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Position Statement: Allergy prevention in children

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ABSTRACT:

The epidemic rise of allergic disease which is most apparent in “westernised” countries has occurred in parallel with many societal and lifestyle changes. It is self-evident that these environmental changes must be responsible for the increasing propensity for allergic disease. There is an ongoing search for causal associations that will facilitate identification of strategies to reverse this trend . At this stage, most allergy prevention strategies are relatively crude with small or unconfirmed effects, and newer strategies are still in experimental stages. This Australasian Society of Clinical Immunology and Allergy (ASCIA) position statement reviews current evidence and generates revised national guidelines for primary allergy prevention. It also identifies key research priorities in this area.

KEY WORDS: Allergy prevention; infants; allergens; feeding; avoidance

INTRODUCTION:

In the second half of the 20th century, asthma and allergic disease have dramatically increased in Western Countries [1]. Australia has one of the highest allergy prevalence rates in the world [2]. Up to 40% of Australian children have evidence of allergic sensitization [3] and many of these go on to develop allergic diseases such as food allergies, eczema, asthma and allergic rhinitis. These conditions frequently persist into adulthood, placing a significant burden on individuals and the healthcare system.

Strategies that reduce the risk or the severity of disease expression could have enormous impact.

BACKGROUND:

The purpose of this document is to summarise the existing evidence in order to inform and refine the current guidelines for allergy prevention.

"Strength of Recommendations" based on the World Health Organisation (WHO) "Categories of Evidence" are indicated wherever possible (on **Table 1**). In many areas more research is needed, and recommendations awarded 'D' highlight an absence of evidence at the present time rather than a confirmed absence of merit.

1. GENETIC INFLUENCES

Current knowledge

The clear familial association of asthma and allergic disease suggests genetic factors are important in pathogenesis, however no reliable genetic markers for IgE sensitization or specific allergic diseases have been identified.

Although a number of candidate genes have been defined (reviewed in [4]), none of these has yet been confirmed to play a role in pathogenesis. Genetic studies are currently not of any value in predicting allergic disease outcomes.

Specific allergic conditions such as asthma and atopic dermatitis are strongly associated with allergic sensitization (the predisposition to produce allergen-specific IgE)[5]. However, sensitization and development of allergic disease are likely to be regulated by different processes. The precise relationship between sensitisation and development of disease is still poorly understood.

Children born into atopic families are more likely to develop allergic diseases (50-80% risk) compared to those with no family history of atopy (20%). The risk appears to be higher if both parents are allergic (60-80%) as opposed to only one parent. The risk is also higher if the mother (as compared to the father) has allergic disease [6, 7].

The recent increase in allergic diseases suggests that environmental changes are responsible for unmasking genetic predisposition.

Functional genetic polymorphisms may determine differences in vulnerability to environmental change, underscoring the complexity of gene-environmental interactions. This area is still poorly understood.

Recommendations arising

- Family history of allergy and asthma can be used to identify children at increased risk of allergic disease
- At present genetic markers cannot be used to predict individuals at low or high risk of allergy

2. ENVIRONMENTAL INFLUENCES

At this time, no one environmental factor has been identified as critical in the development of allergic disease. Environmental influences are likely to be variable and multifactorial.

A) THE ROLE OF ALLERGENS

The guiding principle behind allergen avoidance strategies is the hypothesis that reducing allergen levels may reduce the risk of allergen sensitization and hence the risk of allergic disease. However, despite a clear association between sensitization and the development of allergic disease, the processes leading to

sensitization appear to be independent to those leading to disease [5]. Moreover, In many cases, allergen avoidance strategies have been ineffective in reducing allergic sensitization or associated with unexpected paradoxical effects.

i. Allergen exposure during pregnancy

The avoidance of multiple potential **food allergens** in pregnancy has not been shown to reduce the risk of allergic disease in randomized double-blind controlled trials [8-10]. Current consensus is that this practice should be discouraged because of potential nutritional compromise to the mother and fetus.

Preliminary results from large intervention studies which have achieved significant reductions in **house dust mite (HDM) levels** in homes during pregnancy and early childhood reported significant improvement in lung function at 3 and 5 years in the allergen-reduction group, however, sensitization was significantly more common [11]. Other inhaled allergen exposures (pets) are discussed below.

Recommendation arising

- Food avoidance in pregnancy is not recommended for the prevention of allergic disease (Strength of Recommendation – A)
- It is difficult to justify HDM reduction strategies in pregnancy based on current evidence and the possibility of an increased risk of sensitisation. (Strength of recommendation – B)

ii. Breastfeeding versus formula feeding

breastfeeding has multiple health benefits and should be encouraged.

Short duration of breastfeeding is associated with an increased incidence of allergic disease in the early years of life. However, the beneficial effects of exclusive breastfeeding during infancy on prevention of allergic disease in later life remain uncertain

There are inherent limitations in studies of this nature (confounding factors, recruitment and reporting biases, perceptions modifying feeding practices, inability to randomize and blind). Importantly, many studies do not make the distinction between “exclusive breastfeeding” and “any” breastfeeding.

Many studies have shown a weak protective effect on early symptoms of allergic disease (reviewed in [12]), including **atopic eczema** ([13] and others), early **wheezing** [14] and others). A systematic review of 12 prospective studies (8183 infants) [15] found that exclusive breastfeeding in the first months of life was also associated with reduced rates of subsequent **asthma** (OR 0.70. 95%CI 0.60 -0.81). and that the protective effect was greater in high risk children (OR = 0.52; 0.35-0.79). Another recent multidisciplinary review examined over 4000 articles relating to breastfeeding and allergic disease and concluded that breastfeeding in the first 4 months of life reduced the risk of asthma [16]. Conversely, a recent study reported an increased incidence of allergic disease in later childhood associated with breastfeeding, but has been criticised as breastfeeding was not exclusive and supplemental formula feeds were included in the breastfed group [17].

The effect of breastfeeding on sensitisation and atopy is less clear. In a large prospectively followed cohort of 2187 Australian children (enrolled before birth) the risk of developing a positive skin prick test reaction to common aeroallergens at 6 years of age was increased if exclusive breast-feeding was stopped (other milk was introduced) before 4 months (odds ratio 1.30; 95% CI, 1.01-1.62) [14]. While this has been supported by some studies [18], others have shown no long-term benefits, or even increased atopy ([17, 19] and others).

Recommendation arising

- Breastfeeding should be recommended because of many beneficial effects (except where contraindicated, such as with maternal HIV infection).
- The reported protection from breastfeeding against allergic disease in the early years of life is relatively small, and some studies suggest there may instead be an increased risk of disease in later life.
- The current consensus is to recommend breastfeeding for at least the first 4-6 months in children at high risk of allergic disease (Strength of Recommendation – B).

iii. Maternal allergen avoidance during lactation:

There is no convincing evidence that allergen avoidance during lactation has a protective effect. Although several studies indicate that maternal avoidance of potential food allergens (milk, egg, and fish) while

breastfeeding may reduce the risk of atopic eczema in the first years of life [20-22], other studies do not confirm this [23-25]. While a systematic Cochrane review suggested some benefits on early atopic eczema, methodological limitations make the findings difficult to interpret [26].

Recommendation arising

- Maternal dietary restrictions during breastfeeding are not recommended for disease prevention (Strength of Recommendation – A).

iv. Infant formulae

The most recent Cochrane reviews of allergy and infant feeding concluded that **hydrolysed formulas** reduce the risk of infant allergy (compared to cows milk formulae), but that these hydrolysed formulae should not be offered in favour of breast feeding for allergy prevention [27 28].

Use of Extensively hydrolysed formulas (eHF) in combination with avoidance of cow's milk proteins and solid foods during the first 4 months of life in high-risk infants is associatedwith a reduced cumulative incidence of atopic eczema and food allergy, especially cows milk allergy until the age of 4 years. A recent meta-analysis of 4 studies (386 infants) found a significant reduction in allergy incidence in infancy (typical RR 0.63, 95% CI 0.47, 0.85; RD -0.15, 95% CI -0.25, -0.06) [29]. There is no evidence to support feeding with a hydrolysed formula for the prevention of allergy in preference to exclusive breastfeeding [29].

Partially hydrolysed formulas (pHF) (with moderately reduced allergenicity) have also been reported to have an allergy preventive effect in randomised prospective studies of high-risk infants ([30-32] and others). A recent meta-analysis found no difference between the effects of extensive versus partially hydrolysed formula [29]. Because of great variations in study design and diagnostic criteria, the relative efficacy of the different formulae tested in different studies cannot be compared directly.

Prospective studies have shown that **soy formulas** are as allergenic as normal cows milk formulae [33 34 35], but some controversy remains. Soy formulas and other milks (such as goats formula) are not recommended for the prevention of allergic disease.

All studies have been in high risk infants

Recommendation arising

- If breastfeeding is not possible in high risk infants a hydrolysed formula is recommended (rather than a conventional cows milk based formulae) (Strength of Recommendation – A)
- Both extensively hydrolyzed and partially hydrolyzed formulas have been shown to have protective effects (Strength of recommendation – A). Partially hydrolysed formula is available in Australia without prescription. Extensively hydrolyzed formula is available with prescription but is only subsidised for the treatment of infants with combined cow's milk and soy allergy.
- These preventive effect have **only** been demonstrated in **high risk infants with atopic heredity** (Strength of Recommendation – A).
- Soy formulae are not recommended for the reduction of food allergy risk (Strength of Recommendation – B).
- Other formulae (eg. goats milk) are not recommended for the same reason (Strength of Recommendation – D).

v. Infant diet

Solid foods: Studies suggest that delayed introduction of solid foods may reduce or delay the onset of infantile allergic diseases in the first year of life, including atopic dermatitis and food allergies ([9, 36] and others). However, these effects are modest, and long term benefits are not certain. A 2002 Cochrane meta-analysis [28] reviewed 6 randomised control trials of dietary restriction (in combination with hydrolysed formulae) in infants at high risk of allergy and concluded that these interventions were associated with reduced risk (RR 0.4, 95%CI 0.19-0.85) of wheezing at 1 year of age. A recent study [37] reported increased risk of atopic eczema in preterm infants (odds ration 3.49) if solid foods were introduced before 17 weeks of age, however, long term effects were not examined.

Duration of restriction diet: There is currently no evidence that dietary restrictions for longer periods (after 6 months of age) have additional benefits.

NB: In children with existing sensitisations or overt allergic disease (or those deemed to be at high risk for other reasons) it has been common clinical practice to recommend avoidance of potentially allergenic foods

such as egg and milk until 12 months of age, and peanuts, nuts and shellfish until after 2-4 years of age. This practice is based on a theoretical benefit to protect an "immature immune system". There is no evidence that avoiding peanuts, nuts, shellfish during early life is harmful for high-risk children. Nevertheless, although the "benefit" is not known, the "costs" of doing nothing are perceived as high, and the "cost" of this intervention are relatively low.

Recommendations arising

- Complementary foods (including normal cows milk formulae) should be delayed for at least 4-6 months. (Strength of Recommendation – B; the meta-analysis [28] did not look at this intervention in isolation). This preventive effect has **only** been demonstrated in **high risk infants with atopic heredity**, and **preterm** infants (Strength of Recommendation – B).
- There is no evidence that dietary elimination after the age of 4-6 months has a preventive effect, though this needs additional investigation. (Strength of Recommendation – B)
- **Avoidance of peanut, nut and shellfish for the first 2-4 years of life may be recommended as this is unlikely to cause harm. (Strength of Recommendation – D)**

vi. Exposure to house dust mite (HDM)

Stringent environmental control measures can dramatically reduce HDM levels [38, 39], and even less stringent measures (mite covers for bedding and washing instructions) significantly reduce HDM levels [40]. There is a dose relationship between HDM levels in the home and sensitisation to HDM ([41, 42]).

However, while sensitisation is a strong risk factor for persistent asthma, wheeze and bronchial hyperactivity [43, 44] the relationship between early allergen exposure and the development of clinical symptoms has not been confirmed.

The Manchester Asthma and Allergy Study (MAAS) demonstrated that reduction in HDM levels in pregnancy and the postnatal period was associated with **less respiratory symptoms** at 1 year of age [45] and **better lung function** at 3 and 5 years, but significantly **increased risk of sensitization to HDM** (RR 1.61 95%CI 1.02-2.55) [11]. The Australian CAPS study which implemented HDM avoidance in early childhood showed a small but significant reduction in HDM sensitization at 3 years but no change in respiratory symptoms [46]. HDM reduction interventions in older children (5-7 years) also showed a reduced rate of new sensitization to HDM after 12 months [47].

Although some studies have suggested benefits of reducing early HDM exposure, long term data are still not available. Conflicting evidence (reviewed in [38]) and recent reports of increased sensitization risk have raised concern [11]. Further follow up of ongoing cohorts is required before any recommendations can be made within the public health context [38].

Recommendations arising

- HDM avoidance has been shown to benefit those patients with established disease and sensitivity, but whether reduced exposure will protect against the development of new disease remains uncertain.
- No recommendation can be made at this time regarding the implementation of HDM avoidance measures for prevention of allergic disease. HDM avoidance measures in pregnancy and early infancy may delay the onset of allergic disease but no long-term data are available and the effects on sensitisation are inconsistent (Strength of Recommendation – B).

vii. Exposure to pet allergens

The relationship between pet exposure and development of allergic disease is unclear. Pet exposure in the first year of life has been associated with a **lower prevalence of asthma and airway reactivity** in later childhood [48] and with **less sensitisation** to not only pet allergens, but also less sensitisation to **other allergens** at 6 years of age [49 50, 51 52], particularly in children with a parental history of atopy [51 52]. Other studies have not found a protective effect of early pet exposure on either sensitisation to cat, or the development of cat allergy or asthma [53 54]. A systematic review concluded that exposure to pets increases the risk of asthma and wheezing in older children (>6 years) but not children <6 years [55].

The relationship between pet allergen exposure and sensitization appears to be "bell shaped" rather than linear [56], such that sensitization is less likely at both very low levels and at very high levels (which may induce tolerance). The potential mechanisms are not yet understood but may relate to higher levels of **bacterial endotoxin** [57] in the presence of cats, dogs and cockroaches in the home [58]. These observations have provided ongoing support for the "hygiene hypothesis" that rising rates of allergic disease are due to increasingly "clean" environments, which fail to provide adequate Type 1 stimulation from bacteria for suppression of Type 2 allergic responses [59].

Recommendations arising

- In patients with established allergic disease and sensitization to pet allergen, pet removal may be of benefit
- There is no consistent evidence that either exposure to or avoidance of pet allergens has a protective effect against development of allergic disease. No recommendations can be made regarding pet exposure and prevention of allergic disease. (Strength of Recommendation – B).
- If a family already has pets it is not necessary to remove them for the purposes of allergy prevention, however, it is also not recommended to get new pets for the purposes of allergy prevention (Strength of recommendation – B).

B) THE ROLE OF POLLUTANTS AND IRRITANTS

Maternal smoking in pregnancy has adverse effects on infant lung development [60-62]. Parental smoking has also been associated with wheezing illness in early childhood [63] [64] [65]. The relationship between cigarette smoke exposure and atopy is less clear. Some studies have reported associations with increased risk of atopy [66-69], however, a large prospective study of asthma and wheezing in childhood found that although maternal smoking was associated with wheezing in the first three years of life this was not associated with asthma and allergies at 6 years [65].

The role of other indoor pollutants is poorly understood. In some populations the use of home gas appliances has been associated with an increase risk of HDM sensitisation and subsequent respiratory symptoms [70], but this needs to be confirmed.

Recommendations arising

- Pregnant women should be advised not to smoke in pregnancy.
- Parents should be advised not to smoke. (Strength of Recommendation – B)
- Children should not be exposed to cigarette smoke in confined spaces. (Strength of Recommendation – B).
- Parents should also minimize exposure to indoor air pollutants (Strength of Recommendation – C).

C) THE ROLE OF EARLY INFECTION AND OTHER MICROBIAL EXPOSURE

Although infectious agents have a clear role in triggering established allergic diseases (such as asthma and atopic dermatitis), their role in the development of allergic disease remains controversial. The effects of microorganisms are likely to vary with the timing of exposure and the nature of the organism.

Bacteria are the most powerful T helper Type 1 (Th1) immuno-stimulants in the normal environment. It has been proposed that early microbial encounter, may reduce the risk of Th2 mediated allergic responses. However, studies investigating the relationship between early childhood infection and atopy risk have been inconsistent or difficult to interpret [71] [72]. There is currently no consistent evidence that early bacterial infection reduces allergy risk. A recent large national cohort study (including 24 341 mother child pairs [73] found that early infections do not protect from allergic diseases such as atopic dermatitis. However, other indirect markers of microbial exposure (such as early daycare attendance, having 3 or more siblings, farm residence, and pet keeping) were protective. This highlights the emerging concept that overall "microbial burden" rather than specific infections may be more relevant in early life [74].

While viruses also play a clear role as triggers for asthmatic symptoms in established disease their role in disease pathogenesis remains poorly understood. Respiratory syncytial virus (RSV) or other viral infections in infancy have been implicated as risk factors for subsequent asthma in the first 6 years of life

[72, 75, 76]. These findings suggest that significant infection-induced airway inflammation during the early period of postnatal lung growth and development can have profound long-term effects [77], but the mechanisms remain unclear. Furthermore, it is now recognised that virus associated wheezing in infancy ("infant wheezers") is a heterogeneous group of conditions [78] and only a proportion will ultimately develop asthma and allergic diseases.

The potential for bacterial products to promote Th1 immunity (and immunoregulatory pathways) have made these logical agents for allergy prevention. **Probiotics** and other microbial products have recently emerged as leading microbial candidates for early immune modification. There is growing evidence that nonpathogenic microflora (probiotics) may be protective against allergic disease. Differences in intestinal microflora have been noted in allergic children, including lower levels of probiotic bacteria (such as bifidobacteria) and higher levels of pathogenic bacteria (such as *Staphylococcus aureus* and *Clostridium difficile* ([79, 80] and others). Although the mechanisms are not clear, it has been suggested that early and more extensive colonisation with commensal microbial flora in healthy infants could promote oral tolerance and reduce the risk of allergic disease. Accordingly, Isolauri and colleagues recently demonstrated that administration of probiotics (in the final weeks of pregnancy and the first 6 months of life) protected against the development of atopic eczema at 1 year [81] and 4 years of age [82]. Other studies are underway to further evaluate the benefits of probiotics in allergic disease prevention [81].

Recommendations / comments:

- No conclusions can be made at this time regarding microbial infection and prevention of allergic disease (Strength of recommendation – C).
- No conclusions can be made regarding the role of viral infections in early life and prevention of allergic disease (Strength of recommendation – C)
- There is no conclusive evidence that antibiotic usage in the first year of life is associated with an increased risk of allergic disease. Unnecessary prescription of antibiotics should be discouraged for many reasons (to avoid side effects and the emergence of antibiotics resistant organisms) but there is no indication to avoid these treatments specifically in children at risk of allergy. If antibiotics are indicated clinically they may be prescribed without concern that they will increase the risk of allergic disease. (Strength of Recommendation – B)
- There are no clear relationships between attendance at day care and the development of allergic disease. (Strength of Recommendation – B).
- Although probiotics appear to be safe, follow up studies are needed to confirm long term effects. No recommendations can be made at this time based upon limited evidence.
- The use of other bacterial products for allergy prevention is still experimental

D) THE ROLE OF IMMUNOMODULATORY DIETARY NUTRIENTS

There is growing interest in the role of dietary components with recognized immunomodulatory effects such as **antioxidants** and **polyunsaturated fatty acids** (PUFA) on the development of allergic disease. Preliminary studies examining the role of omega-3 (n-3) PUFA supplementation in infancy have reported reduced prevalence of wheeze at 18 months and allergic cough at 3 years but no effect on wheeze at 3 years[46, 83]. Furthermore, there was no effect on sensitization to foods, or atopic dermatitis.

Recommendations:

- No recommendations can be made at this time due to limited evidence.

SECONDARY PREVENTION IN CHILDREN WITH EARLY SENSITISATION OR DISEASE

Existing strategies to prevent allergies are relatively ineffective and a significant proportion of "high risk" children will still develop sensitisation or disease. If these children can be identified when they have early disease, future strategies may provide avenues for:

a) reducing the risk of progression to new sensitisations, and other persistent forms of disease (in the "atopic march"), and / or
b) reducing the severity of disease.

Preliminary evidence suggests that early interventions in allergic children may modify progression of sensitization patterns and / or the development of new allergic diseases. Moller and colleagues [84] observed that children treated with specific (pollen) immunotherapy for allergic rhinitis are significantly

less likely to develop asthma than those who do not receive active treatment. Immunotherapy can also reduce the development of new sensitisations in patients monosensitised to aeroallergens (HDM) [85]. Other interventions, such as the use of antihistamines (cetirazine) in children with early disease are also being investigated because of preliminary evidence that this may modify disease progression [86].

Recommendations:

- Immunotherapy in children with allergic rhinitis may prevent the subsequent development of asthma (Level of evidence – 1b).

THE FUTURE : PRIMARY ALLERGY VACCINATION?

The use of **allergen vaccines** / **preventative immunotherapy** has been long proposed as one method of primary prevention [87]. Potential strategies involve utilising and enhancing the natural processes which usually efficiently terminate IgE responses to allergens. Accordingly, vaccines for primary prevention would need to be administered in early infancy, when immune responses are still "plastic" and not "committed". In murine systems neonatal administration of allergen can inhibit the development of Th2 type airways disease, but the dose and delivery method appear crucial [88].

The enteric mucosal immune system plays an extremely efficient and pivotal role in the development of tolerance. Repeated exposure to allergen through the gastrointestinal tract during early life leads to the development of tolerance, even in highly atopic individuals (reviewed in [87]). It is proposed that exposure to aeroallergens through this route may promote the local (IgA) immune responses which promote persistent systemic tolerance, preventing the emergence of pathogenic Th2 responsive memory T cells. Intranasal administration of allergen may theoretically have similar benefits. Parenteral administration of allergen with appropriate immunoregulatory adjuvants (e.g. CpG-motifs) may also be an avenue for promoting normal immune maturation during immune development. Studies using "high dose" mucosal delivery of aeroallergen combinations in infants at high risk of allergic disease (or those with early evidence of sensitization such as food allergy) are about to commence. Future methods of safely promoting tolerance in humans may include novel "allergen vaccine" strategies.

CONCLUDING COMMENTS:

There is a growing need to reduce the mounting personal, social and economic cost of allergic disease. While there has been some success in managing established disease, strategies to prevent the development of these processes will be of greater value in the long term. Currently, our capacity to prevent allergic disease is constrained by limited understanding of disease pathogenesis and aetiological factors, particularly of the early exposures responsible for the recent increase in allergic disease. There is also an inability to accurately identify atopic individuals before sensitisation occurs. All of these areas need to be investigated more fully in order to determine how tolerance mechanisms can be promoted without adverse effects.

For further information on allergy, asthma or immune diseases, visit www.allergy.org.au, the web site of the Australiasian Society of Clinical Immunology and Allergy (ASCIA). ASCIA is the peak professional body of Clinical Allergists and Immunologists in Australia and New Zealand.

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TABLE 1: WHO Categories of Evidence and Strength of recommendations

WHO Categories of Evidence

Ia: Evidence from meta-analysis of randomised controlled trials
Ib: Evidence from at least one randomised controlled trial
IIa: Evidence from at least one controlled study without randomisation
IIb: Evidence from at least one other type of quasi-experimental study
III: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV. Expert opinion

WHO Strength of Recommendations:

A: Directly based on category I evidence
B: Directly based on category II evidence or extrapolated recommendation from category I evidence
C: Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D: Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

TABLE 2: SUMMARY OF SPECIFIC RECOMMENDATIONS:

Identifying infants at risk of allergic disease	A family history of allergy and asthma can be used to identify children at increased risk of allergic disease
Allergen avoidance in pregnancy	Dietary restrictions in pregnancy are not recommended. Aeroallergen avoidance in pregnancy has not been shown to reduce allergic disease, and is not recommended.
Breastfeeding	Breastfeeding should be recommended because of other beneficial effects. Maternal dietary restrictions during breastfeeding are not recommended.
Infant formulae	In high risk infants only, If breast feeding is not possible a hydrolysed formulae is recommended (rather than conventional cows milk based formulae). Partially hydrolysed formula is available in Australia without prescription. Extensively hydrolyzed formula is more expensive, only available on prescription, and only subsidised for treatment of combined cow's milk and soy allergic infants. Soy formulae and other formulae (eg. Goat's milk) are not recommended for the reduction of food allergy risk.
Infant diet	Complementary foods (including normal cows milk formulae) should be delayed for at least 4-6 months This preventive effect has **only** been demonstrated in **high-risk infants** There is no evidence that an elimination diet after the age of 4-6 months provides a protective effect, though this needs additional investigation Avoidance of peanut, tree nuts, and shellfish may be recommended in high risk children during the first years of life pending further study as this is unlikely to cause harm, however it must be emphasised that there is no evidence to support this recommendation.
House dust mite exposure	Before definitive recommendations can be made, further research is needed to determine the relationship between early HDM exposure and the development of sensitisation and disease. No recommendation can be made at this time regarding the implementation of HDM avoidance measures for prevention of allergic disease.
Pet exposure	No recommendations can be made at this time regarding exposure to pets in early life and the development of allergic disease. If a family already has pets it is not necessary to remove them, unless the child develops evidence of pet allergy (as assessed by an allergy specialist). However, at this stage we do not recommend getting new pets to reduce allergy.
Smoking and other irritants	Pregnant women should be advised not to smoke in pregnancy.

	Parents should be advised not to smoke.
The role of microbial agents	No recommendations can be made at this time regarding the use of probiotic supplements for the prevention of allergic disease
Secondary prevention strategies	Immunotherapy may be considered as a treatment option for children with allergic rhinitis, and may prevent the subsequent development of asthma.

TABLE 3: FURTHER RESEARCH REQUIRED

1. Genetic factors:
    - genetic pathways involved in pathogenesis
    - the relationship between “sensitization” and “disease”
    - better predictive markers
    - gene – environment interactions
2. Formulas:
    - protective effects of different hydrolysed formulae
3. HDM exposure:
    - the relationship between HDM exposure and sensitization or development of allergic disease
4. Pet exposure:
    - the relationship between pet allergens and sensitization or development of allergic disease, including the possible interplay of other immunomodulatory factors (such as endotoxin) which could also be associated with pet exposure.
5. Smoking and other pollutants:
    - effects on the developing immune system
    - role in development of allergic disease
6. Microbial agents:
    - the interaction between viral respiratory tract infections and subsequent predisposition to allergic airways inflammation.
    - the interaction between other early childhood infections and the risk of allergic disease.
    - the role of endotoxin and other bacterial products (including probiotics) on immune development or disease prevention.
    - confirm preliminary findings that probiotics may reduce the risk of allergic disease.
7. The role of dietary nutrients with immunomodulatory properties:
    - confirm the potential benefits of dietary supplements (such as n-3 PUFA).
    - examine risks associated with the use of vitamin supplements.
8. Secondary prevention strategies:
    - Further research is needed to clearly define specific strategies that could modify the progression of the “atopic march” in children with early evidence of disease.
9. Primary prevention strategies:
    - Further research is needed to develop more effective strategies need to be developed to prevent allergic disease.

References

1. Lewis S. ISAAC--a hypothesis generator for asthma? International Study of Asthma and Allergies in Childhood. Lancet 1998; 351:1220-1.
2. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998; 351:1225-32.
3. Peat J, van-den-Berg R, Green W, Mellis C, Leeder S, Woolcock A. Changing prevalence of asthma in Australian school children. Br Med J 1994; 308:1591-96.
4. Halapi E, Hakonarson H. Recent development in genomic and proteomic research for asthma. Curr Opin Pulm Med 2004; 10:22-30.
5. Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von Mutius E, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. Lancet 2000; 356:1392-7.
6. Kjellman NI. Prediction and prevention of atopic allergy. Allergy 1998; 53:67-71.
7. Zeiger R, Heller S, Mellon M, Halsey J, Hamburger R, Sampson H. Genetic and environmental factors affecting the development of atopy through age 4 in children with atopic parents : a prospective radomised study of food allergen avoidance. Pediatr Allergy Immunol 1992; 3:110-27.
8. Kramer MS. Maternal antigen avoidance during pregnancy for preventing atopic disease in infants of women at high risk. Cochrane Database Syst Rev 2000; 2.
9. Falth-Magnusson K, Kjellman N-I. Allergy prevention by maternal elimination diet during late pregnancy - a five year follow-up of a randomised trial. J Allergy Clin Immunol 1992; 89:709-13.
10. Falth-Magnusson K, Kjellman NIM. Development of atopic disease in babies whose mothers were receiving exclusion diet during pregnancy - a randomized study. J Allergy Clin Immunol 1987; 80:869-75.
11. Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P, et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. NAC Manchester Asthma and Allergy Study Group. Am J Respir Crit Care Med 2004; 170(4) Epub:433-9.
12. Foucard T. Is prevention of allergy and asthma possible? Acta Paediatr Suppl 2000; 89:71-5.
13. Schoetzau A, Filipiak-Pittroff B, Franke K, Koletzko S, Von Berg A, Gruebl A, et al. Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age. Pediatr Allergy Immunol 2002; 13:234-42.
14. Oddy WH, Holt PG, Sly PD, Read AW, Landau LI, Stanley FJ, et al. Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. Bmj 1999; 319:815-9.
15. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. J Pediatr 2001; 139:261-6.
16. van Odijk J, Kull I, Borres MP, Brandtzaeg P, Edberg U, Hanson LA, et al. Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966-2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. Allergy 2003; 58:833-43.
17. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. Lancet 2002; 360:901-7.
18. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. Lancet 1995; 346:1065-9.
19. Bergmann RL, Diepgen TL, Kuss O, Bergmann KE, Kujat J, Dudenhausen JW, et al. Breastfeeding duration is a risk factor for atopic eczema. Clin Exp Allergy 2002; 32:205-9.
20. Chandra RK. Five-year follow-up of high-risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas. J Pediatr Gastroenterol Nutr 1997; 24:380-8.
21. Businco L, Marchetti F, Pellegrini G, Cantani A, Perlini R. Prevention of atopic disease in "at-risk newborns" by prolonged breast-feeding. Ann Allergy 1983; 51:296-9.
22. Chandra RK, Puri S, Suraiya C, Cheema PS. Influence of maternal food antigen avoidance during pregnancy and lactation on incidence of atopic eczema in infants. Clinical Allergy 1986; 16:563-9.
23. Lilja G, Dannaeus A, Foucard T, Graff-Lonnevig V, Johansson SG, Oman H. Effects of maternal diet during late pregnancy and lactation on the development of atopic diseases in infants up to 18 months of age--in-vivo results. Clin Exp Allergy 1989; 19:473-9.

24. Sigurs N, Hattevig G, Kjellman B. Maternal avoidance of eggs, cow's milk, and fish during lactation: effect on allergic manifestations, skin-prick tests, and specific IgE antibodies in children at age 4 years. Pediatrics 1992; 89:735-9.
25. Hattevig G, Sigurs N, Kjellman B. Effects of maternal dietary avoidance during lactation on allergy in children at 10 years of age. Acta Paediatr 1999; 88:7-12.
26. Kramer MS. Maternal antigen avoidance during lactation for preventing atopic disease in infants of women at high risk. Cochrane Database Syst Rev 2000; 2.
27. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev 2003:CD003664.
28. Ram FS, Ducharme FM, Scarlett J. Cow's milk protein avoidance and development of childhood wheeze in children with a family history of atopy. Cochrane Database Syst Rev 2002; 3.
29. Osborn D, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev 2003; 4:CD003664.
30. Vandenplas Y, Hauser B, Van den Borre C, Clybouw C, Mahler T, Hachimi-Idrissi S, et al. The long-term effect of a partial whey hydrolysate formula on the prophylaxis of atopic disease. Eur J Pediatr 1995; 154:488-94.
31. Chandra RK, Singh G, Shridhara B. Effect of feeding whey hydrolysate, soy and conventional cow milk formulas on incidence of atopic disease in high risk infants. Ann Allergy 1989; 63:102-6.
32. Chan YH, Shek LP, Aw M, Quak SH, Lee BW. Use of hypoallergenic formula in the prevention of atopic disease among Asian children. J Paediatr Child Health 2002; 38:84-8.
33. Burr ML, Limb ES, Maguire MJ, Amarah L, Eldridge BA, Layzell JC, et al. Infant feeding, wheezing, and allergy: a prospective study. Archives of Disease in Childhood 1993; 68(6):724-8.
34. Businco L, Bruno G, Giampietro PG, Cantani A. Allergenicity and nutritional adequacy of soy protein formulas. J Pediatr 1992; 121:S21-8.
35. Chandra RK, Puri S, Hamed A. Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants. Bmj 1989; 299:228-30.
36. Zeiger R, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. J Allergy Clin Immunol 1995; 96 (6):1179-90.
37. Morgan J, Williams P, Norris F, Williams CM, Larkin M, Hampton S. Eczema and early solid feeding in preterm infants. Arch Dis Child 2004; 89:309-14.
38. Gore C, Custovic A. Can we prevent allergy? Allergy 2004; 59:151-61.
39. Simpson A, Simpson B, Custovic A, Craven M, Woodcock A. Stringent environmental control in pregnancy and early life: the long-term effects on mite, cat and dog allergen. Clin Exp Allergy 2003; 33:1183-9.
40. Koopman LP, van Strien RT, Kerkhof M, Wijga A, Smit HA, de Jongste JC, et al. Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. Am J Respir Crit Care Med 2002; 166:307-13.
41. Platts-Mills TA, Rakes G, Heymann PW. The relevance of allergen exposure to the development of asthma in childhood. J Allergy Clin Immunol 2000; 105:S503-8.
42. Wahn U, Bergmann R, Kulig M, Forster J, Bauer CP. The natural course of sensitisation and atopic disease in infancy and childhood. Pediatr Allergy Immunol 1997; 8:16-20.
43. Ponsonby AL, Kemp A, Dwyer T, Carmichael A, Couper D, Cochrane J. Feather bedding and house dust mite sensitization and airway disease in childhood. J Clin Epidemiol 2002; 55:556-62.
44. Lau S, Nickel R, Niggemann B, Gruber C, Sommerfeld C, Illi S, et al. The development of childhood asthma: lessons from the German Multicentre Allergy Study (MAS). Paediatr Respir Rev 2002; 3:265.
45. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. Lancet 2001; 358:188-93.
46. Peat JK, Mihrshahi S, Kemp AS, Marks GB, Tovey ER, Webb K, et al. Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. J Allergy Clin Immunol 2004; 114:807-13.
47. Arshad SH, Bojarskas J, Tsitoura S, Matthews S, Mealy B, Dean T, et al. Prevention of sensitization to house dust mite by allergen avoidance in school age children: a randomized controlled study. Clin Exp Allergy 2002; 32:843-9.
48. Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergy development? Clin Exp Allergy 1999; 29:611-7.

49. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. Jama 2002; 288:963-72.
50. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. Lancet 2001; 357:752-6.
51. Roost HP, Kunzli N, Schindler C, Jarvis D, Chinn S, Perruchoud AP, et al. Role of current and childhood exposure to cat and atopic sensitization. European Community Respiratory Health Survey. J Allergy Clin Immunol 1999; 104:941-7.
52. Svanes C, Jarvis D, Chinn S, Burney P. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. J Allergy Clin Immunol 1999; 103:415-20.
53. Sporik R, Squillace SP, Ingram JM, Rakes G, Honsinger RW, Platts-Mills TA. Mite, cat, and cockroach exposure, allergen sensitisation, and asthma in children: a case-control study of three schools. Thorax 1999; 54:675-80.
54. Ingram JM, Sporik R, Rose G, Honsinger R, Chapman MD, Platts-Mills TA. Quantitative assessment of exposure to dog (Can f 1) and cat (Fel d 1) allergens: relation to sensitization and asthma among children living in Los Alamos, New Mexico. J Allergy Clin Immunol 1995; 96:449-56.
55. Apelberg BJ, Aoki Y, Jaakkola JJ. Systematic review: Exposure to pets and risk of asthma and asthma-like symptoms. J Allergy Clin Immunol 2001; 107:455-60.
56. Platts-Mills TA, Perzanowski M, Woodfolk JA, Lundback B. Relevance of early or current pet ownership to the prevalence of allergic diseases. Clin Exp Allergy 2002; 32:1259.
57. von Mutius E, Braun-Fahrlander C, Schierl R, Riedler J, Ehlermann S, Maisch S, et al. Exposure to endotoxin or other bacterial components might protect against the development of atopy. Clin Exp Allergy 2000; 30:1230-4.
58. Heinrich J, Gehring U, Douwes J, Koch A, Fahlbusch B, Bischof W, et al. Pets and vermin are associated with high endotoxin levels in house dust. Clin Exp Allergy 2001; 31:1839-45.
59. von Mutius E. Pro: the increase in asthma can be ascribed to cleanliness. Am J Respir Crit Care Med 2001; 164:1106-7; discussion 8-9.
60. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouef PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet 1996; 348:1060-64.
61. Brown RW, Hanrahan JP, Castille RG, Tager IB. Effect of maternal smoking during pregnancy on passive respiratory mechanics in early infancy. Pediatr Pulmonol 1995; 19:23-8.
62. Hoo A, Matthias H, Dezateux C, Costeloe K, Stocks J. Respiratory function among preterm infants whose mothers smoked during pregnancy. Am J Respir Crit Care Med 1998; 158:700-5.
63. Martinez FD, Cline M, Burrows B. Increased incidence of asthma in children of smoking mothers. Pediatrics 1992; 89:21-6.
64. Halken S, Host A, Nilsson L, Taudorf E. Passive smoking as a risk factor for development of obstructive respiratory disease and allergic sensitization. Allergy 1995; 50:97-105.
65. Martinez F, Wright A, Taussig L, al e. Asthma and wheezing in the first years of life. N Eng J Med 1995; 332:133-8.
66. Weiss ST, Tager IB, Munoz A, Speizer FE. The relationship of respiratory infections in early childhood to the occurrence of increased levels of bronchial responsiveness and atopy. Am Rev Respir Dis 1985; 131:573-8.
67. Kulig M, Luck W, Lau S, Niggemann B, Bergmann R, Klettke U, et al. Effect of pre- and postnatal tobacco smoke exposure on specific sensitization to food and inhalant allergens during the first 3 years of life. Multicenter Allergy Study Group, Germany [In Process Citation]. Allergy 1999; 54:220-8.
68. Ronchetti R, Macri F, Ciofetta G, Indinnimeo L, Cutrera R, Bonci E, et al. Increased serum IgE and increased prevalence of eosinophilia in 9-year-old children of smoking parents. J Allergy Clin Immunol 1990; 86:400-7.
69. Wjst M, Heinrich J, Liu P, Dold S, Wassmer G, Merkel G, et al. Indoor factors and IgE levels in children. Allergy 1994; 49:766-71.
70. Ponsonby AL, Dwyer T, Kemp A, Couper D, Cochrane J, Carmichael A. A prospective study of the association between home gas appliance use during infancy and subsequent dust mite sensitization and lung function in childhood. Clin Exp Allergy 2001; 31:1544-52.
71. Wickens KL, Crane J, Kemp TJ, Lewis SJ, D'Souza WJ, Sawyer GM, et al. Family size, infections, and asthma prevalence in New Zealand children. Epidemiology 1999; 10:699-705.
72. Ponsonby AL, Couper D, Dwyer T, Carmichael A, Kemp A. Relationship between early life respiratory illness, family size over time, and the development of asthma and hay fever: a seven year follow up study. Thorax 1999; 54:664-9.

73. Benn CS, Melbye M, Wohlfahrt J, Bjorksten B, Aaby P. Cohort study of sibling effect, infectious diseases, and risk of atopic dermatitis during first 18 months of life. Bmj 2004; 328:1223.
74. Martinez FD. The coming-of-age of the hygiene hypothesis. Respir Res 2001; 2:129-32.
75. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999; 354:541-5.
76. Oddy WH, de Klerk NH, Sly PD, Holt PG. The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. Eur Respir J 2002; 19:899-905.
77. Holt PG, Sly PD. Interactions between respiratory tract infections and atopy in the aetiology of asthma. Eur Respir J 2002; 19:538-45.
78. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. New England Journal of Medicine 1995; 332 (3):133-8.
79. Bjorksten B, Naaber P, Sepp E, Mikelsaar M. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. Clin Exp Allergy 1999; 29:342-6.
80. Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol 2001; 107:129-34.
81. Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet 2001; 357:1076-9.
82. Kalliomaki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet 2003; 361:1869-71.
83. Mihrshahi S, Peat JK, Marks GB, Mellis CM, Tovey ER, Webb K, et al. Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS). J Allergy Clin Immunol 2003; 111:162-8.
84. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002; 109:251-6.
85. Pajno GB, Bearberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitisations in asthmatic children monosensitised to house dust mite by specific immunotherapy. A six year follow-up study. Clin Exp Allergy 2001; 31:1392-7.
86. Warner JO. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. J Allergy Clin Immunol 2001; 108:929-37.
87. Holt PG. A potential vaccine strategy for asthma and allied atopic diseases during early childhood. Lancet 1994; 344:456-8.
88. Hogan SP, Foster PS, Charlton B, Slattery RM. Prevention of Th2-mediated murine allergic airways disease by soluble antigen administration in the neonate. Proc Natl Acad Sci U S A 1998; 95:2441-5.