The burden of asthma and atopic disease is growing for patients and society. With the rise in numbers of patients and their associated costs, efforts to find effective primary and secondary preventive measures are growing too. With increasing interest in atopic conditions, the number of well-designed trials has increased and we are now beginning to see more reliable results upon which treatment recommendations could be based. Whilst primary prevention would be ideal, it is likely to be expensive and difficult to implement for the whole population. As targeting the whole population for primary prevention may be impossible, we need accurately to identify, very early on, those who are at risk or focus on secondary prevention of allergic disease in those at the beginning of the atopic march. However, we also lack conclusive long-term data on the effect of prevention measures, thus making it difficult to give clear advice. This article reviews the evidence (or lack of it) for primary and secondary prevention of asthma and allergic diseases.

DEFINITIONS

There are several well-designed longitudinal primary prevention studies in progress. At the other end of the spectrum, i.e. the treatment of established disease, there is a wealth of information from trials investigating the prevention of exacerbation with various avoidance or intervention measures (e.g. avoidance of the various inhalant allergens, administration of antioxidants, dietary and pharmaceutical interventions). Secondary prevention studies, however, are few and far between. We divided the studies into primary and secondary prevention of allergic airways disease according to the following definitions:

Primary prevention: elimination of any risk/aetiological factors BEFORE they cause disease.
Secondary prevention: diagnosis and therapy at the earliest possible point in disease development.
Tertiary prevention: limitation of disease effects (e.g. treatment, rehabilitation).

These definitions can be narrowed down when discussing prevention of allergic airways disease. Boner et al. recently reviewed this topic and, taking house dust mite sensitisation as a major risk factor for the development of asthma, gave the following definition:

Primary prevention: prevention of mite sensitisation
Secondary prevention: prevention of clinical asthma in mite-sensitive children
Tertiary intervention: reduction in severity of asthma due to mite sensitivity

The actual risk factor on which the intervention is targeted is interchangeable and herein lies one of the problems – it is not clear what exactly needs to be prevented and when. Where does primary prevention end and secondary prevention begin? When does secondary prevention turn into tertiary intervention?

Even for primary prevention, it is not clear when avoidance or intervention needs to begin. Data on whether or
not in-utero sensitisation to inhalant allergens is possible and/or important continue to emerge and this topic is still controversial.9–12 Sole antenatal preventative measures have not been shown to be beneficial.13,14 Most of the antenatal measures have been continued, at least to some extent, postnatally and therefore it is not possible to know when the benefit occurred.2,4,15,16 For secondary prevention, it is even more difficult to define a starting point. Studies to date have taken anything from raised IgE, sensitisation to any allergen, atopic dermatitis or allergic rhinitis as a clinical point at which further preventative measures have been implemented.17–22 Insufficient data are available on the long-term progression of the atopic march and the long-term effects of interventions to allow the definition of a precise point at which secondary prevention should occur.

Tertiary prevention/intervention tends to be aimed at reducing morbidity of existing disease. With respect to allergen avoidance, it seems to be viewed mostly as a treatment adjunct.

WHO NEEDS PREVENTION MEASURES?

Predictors of allergic airways disease are poor, especially when considering primary prevention. Family history of atopic disease, maternal asthma and environmental tobacco smoke exposure have been associated with the development of asthma.23–25 Unfortunately, many children who have none of these risk factors will later develop asthma and they will be missed if only 'high-risk' families are targeted.26 Cord IgE levels are not useful in predicting asthma.27,28 Other known risk factors for allergic airway disease appear in infancy or early childhood, and identify the child as being atopic and therefore suitable for secondary rather than primary prevention.

In early childhood, sensitisation to egg, especially when persistent, and early atopic dermatitis have been associated with a higher risk of developing asthma.29,30 Their predictive value increases in conjunction with a family history of atopy. Whilst the specificity of these predictors is fairly good, their sensitivity remains poor.26 Sensitisation to Aeroallergens is an accepted risk factor for asthma, as is allergic rhinitis.31 The group studying the Tucson respiratory cohort have developed a risk index, which takes the different factors into account and may be useful.32

Lung function measures have been used to try and identify at which point the airway becomes affected. Infant lung function has helped to define the difference between early wheezers, transient wheezers and persistent wheezers but this not feasible as a general predictive tool.23 Early bronchial hyper-reactivity has been associated with decreased FEV₁ later in life but the data on its association with asthma are still controversial.23,33 At present, the only way to measure bronchial hyper-reactivity in infants is with the infant squeeze technique, which requires sedation and is thus not practical outside research projects. When spirometry is performed in older children (generally >5 years old), it can prove but perhaps no longer predict impaired airway function, because many of these children may already have established disease. In children as young as 2 years, specific airway resistance (sRaw) has been shown to be a good technique to assess the state of the airways.34 Lowe et al. were careful to describe the children as ‘wheezers’ only, rather than attempting to achieve a diagnosis of asthma at this age.34 Whether or not sRaw will be useful as a predictive test is not yet known. Neither is it clear whether the determination of a baseline sRaw value suffices or if additional post-bronchodilator tests are necessary to increase its predictive capacity. Results from further follow-up in that cohort are needed to show the sensitivity and specificity of sRaw in predicting those who will develop asthma.

Recent findings illustrate that it may not be evident until adolescence or early adulthood, what kind of positive or negative effects have been produced by early life events.35,36 Overall, our current knowledge of risk factors and our current ‘predictive tests’ are not sufficient. We need further results from ongoing long-term birth cohort studies better to understand the progression of the atopic march and identify early childhood events, which determine what happens to the adult. At present, targeting the whole population is neither feasible nor affordable. Preventive interventions often require marked commitment from the parents/patients and generate cost.19,37,38 In addition, it is not yet clear whether avoidance or addition of certain factors is beneficial and safe for everyone. To judge this, we need the long-term results of the ongoing primary prevention cohorts.

TESTED AND TRIED – INTERVENTIONS AND PREVENTIVE MEASURES

Various avoidance and intervention measures have been evaluated for their efficacy, as discussed below.

Indoor allergen avoidance

**House dust mite avoidance**

With strenuous avoidance measures, it is possible to decrease and maintain Der p 1 at very low levels.2,38 Less rigorous interventions have also resulted in decreased exposure.3

**Pets**

Very controversial at present, as it is not clear now whether exposure to cat and/or dog allergen may not actually be protective. The allergen is difficult to eradicate from the home and even then exposure is maintained, as Fel d 1 and Can f 1 are ubiquitous.39–41
Cockroach

Effective avoidance of the allergen is possible. Long-term avoidance is, however, difficult and has cost and compliance implications.42,43

Dietary avoidance

Breastfeeding with no solids until after 4/12

Generally accepted as protective but lifestyle choices may make this difficult. Recent findings in a long-term cohort claim that risk for asthma may be increased due to breastfeeding.36 The overall benefits of breastfeeding still outweigh any perceived risks at present and it should be strongly encouraged.

Cow’s milk avoidance

Difficult to get full compliance, and long-term benefit has not been proven.13,44,45

Multiple food avoidance

Very difficult to implement with full compliance and can cause nutritional deficits.13,44,46 The long-term benefit is unclear.

Dietary additions

Antioxidants

Not much data on intervention trials, conflicting results.37,47

Omega 3 fatty acids

Current trial ongoing, compliance good.7,48

Probiotics

Effect on eczema incidence and severity but not on IgE-mediated sensitisation. No results on wheezing. No compliance problems reported.49,50

Environmental tobacco smoke

Notoriously difficult to implement but some trials have been done. Behavioural intervention with environmental Cotinine feedback has shown some short-term benefit.51,52

PRIMARY PREVENTION – DOES IT WORK?

Long-term observational birth cohort studies are seeing changes and possible effects from early life events many years later.35,36 Results from ongoing primary prevention cohort studies therefore need to be taken with a ‘pinch of salt’. Their long-term data should supply us with more reliable conclusions. A brief summary of primary prevention studies is given in Table 1 (for more detailed summary, see ref. 25).

PRIMARY PREVENTION WITH DIETARY INTERVENTION

Multiple studies have investigated if avoidance of allergenic foods by the mother and/or by the infant has a protective effect. Antenatal dietary avoidance alone does not lead to a reduction in atopic disease in the child and carries the risk of inadequate nutrition for both mother and fetus.13,14,44 Several studies have compared breastfeeding with the use of extensively hydrolysed formula, soya formula and standard formula.45,53,54

Breastfeeding appears to protect infants from atopy, in particular atopic dermatitis in the first 2 years of life. Chandra et al. found that if the mother avoided allergenic foods during lactation, this effect could be significantly increased.55 Soya formula did not convey any benefits when compared with standard cow’s-milk-based formula.7 Extensively hydrolysed formula reduced the incidence of atopic symptoms in the first 18 months in Oldeaus and Chandra’s studies but did not have any effect on asthma. Chandra also performed a study comparing breastfeeding, standard formula, soya formula and partially hydrolysed whey formula and found a decreased cumulative incidence of atopic disease at 5-year follow-up.15 Recent data from the GINI study showed that breastfeeding protects high-risk infants from atopic dermatitis in the first year of life.54 As this cohort study progresses, we should get some data on the incidence of allergic airways disease in infants fed a variety of formulas from birth.

Many of these studies have been terminated in early childhood and thus a possible long-term effect of the interventions will probably remain unknown. As demonstrated by Sears et al., long-term follow-up can yield surprising findings.36 It is as yet unclear, what will be the practical significance of the finding that breastfeeding appeared to increase the risk for asthma in their birth cohort at 9-year and 26-year follow-up. At present, breastfeeding should remain the best way of infant feeding. Sears et al.’s results re-enforce, however, the need for long-term follow-up of children who took part in early life intervention/prevention studies. Delayed introduction of solids and allergenic foods has not been shown to protect children from allergic airways disease, and any effects seen in early infancy on eczema and food allergy tend to be lost at age 3 years.14 Probiotic supplements in the first 6 months of life have been shown to reduce the incidence of atopy (defined as presence of atopic dermatitis) by the age of 2 years. However, there was no effect on total IgE, specific RAST test and skin prick test sensitivity between groups.49 No further follow-up data have been published and it is, at present, not known whether there is any effect on the development of asthma.
<table>
<thead>
<tr>
<th>Name</th>
<th>n</th>
<th>Selection</th>
<th>FU</th>
<th>Intervention</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>San Diego Zeiger et al.(^{34,61})</td>
<td>288</td>
<td>FHx Atopy ≥1 &amp; + ve IgE</td>
<td>Prenatal to 7 years</td>
<td>Antenatal allergenic food avoidance. Infant allergenic food avoidance, some until 3 years</td>
<td>Age 1 year: Active: sign. ↓ any atopic disorder, 2 years: cumulative food allergy sign. ↓ Age 3, 4 and 7 years: no difference, food avoidance failed to prevent rhinitis and asthma</td>
</tr>
<tr>
<td>Wales Infant Feeding Burr et al.(^{45})</td>
<td>497</td>
<td>Hx Atopy: ≥ one first-deg. relative</td>
<td>Birth to 7 years</td>
<td>Restricted dairy in pregnancy and during lactation. Soya milk or breast-milk Dairy avoidance until 4/12 old</td>
<td>Birth to 7 years: No difference in atopic disease between groups at age 7 Breastfeeding protective from wheezing. Beyond 2 years, this effect only for non-atopics. No relation to mite and cat exposure and sensitisation</td>
</tr>
<tr>
<td>Extensively vs partially hydrolysed vs standard formula Oldeus et al.(^{53})</td>
<td>155</td>
<td>Hx Atopy two relatives or one + cord IgE &gt;0.5</td>
<td>Prenatal to 18/12</td>
<td>Maternal (breastfeeding) and infant allergenic food avoidance until 1 year. Bottle feeding: n = 55 eHF, n = 51 pHF, n = 49 standard formula</td>
<td>Age 18 months: Extensively hydrolysed formula: cumulative incidence of atopic symptoms from 6 to 18/12 reduced significantly less wheeze but not asthma No differences for SPT, IgE, final cumulative diagnosis of atopy at 18/12</td>
</tr>
<tr>
<td>Antenatal maternal elimination diet. Faeth-Magnussen et al.(^{13})</td>
<td>209</td>
<td>FHx Atopy ≥ one relative</td>
<td>28/40 to 5 years</td>
<td>Last trimester maternal cow’s milk and egg avoidance until delivery</td>
<td>Age 18 months: No major differences between groups Age 5 years: Outcome: allergic disease at 5 years: No significant differences</td>
</tr>
<tr>
<td>Maternal and infant feeding intervention. Chandra et al.(^{62})</td>
<td>221</td>
<td>FHx Atopy ≥ one family member</td>
<td>Birth to 18/12</td>
<td>Allergic food avoidance in 49/97 breast-feeding mothers. Bottle feeding: n = 41 soya vs n = 40 standard vs n = 43 casein hydrolysate</td>
<td>Age 18 months: Breastfed active: significantly less/milder eczema than breastfed controls Amongst formula groups: hydrolysate group = significantly less and milder eczema than soya and cow’s milk group (no differences between the latter)</td>
</tr>
<tr>
<td>German Infant Nutrition Intervention (GINI) Study Schoetzau et al.(^{54})</td>
<td>2252</td>
<td>FHx Atopy ≥ one family member</td>
<td>Birth to 1 year ongoing</td>
<td>Breastfeeding recommended, or hydrolysed formula (three types) vs standard formula for ≥ first 4/12. No allergenic food during year 1</td>
<td>Age 1 year: At present, analysis of breast-fed and standard formula fed infants only; In high-risk infants, exclusive breastfeeding for at least 4/12 significantly reduces atopic dermatitis. Delaying solid foods did not confer additional benefits</td>
</tr>
<tr>
<td>Isle of Wight Intervention Study Arshad et al.(^{46,63})</td>
<td>120</td>
<td>Two atopic relatives or one &amp; cord IgE &gt;0.5</td>
<td>Birth to 8 years ongoing</td>
<td>Allergic food avoidance during lactation and in first year of life HDM avoidance. (infant mattress, Acarosan)</td>
<td>Age 1 year: Active: signif. Less asthma (all wheezers), eczema, food intolerance, +ve SPTs Age 2: Significantly fewer children with allergic condition in active group Age 4: Control group had more total allergy, eczema, + SPT, symptoms &amp; + SPT</td>
</tr>
<tr>
<td>HDM and diet avoidance Chan-Yeung et al.(^{16})</td>
<td>545</td>
<td>≥ Two first-degree atopic or ≥1 asthma</td>
<td>Prenatal to 12/12</td>
<td>Ante- and postnatal allergenic food avoidance HDM Avoidance (mattress, Acarosan) Pet &amp; ETS avoidance advice</td>
<td>Age 1 year: Reduction of Der p1; Cat allergen levels lower in active group at 2/52 and 4/12. Risk for asthma significantly reduced by 34%. Risk for rhinitis significantly reduced by 49%. No difference in incidence of sensitisation to inhalant or food allergens</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>FHx Atopy</td>
<td>Timing</td>
<td>Intervention</td>
<td>Effect</td>
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<tr>
<td>Manchester Asthma and Allergy Study (MAAS) Custovic et al.²,³⁸</td>
<td>1200</td>
<td>F/Hx Atopy</td>
<td>Prenatal to 5 years ongoing</td>
<td>High-risk active (HRA) n = 145</td>
<td>Age 1 year: Children in HRA group reduced respiratory symptoms in first year vs HRC. Significant for: severe wheeze with SOB, px med. For wheezy attacks, wheezing after exertion.</td>
</tr>
<tr>
<td>Prevention + incidence of Asthma &amp; Mite Allergy Study (PIAMA) Koopman et al.³</td>
<td>810</td>
<td>F/Hx Atopy Mother</td>
<td>Prenatal to 2 years</td>
<td>Active (416): Mite covers for infant, parent bed, parent pillows. Hot wash bed Control: Placebo covers (double-blind), wash</td>
<td>Age 1 year: HDM avoidance = slight, sign. Reduction in ‘night-time cough without a cold’</td>
</tr>
<tr>
<td>Probiotics in primary prevention of atopic disease Kalliomaki et al.⁹</td>
<td>159</td>
<td>F/Hx Atopy ≥ one relative</td>
<td>Prenatal to 2 years</td>
<td>64 active: Lactobacillus GG antenatal, 6/12 postnatal. Control n = 68: Placebo capsules</td>
<td>No effect on: Wheezing, runny nose, specific IgE to HDM, respiratory symptom severity at 2 years. Age 2 years: primary endpoint: atopic eczema at 2 years. Total prevalence of eczema 35%. Probiotic group: sign. less eczema 15/64 (23%), P = 0.008; Placebo group: 31/68 (46%). No differences in total IgE, specific RAST and SPT between groups.</td>
</tr>
<tr>
<td>Probiotics during pregnancy Rautava et al.⁶⁴</td>
<td>62</td>
<td>F/Hx Atopy ≥ one relative</td>
<td>Birth to 2 years</td>
<td>Breastfeeding mum to take probiotic/placebo capsules at least 3/12 postnatally</td>
<td>Age 2 years: TGFβ2 significantly increased in milk from ‘probiotic’ mums, TGFβ1 not different. Atopy (atopic dermatitis at age 2) decreased significantly in probiotic group.</td>
</tr>
</tbody>
</table>

FHx, history; SPT, skin prick test; eHF, extensively hydrolysed formula; pHF, partially HF; TGF, Tumour growth factor; HDM, house dust mite.
COMBINED DIETARY AND ENVIRONMENTAL INTERVENTION

Arshad et al. showed an effect of allergenic food avoidance during lactation and until the age of 1 year in combination with house dust mite avoidance measures. They found significantly less asthma (included were all wheezers), eczema, food intolerance and sensitisation at 1-year follow-up. This effect weakened progressively and was lost at the age of 4 years for allergic airways disease. It remains to be seen if any long-term effect will become apparent at future follow-up of the Isle of Wight cohort. Chang-Yeung et al. also used combined food and dust mite avoidance measures, as well as advice on pet and environmental tobacco smoke exposure. At 1-year follow-up, they saw a significant reduction in the risk for ‘asthma’ and allergic rhinitis without a difference in the incidence of sensitisation to food or inhalant allergens. As the differentiation between asthma and infantile wheezing is very difficult at this age, it remains to be seen which effects are evident at further follow-up. We do not know yet when the ‘infantile’ pattern of wheeze disappears to be replaced by the ‘atopic wheeze’, although it is likely that this happens around the age of 5 or 6 years, when lung function testing in cohorts can often diagnose ‘asthma’ for the first time in the participating children. The need for good objective outcome measures cannot be overemphasised. Neither of the above studies allows us to identify which part of the intervention caused the protective effect. In future, combined studies will have to be designed in a fashion that allows the assessment of each intervention individually as well as in combination. The Australian CAPS study fulfils these criteria: here, the effects of house dust mite avoidance with or without omega-3 fatty acids in the diet, as well as the effect of omega-3 fatty acid supplementation alone, are investigated. No results have been published yet.

INDOOR AEROALLERGEN AVOIDANCE

Pets

The role of pet allergen exposure (particularly cat and dog) and pet ownership has become very controversial in recent years. Cat allergen, especially, is ubiquitous and complete avoidance appears impossible. This is reflected, for example, in the Manchester Asthma and Allergy Study. Families in the high-risk intervention group did not have pets and by 1 year of age, the sensitisation rate to cat was indeed significantly less than that of cat owners. However, at 3-year follow-up, this difference had vanished – and non-cat owners had the same proportion of sensitised individuals as cat owners (unpublished data). Data on the role of dog allergen from this study is pending. It will be interesting to see the results in light of the data from the Tucson cohort, where dog exposure in early life was found to have a protective effect for asthma at 13-year follow-up. More work is also needed to answer the question whether it is the allergen or the animal that causes the effects.

HOUSE DUST MITE AVOIDANCE

The Manchester Asthma and Allergy Study follows a cohort of 1000 children with high, medium and low risk for atopy. The high-risk intervention group (n = 145, randomised controlled arm of cohort) commenced complex avoidance measures from the second trimester of pregnancy and it was demonstrated that a low level of Der p I could be achieved and maintained over a long period of time. The intervention consisted of encasing of parental mattress, pillows and duvet, regular vacuum cleaning with HEPA filter vacuum cleaner, hot washing of the bedding and toys every 2 weeks, and Acarosan to carpets and sofas. The infants received new cot and carrycot mattresses encased in allergen-impermeable material and a vinyl floor was fitted in their bedroom. At 1-year follow-up, the sensitisation for house dust mite was very low in all groups (1–2%, no significant difference). Infants in the active group, however, had fewer respiratory symptoms in the first year of life. The differences were significant for the more severe end of the spectrum, notably severe wheeze with breathlessness, prescribed medication for wheezy attacks and wheezing after vigorous playing, crying or exertion. However, these findings tell us very little about the possible effect of intervention on asthma.

For the PIAMA study, mite avoidance measures were less rigorous. In this randomised double-blind controlled trial, 416 high-risk patients in the active group received mite covers for the infant and parent mattress, as well as the parent pillows. They were advised to hot wash the bedding regularly. The control group received placebo cotton covers. Der I was significantly reduced, but the effect on respiratory symptoms was minor. At 2-year follow-up, it was found that avoidance only resulted in a slight but significant reduction in night-time cough without a cold. Avoidance had no effect on wheezing, house dust mite sensitisation and respiratory symptom severity.

Primary prevention cohort studies are still in their early days. The future data from these studies are crucial for our understanding of the mechanisms of allergic disease, the long-term effects and safety of intervention as well as for the choice of future interventions.

SECONDARY PREVENTION – WHAT IS THE EVIDENCE SO FAR?

Few trials have addressed secondary prevention of allergic disease. To date, information is available on the role of ketotifen, cetirizine, specific immunotherapy and house dust mite avoidance in secondary prevention of further sensitisation and allergic airways disease (Table 2).
<table>
<thead>
<tr>
<th>Study</th>
<th>No. &amp; Year</th>
<th>Selection Criteria</th>
<th>Intervention</th>
<th>Primary endpoint</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iikura et al.</td>
<td>1992 n = 121</td>
<td>Age 2–34/12 Eczema-No ‘asthma’</td>
<td>Ketotifen for 1 year</td>
<td>Presence of asthma (= two wheezy episodes requiring bronchodilator)</td>
<td>Active group: Significantly less asthma in children who also had IgE &gt;50 IU/ml (13.1% vs 41.6% controls)</td>
<td>Diagnosis of asthma ? weak No long-term F.U.</td>
</tr>
<tr>
<td>Bustos et al.</td>
<td>1995 n = 100</td>
<td>Family, Atopy &amp; pos SPT/IgE Child: &lt;2 years No asthma, raised IgE</td>
<td>Ketotifen for 3 years</td>
<td>Presence of asthma (≥ three episodes of bronchial obstruction with distress)</td>
<td>Active group: significantly less asthma in active group (9% vs 35% in control group)</td>
<td>Diagnosis of asthma ? weak No long-term F.U.</td>
</tr>
<tr>
<td>Des Roches et al.</td>
<td>1997 n = 44</td>
<td>Age 2–6 years Asthma +/- AR Monosens. to HDM</td>
<td>SIT for 3 years vs open pharmaco. Tx</td>
<td>Incidence of new sensitisations</td>
<td>Active: 10/22 remained monosensitised Control: 0/22 remained monosensitised</td>
<td>Authors comment that this does not work for polysensitised children</td>
</tr>
<tr>
<td>Sarva et al.</td>
<td>2002 n = 371</td>
<td>Age 18–40 years AR, no asthma</td>
<td>SIT for 3 years vs open pharmaco. Tx</td>
<td>Asthma at 9–10-year follow-up</td>
<td>SIT group: 41.6% developed asthma Non-SIT: 53.1% developed asthma</td>
<td></td>
</tr>
<tr>
<td>Mastruzzo et al.</td>
<td>2002 n = 30</td>
<td>Adults AR, monosens. To Parietora judaica</td>
<td>SIT for 3 years vs placebo</td>
<td>Effect on airways: BHR (Methacholine PC15) AMP PC15</td>
<td>SIT group: ↓ symptoms, ↔ Methacholine BHR, significantly improved AMP PC15</td>
<td>Not powerful enough to show difference</td>
</tr>
<tr>
<td>Moeller et al.</td>
<td>2002 n = 208</td>
<td>Age 6–14 years Birch/grass pollen rhinoconjunctivitis No asthma</td>
<td>SIT for 3 years vs open pharmaco. Tx</td>
<td>Asthma and/or BHR</td>
<td>Active: sign. ↓ rhinoconjunctivitis symptoms BHR sign improved (from baseline) after year 2 and 3 OR 2.52 (1.3–5.1) for SIT preventing asthma in children with polinosis</td>
<td>1/6 centre had reverse findings 2/6 centres no significant difference (small number)</td>
</tr>
<tr>
<td>Diepgen L for ETAC Group</td>
<td>1998 n = 817</td>
<td>Age 12–24 months Atopic dermatitis FHx Atopy</td>
<td>Cetirizine for 18 months vs placebo</td>
<td>Prevention of asthma (= three separate episodes of nocturnal cough with sleep disturbance or wheezing)</td>
<td>No difference in overall numbers who developed asthma. Active: if raised IgE or Specific IgE to grass or HDM then significantly reduced asthma Less urticaria</td>
<td>Long-term data needed</td>
</tr>
<tr>
<td>Study</td>
<td>No. &amp; Year</td>
<td>Selection Criteria</td>
<td>Intervention</td>
<td>Primary endpoint</td>
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<tr>
<td>Tsitoura et al.</td>
<td>2002 n = 636</td>
<td>Age 1.5–5-years FHx Atopy/+SPT Child A or AR or AD not sens. To HDM</td>
<td>Child mattress cover and specific advice vs advice only</td>
<td>Sensitisation to HDM</td>
<td>Active: 3% sens. to HDM ($P = 0.04$; RR for sens. 0.36, 95% CI 0.16–0.83)</td>
<td>95% CI 0.16–0.83</td>
</tr>
<tr>
<td>Arshad et al.</td>
<td>2002 n = 242</td>
<td>Age 5–7 years FHx Atopy Sensitised to ≥one aero-allergen except HDM</td>
<td>Child mattress cover and specific advice, vs advice only</td>
<td>Sensitisation to HDM</td>
<td>Active 2.56% sens. to HDM ($P = 0.03$, OR 0.14, 95%CI 0.03–0.079)</td>
<td>Control: 9.38% sens. to HDM</td>
</tr>
<tr>
<td></td>
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<td>Pet advice was not heeded</td>
<td>15 children needed to treat to prevent one sensitisation</td>
</tr>
</tbody>
</table>

HDM, house dust mite; SIT, specific immunotherapy; FHx, family history; RCT, randomised controlled trial; A, asthma; AR, allergic rhinitis; AD, atopic dermatitis; BHR, bronchial hyperreactivity.
THE ORAL ROUTE – A ‘PILL’ FOR PREVENTION?

Iikura et al. investigated the effect of ketotifen in the prevention of asthma in infants with atopic dermatitis. Their randomised controlled double-blind trial included 121 infants aged 2–34 months with eczema and without any symptoms suggestive of asthma (i.e. coughing or wheezing). The children were treated with ketotifen for 1 year and after the treatment period were assessed for the presence of asthma (defined as two separate wheezing episodes treated with bronchodilator drugs). Children in the active group developed significantly less asthma (13.1%) compared with those in the placebo group (41.6%). Some children were followed-up for a total of 2 years and the effect persisted. Unfortunately, no further long-term data are available. Thus it is not clear if the diagnosis of asthma encompassed transient wheezers as well as true allergic asthma. Bustos et al. reported data on the 3-year follow-up of ‘pre-asthmatic’ children treated with ketotifen to prevent asthma. One hundred infants aged less than 2 years with a family history of atopic disease and elevated serum IgE were randomised to 3 years of ketotifen or placebo. None of the infants had a history of bronchial obstruction. The primary outcome was the development of asthma, which was defined as at least three episodes of bronchial obstruction with respiratory distress. The results were encouraging: only 14% of infants in the active group developed asthma compared with 35% in the placebo group. The rate of sensitisation at the end of the study was not different between groups. Unfortunately, no further follow-up data have been published. It is therefore not possible to judge if the effect was sustained. The ETAC (Early Treatment of the Atopic Child) study investigated the preventive effect of cetirizine on the development of asthma in infants with atopic dermatitis. Eight hundred and seventeen infants aged 1–2 years with atopic dermatitis and a family history of atopic disease were randomised to an 18-month course of cetirizine or placebo. Infants with a history of recurrent wheeze or nocturnal cough beyond the age of 6 months were excluded. The primary endpoint was the development of asthma (three separate episodes of nocturnal cough with sleep disturbance or wheezing). The overall numbers of children who developed asthma did not differ significantly between the cetirizine and placebo group. A significant reduction in the development of asthma was only seen in the ‘post-hoc’ analysis of those children on cetirizine who had raised total IgE or were sensitised to grass pollen and/or house dust mite at the start of the study. The other significant finding was a decreased rate of urticaria in the active group. The severity and clinical course of atopic dermatitis was not affected by cetirizine. The authors propose the use of cetirizine as a ‘primary intervention treatment to prevent the development of asthma in eczematous children sensitised to mite and pollen allergens’. However, as the primary outcomes of this study were negative, these results should not be used as an incentive to address this question in an appropriately designed study, rather than, as a basis for advice on secondary prevention.

No further follow-up findings from the ETAC study have been published and whilst the authors observed a favourable side-effect profile for the drug, it is necessary to know if the effect is sustained and safe in the long term.

THE NEEDLE – CAN IT TAKE THE STING OUT OF ASTHMA?

Specific immunotherapy (SIT) has recently emerged as another potential secondary prevention tool. Des Roches et al. published the first case-controlled trial assessing the preventive effect of SIT in 1997. They studied 22 children aged 2–6 years on SIT and 22 age-matched children as controls. The children suffered from asthma and some had additional allergic rhinitis. On enrolment, all children were monosensitised to house dust mite. Three years of SIT resulted in significantly fewer new sensitisations to aero-allergens in the active group (55% new sensitisations in active group, 100% in control group). Sarva et al. presented data on a retrospective survey on 371 non-asthmatic allergic rhinitis sufferers. They found that patients who had received SIT for allergic rhinitis had a significantly reduced risk for developing asthma (41.6% in SIT group, 53.1% in non-SIT group; P < 0.05). The same group performed a randomised placebo controlled trial investigating the effect on bronchial hyper-responsiveness and the development of asthma in 30 monosensitised patients with seasonal rhinitis. They saw decreased numbers of asthmatics in the active group (2/15 in SIT group vs 7/15 in placebo group; P = 0.056). The difference was not significant, however, probably due to insufficient power. The multicentre PAT study investigated the potential of SIT to prevent asthma in children with rhinitis prospectively in a larger number of patients. Two hundred and five children with symptomatic allergic rhinitis due to grass and/or birch pollen allergy (defined as the risk factor for the development of asthma) were randomised to 3 years of SIT or an open control group. The primary endpoint was the development of asthma and/or influence on bronchial hyper-reactivity. After enrolment, it was found that 40% of patients had mild asthma (equal in each group) and symptoms improved more in the SIT group. As expected, SIT also reduced conjunctivitis and rhinitis symptoms significantly. A significant improvement in bronchial hyper-reactivity (measured as change from baseline) was seen after 2 and 3 years of treatment in the SIT group. The final outcome was presented as an ‘odds ratio of 2.52 (1.3–5.1; P < 0.05) in favour of the hypothesis that SIT can prevent the development of asthma in children with pollinosis’. These findings were not seen at all centres. One centre had more cases of asthma in the SIT group, which was explained by a different way of bronchial challenge testing (cold air instead of methacholine). The results of these
studies are promising but whether or not SIT can be widely utilised as a secondary prevention measure is debatable. It involves uncomfortable treatment and takes at least 3 years. Acceptance amongst the population who are – or whose children are – ‘only’ suffering from hay fever (especially if mild) is likely to be poor. More studies are needed, defining more accurately which patients would benefit the most and exploring alternative routes of administration. One of these alternative routes might be sublingual immunotherapy. Mastrandrea et al. showed in their trial of specific sublingual immunotherapy in patients with atopic dermatitis that resolution of eczema was faster in the active group, and they saw a trend of reduced asthma in the treatment group. \(^{59}\) Interestingly, the patients received additional ketotifen for the first 3 months. This study was underpowered though, and did not look specifically at prevention – however, it may point towards a more acceptable way of administering SIT, especially in paediatric patients. Further research in this area is needed, as the results are far from conclusive at present. New studies need to overcome some of the design problems, such as lack of power and lack of double-blind placebo controlled trials.

THE MITE COVER – BACK TO BASICS?

Results from two studies investigating the prevention of further sensitisation in children as part of the multicentre SPACE (Study of Prevention of Allergy in Children of Europe) study have been published recently.\(^{22,60}\) The potential for prevention of mite sensitisation in toddlers/pre-schoolers and older schoolchildren was assessed.\(^{60}\) Six hundred and thirty-six young children (mean age 3.1 years) who were not sensitised to mite allergens and who had a family history of atopic symptoms were randomised to a combination of education and mattress encasement or a control arm (general advice only). At 1-year follow-up, the incidence of sensitisation to mite allergens was significantly reduced in the intervention arm (3% vs 6.5% in control). It was also observed that allergic symptoms and prevalence of physician-diagnosed asthma, eczema and food allergy was more common in the sensitised children. Future findings on sensitisation patterns and prevalence of asthma in this group are important.

The second study published by the SPACE group reports the effect of house dust mite avoidance in older children (age 5–7 years).\(^{22}\) Two hundred and forty-two children with a family history of atopy and a positive skin prick test to an aeroallergen other than house dust mite were randomised to a prophylactic group (mattress covers and advice on how to reduce mite exposure) or a control group (non-specific advice only). After 1 year, the incidence of house dust mite sensitisation was significantly less in the active group (2.56% vs 9.38% in control group). This study was designed to prevent further sensitisation and not to prevent asthma. A trend for children with wheezing in the active group to be less symptomatic was observed, however. It was also observed that amongst the centres in this study, the lowest rate of mite sensitisation occurred in Greece (0%) and the highest in the UK (12.9%). Unfortunately, only mite skin prick testing was performed at 1-year follow-up, preventing any conclusion on a further protective effect on sensitisation to other allergens.

The above secondary prevention studies have yielded interesting and promising results, and serve to emphasise that more research into this type of prevention is needed. Target groups and target measures need to be identified, and their effect assessed carefully, and only then can a debate on possible population-wide screening and prevention commence.

CONCLUSION

Recent years have seen much better trial designs, and consequently more reliable data. Primary prevention cohort studies are ongoing and it is still too early to draw any conclusions on which advice can be based. There is a need for more true secondary prevention trials, addressing the question if clinical asthma can be prevented after sensitisation has occurred or other atopic conditions such as eczema and hay fever have developed. The timing of this needs to be investigated and the evolution of allergic airways disease in early childhood needs to be better characterised. Results from further properly designed studies would allow insight into whether or not screening for atopy could be useful or feasible. Only when we have the evidence base will we be able to recommend screening and intervention for prevention of asthma.

PRACTICE POINTS

- Long-term results from primary prevention cohorts are necessary before any advice can be based on the findings.
- Whole-population prevention measures are not feasible at present.
- More well-designed secondary prevention trials are needed to allow effective early intervention in at-risk individuals.

RESEARCH DIRECTIONS

- Long-term (decades) effects from early life interventions need to be better understood.
- Secondary prevention trials are required.
- Better characterisation of who should be the target for secondary prevention is needed.
- Objective outcome measures need to be used consistently.
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