sup>].

The epidermal barrier plays a crucial role in protecting the body against infection and other exogenous insults through both minimizing trans-epidermal water loss and conferring immunological protection. Adequate functioning of the skin barrier is dependant on the FLG-based keratin cytoskeleton, intracellular lipids and epidermal proteases [20,21<sup>••</sup>,22]. This defect in barrier functioning predisposes such individuals to dryness of the skin, which results in the characteristic features of scaly, itchy skin, and also increased permeability of the skin to exogenous proteins resulting in increased risk of infection and possibly exposure of the innate immune system to allergens [22].

The FLG gene resides on human chromosome 1q21, within the epidermal differentiation complex [20]. FLG mutations affect some 12–15% of the general population, the R501X and 2282del4 being the most common mutations, although a number of other mutations are also now recognized.

A recent systematic review [21<sup>••</sup>] and meta-analysis of genetic epidemiological studies found that FLG gene defects are associated with a substantial increased risk of atopic eczema – odds ratio (OR) 1.99 [95% confidence interval (CI) 1.72–2.31] in the family studies and 4.78 (3.31–6.92) in the case control studies. The reviewers also found that the risk of early onset and severe, persistent eczema was substantially increased in those with FLG mutations.

An interesting observation was that risk of both asthma and allergic rhinitis was only increased in the subset of individuals with a prior history of atopic eczema, but not in those who did not have a history of atopic eczema, this suggesting a possible causal relationship between FLG status, development of eczema and progression to subsequent allergic airway disease [21<sup>••</sup>]. More interesting still was the finding that the risk of allergic sensitization was substantially increased in those who were FLG-deficient – OR 1.91 (95% CI 1.44–2.54) in the family studies and 1.57 (1.20 to 2.07) in the case-control studies, this suggesting a possible causal mechanism for the development of the allergic march, and offering potential new opportunities for prevention [22].

Although this systematic review failed to identify any studies investigating the role of FLG gene defects in food allergy or other systemic allergic disorders [21<sup>••</sup>], there is work now underway both in the UK and elsewhere aiming to plug this evidence gap.

An important up-shot of this flurry of genetic epidemiological work is the suggestion that cutaneous exposure to allergens in early life in those with barrier skin defects appears to increase the risk of trans-cutaneous allergic sensitization and the subsequent risk of developing atopic eczema and related allergic airway disease. This conclusion is supported by the findings from a recent cohort study [23<sup>••</sup>], which found that in infants with atopic eczema and sensitization to food allergens within the first 3 years of life, the presence of a FLG loss-of-function mutation predicts the future development of asthma with a positive predictive value of 100%. The high positive predictive value was attributed to an interaction between the FLG-null alleles and sensitization to food allergens, which substantially increased the risk of disease progression from eczema to asthma.

Although FLG clearly appears to be important, it should be borne in mind that up to 50% of those with FLG gene defects do not develop atopic eczema and that, even in those with the gene defects, the majority of individuals will outgrow their eczema, this pointing to the role of a range of other as yet poorly understood genetic and environmental influences [24].

---

### Clinical considerations

Food allergy is commonly implicated in eczema, particularly in children, and on this basis avoidance measures are sometimes initiated either by parents or on the advice of physicians. A Cochrane review has found that blanket avoidance of possible food allergens does not, however, translate into clinical benefits – suggestions of improvements in eczema outcomes were only found in the trials that excluded food allergens on the basis of proven sensitivities as determined by the results of objective allergy tests [25].

In those with suspected food allergy which is thought to be aggravating eczema, it is therefore important that any food avoidance measures suggested are based on a detailed history and supportive evidence from objective allergy tests. Key here is the role of skin prick testing, measure of specific IgE and in cases of diagnostic doubt, oral food challenge. Patch testing may have a role in those in whom delayed cell-mediated hypersensitivity reactions are thought to be implicated. Occasionally, a trial of dietary elimination may be needed in those with diagnostic uncertainty, but it is important that this is carefully supervised because of the risk of nutritional

deficiencies, particularly if calcium-rich foods are avoided [26].

The hygiene hypothesis suggests that exposure to Th1 promoting microbial organisms should result in a shift in immunological balance that improves allergic disease outcomes [27]. As a result there has been interest in investigating the role of probiotics in the management of atopic eczema. These trials have, however, overall proven unsuccessful [28]. As a result there is currently no place for probiotics in the clinical management of atopic eczema. The role of prebiotic containing foods in the management of atopic eczema has yet to be studied [29].

There has also been substantial recent interest in the role of oral desensitization in patients with food allergy [30–32], this now also beginning to be studied in randomized controlled trials [33–34]. This small, but rapidly accruing body of evidence suggests that in those with serious IgE-mediated food allergy, tolerance induction can be induced in many patients with milk, egg and peanut allergy, and possibly also other food allergens. Oral desensitization therapy is, however, not without risk – particularly if patients have intercurrent illness or if treatment doses are missed. Despite these early encouraging results, this remains at present an experimental treatment strategy and should only be instituted in the context of clinical studies.

---

### Implications for prevention

There has been interest in the role of allergen avoidance as a primary prevention approach for atopic eczema and other allergic conditions for many years, but most trials of allergen avoidance have proven unsuccessful. The one real exception to this remains the Isle of Wight trial [35] in which both house dust mite and a range of potentially allergenic foods were avoided, from birth until 9 months of age in high-risk infants. This found that this time-limited intervention substantially reduced the risk of allergic sensitization and atopic eczema, this benefit persisting until at least 8 years of age [36].

The comprehensive nature of the allergen avoidance, it has been suggested, was the critical factor in determining the success of the intervention. Supporting evidence comes from a recent systematic review and meta-analysis [37] comparing the effectiveness of mono-faceted vs. multifaceted allergen avoidance measures for prevention, which found that multifaceted measures were significantly more effective in the prevention of asthma. There may thus be a role for comprehensive food and aero-allergen avoidance measures to prevent allergic sensitization, atopic eczema and subsequent manifestations of allergy, but the intervention used in the Isle

of Wight study is challenging to implement and this study therefore needs to be replicated before any decision on routine implementation of this approach can be advocated. There is also a need to investigate whether the allergen avoidance approach might prove particularly differentially effective depending on FLG status.

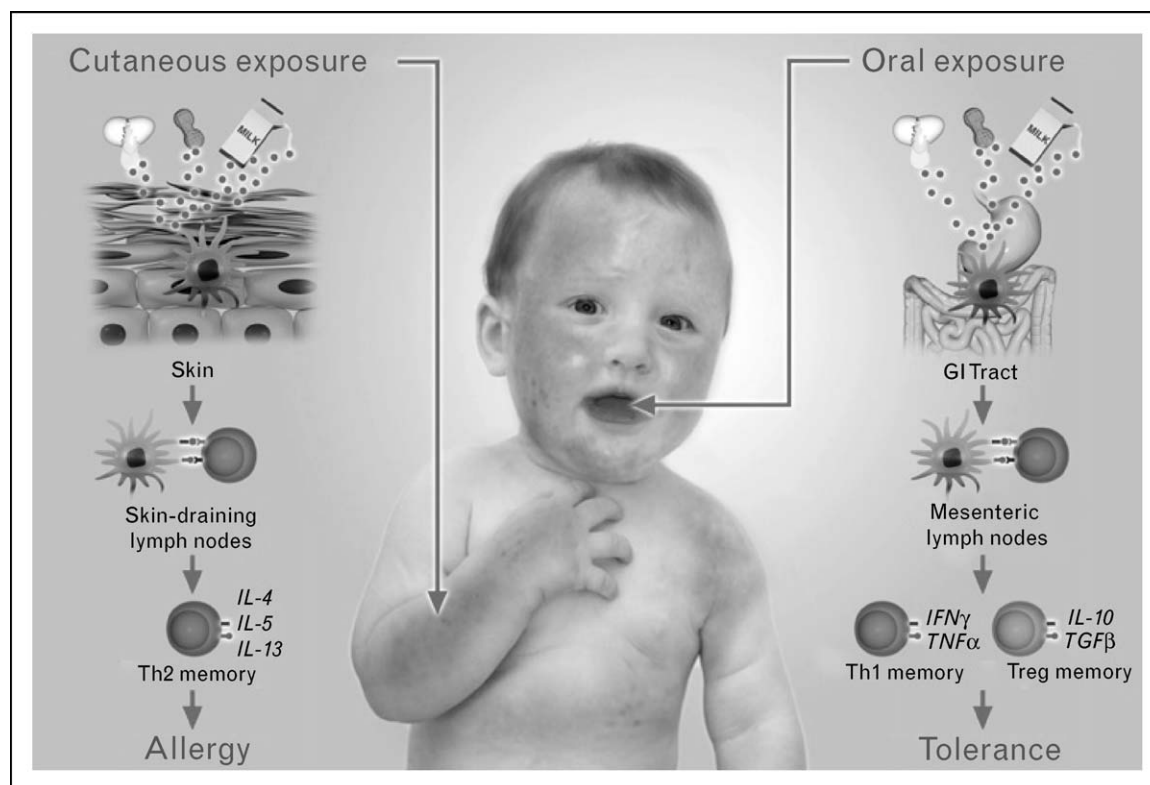
The lack of supporting evidence with respect to mono-faceted allergen avoidance measures has contributed to a recent reversal in policy advice in several countries with respect to the avoidance of peanuts in pregnancy and early life in an attempt to prevent peanut allergy [38,39]. Also contributing to this reappraisal has been the finding from epidemiological work showing that peanut allergy was some 10 times less common in Jewish populations living in Israel where regular exposure to peanut-containing foods in early life is the norm compared with Jewish-origin populations in the UK where peanut ingestion is far less common [16]. This has led to the suggestion that oral exposure to food allergens may be important to induce oral tolerance to foods [38,39]. There is currently a trial [40] underway seeking formally to compare early exposure to peanut-containing foods with delayed introduction to see if this reduces the risk of peanut allergy; this is expected to report in 2013.

Nondietary routes of exposure to peanut such as through the skin or via inhalation may also be important in the development of sensitization and allergy. An important study investigating the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, for example, found that using peanut oil-containing skin creams on inflamed skin in young children was associated with an increased risk of sensitizing children to peanuts [41]. This risk is possibly heightened in those with underlying FLG gene defects [21\*\*] and these peanut oil-containing creams should therefore be avoided in children with an atopic family history and/or a personal history of atopic eczema.

## Conclusion

There have been parallel increases in the prevalence of food allergy and atopic eczema in recent years, this suggesting that common environmental factors are important to the cause of these herald conditions in the allergic march. The search for these environmental factors has hence understandably been the focus of a considerable body of research in recent decades. The finding that FLG gene defects substantially increase the risk of allergic sensitization, atopic eczema and other allergic disease outcomes has, however, rekindled

**Figure 1** Lack's dual-allergen-exposure hypothesis for pathogenesis of food allergy



(Reprinted from *J Allergy Clin Immunol* 121, Lack G. Epidemiologic risks for food allergy, 1331–1336, 2008, with permission from Elsevier) [42].

interest in genetic considerations, this body of work suggesting that in a substantial minority of sufferers this barrier defect may be of fundamental importance in the causal pathway. Work internationally is seeking to exploit this new insight in terms of both developing new treatments and preventive strategies. Particularly important in this respect is whether repeated oral exposure to allergenic foods can result in the development of immune tolerance and assessing whether cutaneous avoidance of potential food allergens in early life – particularly in those with FLG gene defects – may reduce the risk of sensitization and clinical manifestations of food allergy, atopic eczema and other allergic problems (see Fig. 1) [42].

## 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 (pp. 000–000).

- 1 Puneekar YS, Sheikh A. Establishing the incidence and prevalence of clinician-diagnosed allergic conditions in children and adolescents using routinely collected data from general practices. *Clin Exp Allergy* 2009; 39:1209–1216.
- 2 Ostblom E, Lilja G, Pershagen G, *et al.* Phenotypes of food hypersensitivity and development of allergic diseases during the first 8 years of life. *Clin Exp Allergy* 2008; 38:1325–1332.
- 3 Puneekar YS, Sheikh A. Establishing the sequential progression of multiple allergic diagnoses in a UK birth cohort using the General Practice Research Database. *Clin Exp Allergy* 2009 [Epub ahead of print].
- 4 Kim JS. Pediatric atopic dermatitis: the importance of food allergens. *Semin Cutan Med Surg* 2008; 27:156–160.
- A comprehensive review of the subject, including clinical management.
- 5 Rancé F, Boguniewicz M, Lau S. New visions for atopic eczema: an iPAC summary and future trends. *Pediatr Allergy Immunol* 2008; Suppl 19:17–25.
- 6 Rancé F. Food allergy in children suffering from atopic eczema. *Pediatr Allergy Immunol* 2008; 19:279–284.
- Case studies focusing on dietary manipulation, with useful clinical recommendations.
- 7 Werfel T, Ballmer-Weber B, Eigenmann PA, *et al.* Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA<sup>2</sup>LEN. *Allergy* 2007; 62:723–728.
- 8 Leung DYM. Our evolving understanding of the functional role of filaggrin in atopic dermatitis. *J Allergy Clin Immunol* 2009; 124:494–495.
- 9 Johansson SG, Bieber T, Dahl R, *et al.* Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; 113:832–836.
- 10 Gupta R, Sheikh A, Strachan DP, *et al.* Time trends in allergic disorders in the UK. *Thorax* 2007; 62:91–96.
- 11 Simpson CR, Newton J, Hippisley-Cox J, *et al.* Incidence and prevalence of multiple allergic disorders recorded in a national primary care database. *J Roy Soc Med* 2008; 101:558–563.
- 12 Simpson CR, Newton J, Hippisley-Cox J, *et al.* Trends in the epidemiology and prescribing of medication for eczema in England. *J Roy Soc Med* 2009; 102:108–117.
- 13 Sheikh A. Itch, sneeze and wheeze: the genetics of atopic allergy. *J Roy Soc Med* 2002; 95:14–17.
- 14 Asher MI, Montefort S, Björkstén B, *et al.* Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368:733–743.
- 15 Newton J. An epidemiological report for the Department of Health's review of services for allergy. London: Department of Health; 2006.
- 16 Du Toit G, Katz Y, Sasieni P, *et al.* Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008; 122:984–991.
- 17 Gupta R, Sheikh A, Strachan D, *et al.* Increasing hospital admissions for systemic allergic disorders in England: analysis of national admissions data. *Br Med J* 2003; 327:1142–1143.
- 18 Hill DJ, Hosking CS, de Benedictis FM, *et al.* Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin Exp Allergy* 2007; 38:161–168.
- 19 Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis and management. *J Allergy Clin Immunol* 1999; 104:S114–S122.
- 20 Palmer CN, Irvine AD, Terron-Kwiatkowski A, *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; 38:441–446.
- 21 Van den Oord RAHM, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *Br Med J* 2009; 339:b2433.
- A comprehensive systematic review and meta-analysis demonstrating the association between FLG gene deficits and significantly increased risk of atopic eczema.
- 22 Jung T, Stingl G. Atopic dermatitis: therapeutic concepts evolving from new pathophysiologic insights. *J Allergy Clin Immunol* 2008; 122:1074–1081.
- 23 Marenholz I, Kerscher T, Bauerfeind A, *et al.* An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. *J Allergy Clin Immunol* 2009; 123:911–916.
- An important study which demonstrates that in infants with eczema and food sensitization, genotyping of FLG mutations allows the prediction of asthma before the onset of symptoms.
- 24 O'Regan GM, Sandilands A, McLean WH, *et al.* Filaggrin in atopic dermatitis. *J Allergy Clin Immunol* 2009; 124 (Suppl 2):R2–R6.
- 25 Bath-Hextall F, Delamere FM, Williams HC. Dietary exclusions for improving established atopic eczema in adults and children: systematic review. *Allergy* 2009; 64:258–264.
- 26 Fox AT, Du Toit G, Lang A, *et al.* Food allergy as a risk factor for nutritional rickets. *Pediatr Allergy Immunol* 2004; 15:566–569.
- 27 Sheikh A, Strachan DP. The hygiene theory: fact or fiction? *Curr Opin Otolaryngol* 2004; 12:232–236.
- 28 Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, *et al.* Probiotics for the treatment of eczema: a systematic review. *Clin Exp Allergy* 2009; 39:1117–1127.
- 29 Williams HC, Grindlay DJC. What's new in atopic eczema? An analysis of systematic reviews published in 2007 and 2008. Part 2. Disease prevention and treatment. *Clin Exp Dermatol* 2009. doi: 10.1111/j.1365-2230.2009.03734.x.
- 30 Wood RA. Food-specific immunotherapy: past, present, and future. *J Allergy Clin Immunol* 2008; 121:336–337.
- 31 Lemon-Mule H, Sampson HA, Sicherer SH, *et al.* Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol* 2008; 122:977–983.
- 32 Nowak-Węgrzyn A, Bloom KA, Sicherer SH, *et al.* Tolerance to extensively heated milk in children with cow's milk allergy. *J Allergy Clin Immunol* 2008; 122:342–347.
- 33 Jones SM, Scurlock AM, Pons L, *et al.* Double-blind, placebo-controlled trial of oral immunotherapy in peanut allergic children. *J Allergy Clin Immunol* 2009; 123:S211.
- 34 Clark AT, Islam S, King Y, *et al.* Successful oral tolerance induction in severe peanut allergy. *Allergy* 2009; 64:1218–1220.
- 35 Arshad SH, Matthews S, Gant C, *et al.* Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992; 339:1493–1497.
- 36 Arshad SH, Bateman B, Sadeghnejad A, *et al.* Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007; 119:307–313.
- 37 van Schayck OCP, Maas T, Kaper J, *et al.* Is there any role for allergen avoidance in the primary prevention of childhood asthma? *J Allergy Clin Immunol* 2007; 119:1323–1328.
- 38 Wennergren G. What if it is the other way around? Early introduction of peanut and fish seems to be better than avoidance. *Acta Paed* 2009; 98:1085–1087.
- 39 McLean S, Sheikh A. Does avoidance of peanuts in early life reduce the risk of peanut allergy? *Br Med J* 2010; 340:c424 doi:10.1136/bmj.c424
- 40 ISRCTN LEAP Trial. Learning early about peanut allergy. <http://controlled-trials.com/ISRCTN94818122/leap>. [Accessed 4 January 2010]
- 41 Lack G, Fox D, Northstone K, *et al.* Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003; 348:977–985.
- 42 Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008; 121:1331–1336.