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Asthma (M Jutel, Section Editor)

Allergen Avoidance in Asthma: Is There a Role?

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Opinion statement

Asthma is a heterogeneous disease with symptoms that fluctuate in scale and severity throughout life. Whilst allergic triggers have been implicated in both its development and subsequent exacerbations, there is no conclusive evidence that allergen avoidance in infancy prevents subsequent development of asthma. Recent studies suggest that allergen avoidance is not an important management strategy in established asthma.

Introduction

Epidemiology

Asthma is one of the more common chronic diseases, affecting approximately 300 million people worldwide [1]. Until recently, prevalence in the West has been increasing, but figures now seem to have stabilised [2]. Asthma spans all age groups and carries significant direct healthcare costs as well as the indirect costs of work days/school days lost due to illness [3]. As the population ages, asthma is likely to become an increasing problem in the elderly, where drug interactions and comorbidities may make treatment more complicated [4]. The worldwide death rate from asthma is estimated at around 250,000 per year [5]. In the UK, deaths from asthma have been linked to socioeconomic disadvantage, suggesting that some deaths may be preventable [6].

Diagnosis

There is no "gold-standard" definition of asthma, which can be problematic with respect to accurate diagnosis of the disease, particularly in children. This is especially relevant when asthma development is an endpoint in clinical trials. Classic symptoms common to all definitions include dyspnoea, chest tightness, cough, wheeze, and variable airflow obstruction. Common triggers include exercise, exposure to pets, and cold or damp air.

The diagnosis of asthma in children relies on the recognition of classical signs and symptoms described above. However, these features are also present in other conditions. Viral infections, for example, often present very similarly to asthma in childhood. Indeed, children presenting with wheeze before the age of 2 years are less likely to have asthma later in childhood [7], although frequent or severe wheezing episodes are associated with increased risk of

asthma development [8]. Coexistent atopic disease such as eczema and rhinitis is also linked to the development of asthma, as is maternal atopy [7, 9]. Clinical history, therefore, can be used to assess the probability of asthma, and initial treatment can begin without the need for further tests.

Where the history is less convincing, an assessment of airflow obstruction can be used to support a diagnosis of asthma. Normal spirometry does not preclude diagnosis of asthma, particularly if testing is performed when the child is asymptomatic. Asthma is the most common cause of airway obstruction in children. A FEV_1/FVC ratio of less than 0.7 lends support to the diagnosis of asthma. An increase of greater than 12 % from baseline in forced expiratory volume in 1 second (FEV_1) or increase in peak expiratory flow (PEF) following treatment with bronchodilators is also highly suggestive of the disease. Spirometric values correlate poorly with reported symptoms and the use of asthma medications [10], and formal lung function testing in children under the age of 5 years is challenging and involves the use of techniques that are not widely available. When diagnostic uncertainty exists, a trial of treatment may be indicated. This strategy is recommended by the British Thoracic Society in its asthma guidelines [11].

In adults, when there is a good history of asthma symptoms and spirometric evidence of obstruction (FEV_1/FVC ratio <0.7), most clinicians would initiate a trial of treatment for 6 to 8 weeks, and then reassess. In cases with normal spirometry where history is atypical or with typical history yet normal spirometry, further investigation may be required. A significant increase in FEV_1 (>12 % from baseline) or PEF following bronchodilation can provide additional evidence for an asthma diagnosis. Airway hyperresponsiveness (AHR) can be assessed with a methacholine or histamine challenge, in which FEV_1 is assessed at set intervals following inhalation of the challenge substance. Increasing doses are used, and the response is quantified as the provocative dose causing a 20 % fall in FEV_1 (PC_{20}). In a normal population, 90–95 % have a PC_{20} of >8 mg/ml, and the likelihood of asthma increases when small doses are required. Fractional exhaled nitric oxide concentration (FE_{NO}) can be used to assess eosinophilic airway inflammation. A FE_{NO} of >25 ppb at 50 ml/sec is seen in 70–80 % of patients with untreated asthma. As increased FE_{NO} may be present in other conditions, this test may be better as a predictor of response to treatment with corticosteroids than as diagnostic for asthma.

Pathophysiology

Asthma is a clinical syndrome involving several different pathways that can lead to variable airflow limitation and breathlessness. As such, although its pathogenesis is still not entirely understood, it seems likely that both genetic and environmental factors are involved. Genome-wide association studies have identified a number of genes thought to be linked to asthma. Not all of the data have been reproducible, and the loci identified account for only a small proportion of the heritability of the disease [12]. None of the loci discovered overlap with those responsible for IgE concentrations, which may support the theory that atopy is not the primary driver of asthma susceptibility. However, it may also be possible that the correct locus has not yet been identified.

Asthma itself has a wide range of clinically observable characteristics, which has led investigators to describe multiple asthma phenotypes. Whether these remain stable or change during the course of the disease is unclear [13]. Some of the postulated asthma phenotypes are described in Table 1. This is subject to change, and different investigators have described different phenotypes [13–15].

In most cases of asthma, symptoms occur due to chronic inflammation of the airways. It has been proposed that aeroallergens such as pollens, moulds, house dust mites, cockroaches, and animal dander encountered in infancy induce allergic sensitisation, which in turn primes the airway mucosa, allowing asthma to develop in genetically susceptible individuals. Airborne allergens deposited in the airways are captured by dendritic cells and presented to T lymphocytes. This stimulates the production of Th2 cytokines, including interleukin 4 (IL-4), interleukin 5 (IL-5), and interleukin 13 (IL-13). These cytokines (IL-4 and IL-13 in particular) promote the formation of IgE antibodies, which attach to receptors on the surface of mast cells and basophils. Upon the next allergen encounter, IgE cross-linking results in mast cell degranulation and the release of histamine, leukotrienes, and prostaglandins, all of which are potent bronchoconstrictors. Additional Th2 cytokines (mainly IL-5) cause eosinophils to migrate to and accumulate in the airways. Persistence of eosinophils in the airway mucosa is a hallmark of allergic asthma, but it is also seen in non-allergic forms of the disease.

Sensitisation to allergens, particularly house dust mite, has been shown to increase the risk of developing asthma, and exposure to these allergens increases morbidity [9, 16]. Some studies have found that multiple early allergen exposures predict the presence and persistence of asthma in children [16, 17]. It has been hypothesised that preventing allergen sensitisation in children may reduce the chances of developing asthma later in life. Avoidance of allergic triggers in established asthma has also been postulated to be of benefit in the management of the disease [18, 19].

Despite novel therapies, asthma remains an incurable disease, and so the prevention and reduction of exacerbations are attractive prospects.

Table 1. Asthma phenotypes

	Natural History	Clinical features	Pathobiology
Early-onset allergic	Usually begins in childhood Responsive to corticosteroids	Allergic symptoms Atopy Mild–severe Severe disease is probably progressive	Basement membrane thickening Specific IgE present Eosinophilia Th2 cytokines
Persistent eosinophilia	Presents in adulthood Responds to leukotriene blockers, often refractory to steroids unless high doses used	Persistence and progression uncertain Sinusitis, nasal polyps, and aspirin sensitivity (subset with (AERD) Fewer allergic symptoms Often more severe than atopic asthma	Eosinophilia Th2 cytokines
Allergic bronchopulmonary mycosis	Adult onset Responds to corticosteroids, antifungals, and possibly anti IgE	Increased productive cough Bronchiectasis	Fungus-specific IgE and IgG Blood and lung eosinophils Bronchocentric granulomatosis
Non-eosinophilic asthma	Often adult asthma	Often severe symptoms Not responsive to corticosteroids, may respond to macrolides	No evidence of basement membrane thickening in adults Airway neutrophilia Activation of neutrophil elastase IL8 and IL17A
Aspirin intolerant asthma or Aspirin exacerbated respiratory disease (AERD)	5–10 % of adult asthmatics	Often starts with rhinitis following viral infection Polyps Symptoms worsen following non-steroidal anti-inflammatory use Steroid responsive	Eosinophilic inflammation of bronchial tissue Increased production of cysteinyl leukotrienes
Extensive remodelling asthma	Little data in children Usually affects those with long standing asthma	Often asthma is difficult to control or insufficiently treated	Minimal inflammation Extensive remodelling- thickened small airways, smooth-muscle hypertrophy, and loss of elastin

Allergen avoidance

Primary prophylaxis

Seven large studies have investigated whether allergen avoidance in infancy can affect the subsequent development of asthma. Four of these have recently published follow-up data. These studies are discussed below.

The Isle of Wight study

In a study commenced in 1990, 120 infants considered at birth to be at high risk of atopy were recruited and then followed up at ages 1, 2, 4, 8, and 18 years [20•, 22, 23]. Participants were randomised to prevention and control groups. In the prevention group, lactating

mothers and infants avoided dairy, egg, soya, fish and shellfish, peanut, and tree nut until the infant reached 12 months of age [20•]. House dust mite (HDM) reduction measures were also undertaken by use of both mattress covers and acaricides [20•, 21]. At follow-up, questionnaires regarding asthma and allergy symptoms were administered, and physical examination and skin prick tests (SPTs) were performed [21]. At ages 8 and 18 years, participants underwent spirometry and methacholine challenge testing [20•, 21]. There was no significant difference in the rates of physician-diagnosed asthma at age 2 or 4 years [22]. At age 8, there was no difference in symptoms ofcurrent wheeze ($p=0.08$) and exercise-induced wheeze ($p=0.3$), as assessed by questionnaires [21]. Nocturnal cough was more common in the control group ($p=0.02$). When asthma was defined as the presence of wheeze and bronchial hyperresponsiveness, there was no significant difference between the groups at age 8 [21].

At 18 years of age, 114 of the original 120 participants were assessed, and patients were classified into one of four groups: persistent asthma, late-onset asthma, remitted asthma, or never asthma [20•]. Rates of persistent asthma were lower in the prevention group than the control group ($p=0.04$) [20•]. However, there was no difference between the groups for late-onset asthma ($p=0.38$), remitted asthma ($p=0.5$) or never having been diagnosed with asthma ($p=0.18$) [20•].

The childhood asthma prevention study (CAPS)

This was a randomised controlled trial investigating the effectiveness of HDM avoidance and omega-3 fatty acid supplementation from birth through 11.5 years [24••, 25]. High-risk infants (one or more parents or siblings had asthma or wheeze) were recruited before birth. Those living in homes with cats were excluded. Participants were allocated to one of four groups (Table 2) [25]. All groups were given advice on appropriate ventilation, regular vacuuming, and avoidance of humidifiers/vaporisers [25, 26].

Participants were followed up at 18 months and 3, 5, 8, and 11.5 years, at which time they were interviewed via questionnaire about symptoms relevant to asthma. At age 5 years and older, spirometry was measured and SPTs were performed [24••, 25, 26]. Probable current asthma was defined as a parental report of any

Table 2. Group allocation and interventions performed in the CAPS study

Group	Intervention
A	Placebo diet – polyunsaturated margarines and oils, Sunola oil supplements No HDM reduction – standard advice and normal washing routines
B	HDM reduction – standard advice, allergen impermeable covers, acaricide wash Placebo diet- Polyunsaturated margarines and oils, Sunola oil supplements
C	No HDM reduction – standard advice and normal washing routines Active dietary intervention – canola margarines and oils, tuna oil supplements
D	HDM reduction –standard advice, allergen-impermeable covers, acaricide wash Active dietary intervention – canola margarines and oils, tuna oil supplements

(Adapted from Mihrshahi et al. [25])

wheeze in the last 12 months and *either* parental reporting of diagnosed asthma at age 18 months or 3 or 5 years, *or* a >12 % increase in FEV_1 after bronchodilator at age 5.

At age 5, despite effective reduction in HDM allergen levels, there was no difference in asthma between the two groups and no difference in clinical or lung function outcome [26]. At age 8, there was a suggestion that HDM avoidance in atopic individuals did result in a 10.6 % absolute risk reduction in the development of asthma [27], but by age 11.5, this risk reduction was no longer evident [24••]. Further analysis of the data seems to suggest that those who went on to develop asthma had mixed food and inhalant sensitisations rather than single-sensitisation profiles [28].

NAC Manchester asthma and allergy study (NACMAAS)

This was a randomised controlled trial recruiting high-risk infants (both parents atopic, mother sensitised to an indoor allergen) living in homes without pets [29, 30]. In parallel, a low-risk cohort with no pets was followed prospectively [29]. The high-risk participants were randomised to stringent environmental control (allergen-impermeable covers for the mother's and child's beds, weekly hot washing of bed linen, a high-filtration vacuum cleaner for carpets, and hard flooring in the child's bedroom).

Children were assessed at 12 months and 3 years by questionnaires and physical examination [29]. Lung function testing was performed at 3 years [30]. At 12 months, children in the active arm of the study were less likely to have severe wheeze. Lung function was significantly better in the active group at age 3. HDM allergen levels were significantly reduced in the active group, yet interestingly, sensitisation rates in the active group were higher ($p=0.04$) [30].

The relationship between asthma and atopy was assessed at 11 years in low-risk children who had not undergone active environmental manipulation. Children with early sensitisation to multiple allergens, including mites, pollens, and animal dander, were found to be more likely to have asthma at age 11 than those who remained non-atopic. Lung function parameters were also lower, with more hyperresponsiveness airways in the early-sensitisation group [31•].

Prevention and incidence of asthma and mite allergy (PIAMA) study

PIAMA is a prospective birth cohort study undertaken in the Netherlands between 1996 and 1997 [32] that involved a randomised controlled trial of house dust mite allergen avoidance as well as a prospective natural history study [33••]. A total of 855 high-risk children (defined as those born to allergic mothers) were recruited to the intervention study and randomised to receive mite-impermeable covers and mattresses for the parents'/child's bed or placebo. Questionnaires were completed by parents during pregnancy, at 3 months, and then annually from 1 to 8 years of age [34•]. Parents and children were asked to complete questionnaires at 11 and 14 years, but data is not yet available for the 14-year time point [33••]. Dust samples, blood samples, and pulmonary function tests (PFTs) were performed at 3 months and 1, 4, 8, and 12 years of age.

Approximately 400 high-risk children and 2,500 low-risk children were recruited to the natural history group. All high-risk children

were followed up as described above, along with a random sample of the low-risk children.

Early intervention with mite-impermeable mattress covers was not found to be associated with reduction in mite allergen exposure [34•]. There appeared to be a temporary decrease in asthma symptoms up to the age of 2 years, but by the age of 8 years, there was no difference between the groups. The relative risk (RR) of asthma in the last 12 months was 0.87 (95 % CI; 0.6–1.28), and the RR of bronchial hyperresponsiveness was 1.07 (95 % CI; 0.86–1.33) [34•]. The intervention had no effect on hay fever, eczema, or allergic sensitisation.

Other studies

The Prevention of Asthma in Susceptible Children (PREVASC), the Canadian Childhood Asthma Primary Prevention Study (CCAPPS), and the Study on the Prevention of Allergy in Children in Europe (SPACE) all looked at primary prevention of asthma by allergen avoidance in infants. No benefits were found in any of these studies, which are summarised in Table 3.

Secondary prophylaxis

Early non-randomised studies of HDM allergen avoidance in patients with established asthma have shown that moving patients to high altitudes improved their asthma symptoms [18, 35].

A recent prospective observational cohort study recruited patients with severe refractory asthma. Patients were assessed via asthma questionnaire, spirometry, fractional exhaled nitric oxide tests, a 6-minute walking test, and specific IgEs to common aeroallergens at baseline and after 12 weeks at altitude. Of the total 137 patients, 68 were sensitised to HDM, 92 were sensitised to at least one common aeroallergen, and 45 had no sensitisations [36••]. Both HDM-sensitised and non-sensitised patients experienced a significant improvement in their asthma quality-of-life questionnaires at the end of 12 weeks. They also had an improved FEV_1 and 6-minute walking distance and a reduction in oral corticosteroid use. Only sensitised individuals were found to have a significant drop in exhaled nitric oxide, although there was not a significant difference between the two groups. Total IgE to HDM also dropped in both groups, but was only significantly reduced in the sensitised group [36••]. High-altitude treatment may be effective in both atopic and non-atopic asthma, suggesting that altitude may have beneficial effects that are not due to allergen avoidance [36••].

A randomised controlled trial on the effect of allergen avoidance on asthma control in primary care was completed in 2010 [37]. The control group consisted of assessment of asthma symptoms, inhaler-technique medication usage, and the provision of self-management action plans. The intervention group had the usual review, but also received an allergy assessment consisting of completion of a structured allergen inventory and asthma trigger inventory, as well as SPTs to common aeroallergens and individual advice about allergen avoidance. 107 patients were randomised to each group. Although there appeared to be an improvement in lung function measured by FEV_1 in the intervention group compared to the control group, there was no difference in the perceived symptoms. Furthermore, the intervention group used more medication, suggesting that even targeted allergen avoidance may not have the impact required for adequate asthma management.

Table 3. A table to summarise other important studies investigating allergen avoidance in infancy

	CCAPPS	PREVASC	SPACE
Country	Canada	Netherlands	Europe
Study population	High-risk	High-risk	High-risk
Design	Prospective randomised controlled trial to determine the effectiveness of a multifaceted intervention programme in the primary prevention of asthma in high-risk infants in two Canadian centres [39, 51]	A multi-faceted intervention study to reduce environmental exposure to inhalant and food allergens and cigarette smoke in genetically susceptible children [52]	A prospective randomised controlled trial of multifaceted design [53, 54].
Intervention	Allergen-impermeable covers Weekly bed sheet laundering Acaricide washes Removal of pets Smoking cessation advice Breastfeeding encouraged for entire first year Delay introduction of solids until 6 months Cow's milk, peanuts, and seafood discouraged in infancy Avoid day care until after the first year	Pets to be kept outside Allergen-impermeable covers Exclusive breastfeeding to 6 months Smoking cessation advice Avoid solid food and cow's milk until 6 months	Exclusive breastfeeding for as long as possible Delay solids until 6 months Cow's milk, egg, and fish avoided until 12 months Peanut/tree nut avoided until 3 years Allergen-impermeable bed covers Remove carpet from the infant's room Hot-wash soft furnishings weekly Ventilate infant's room at least once a day and vacuum weekly Pets and smoking discouraged
Numbers	545	476	696
Age last assessed	7 years	6 years	2 years
Clinical outcome	The proportion of children with probable asthma (as defined by wheeze in the last 12 months plus bronchial hyper-responsiveness) was lower in the intervention group when adjusted values were used 25 % vs. 12.9 % (p=0.002) [39]. Bronchial hyperresponsiveness was not statistically different between the two groups.	No significant influence on the diagnosis of asthma diagnosis at the age of 6 years There was also no effect on the lung function tests.	No significant difference between the two groups in the diagnosis of asthma/ wheezy bronchitis (18.1 % in the active vs. 17.8 % in the control group) (54) The number of children sensitised to HDM allergen was lower in the active group, but this was probably not significant (1.86 % vs. 5 %) [54].
Additional information	More of the intervention group had been to hospital emergency departments with wheeze in the preceding 12 months. The level of house dust mite allergen found in the homes of each group was significantly different; however, there was no significant difference in the SPTs between the two groups.	HDM exposure is low in the Netherlands, making improvements difficult. The number of weeks children were breastfed didn't significantly differ between the groups.	It was postulated that HDM-induced asthma usually presents later in childhood, and an effect may be seen at a later date. However, a follow-up was published at 24months that did not show any evidence of an improvement in symptomatic allergy [55], and no further follow-up studies have been published.

Discussion

A common assumption in the field of medicine is that factors associated with a disease are causal. Although there is good evidence that atopy is associated with asthma, the evidence for cause and effect is less convincing. In developed countries, up to 40 % of children and young adults are atopic, yet only around one-third of these individuals develop asthma [38]. Additionally, in the above-described multifaceted intervention studies, differences reported in the development of asthma saw no associated reduction in allergic sensitisation [20•, 39]. Indeed, the PIAMA natural history study found no association between allergic sensitisation and asthma development [33••]. Recent work on different asthma phenotypes also suggests that allergens are not the only drivers of airway inflammation. The 2000 Copenhagen Prospective Study on Asthma in Childhood (COPSAC) found that episodes of wheezing in high risk-children are associated with both bacterial and viral infections, which may be the inflammatory driver in a subset of cases [40].

All of the multifaceted intervention studies encouraged mothers in the active group to breastfeed. Recent work has shown that breastfeeding improves lung function in children, which may in turn impact on the development of asthma [41]. The PIAMA natural history study has also reported a lower incidence of asthma in infants who were breastfed for more than 16 weeks [33••]. Other factors associated with the development of asthma in the PIAMA natural history study include variables not reported in the multifaceted intervention studies, such as:

1. Caesarean section; there was a twofold risk in the development of asthma at age 8 (an effect that was particularly marked if parents were allergic).
2. Being overweight at 6–7 years of age was a risk factor for having both asthma and bronchial hyperresponsiveness at age 8.
3. Children of mothers who were overweight during pregnancy were more at risk of being asthmatic at age 8, irrespective of the child's BMI.
4. Early day care attendance was associated with increases in airway symptoms up to the age of 4 years, followed by fewer symptoms between ages 4 and 8 years.
5. Air pollution was associated with asthma development at age 8.

In the studies where allergen avoidance was limited to HDM reduction, there was no difference in the diagnosis of asthma. Indeed, the value of HDM avoidance in asthma has been called into question with the publication of the most recent high-altitude study, conducted in the Alps, that showed benefit even in non-atopic individuals. These benefits may be attributable to lower levels of environmental pollution found in a high-altitude environment, as well as decreased viscosity of air and lower oxygen pressure [36••]. Other possible benefits of this treatment include reduced psychological stress due to the home environment (remedied by a move to the Alps) [36••]. Finally, the Alps have a high level of UV light exposure, which is known to increase vitamin D synthesis. The fact that vitamin D has been implicated as an asthma modulator may play a role in the improvements noted in this study [42]. While observational studies have seemed to indicate that higher vitamin D levels protect against asthma, ongoing clinical trials may help determine whether this really does have an effect [43].

More recently, it has been postulated that Th17 cells may play a role in the development of asthma. Th17 cells are a subgroup of CD4 cells

that produce a family of IL-17 cytokines. IL-17 controls bronchial hyperresponsiveness and airway remodelling, and high IL-17 levels are often associated with severe asthma [44]. Interestingly, elevated levels of IL-17 also correlate with increased neutrophilic inflammation in asthma [45]. IL-17A has induced steroid insensitivity in bronchial epithelial cells in mouse models [46]. Exactly why this happens and whether allergen sensitisation is involved is not clear, but it could explain the differences in certain asthma phenotypes.

Recent work has suggested that a defective respiratory epithelium may facilitate the passage of allergens into the airway tissue, triggering allergen sensitisation and asthma in susceptible patients [38]. However, another group found that aeroallergen sensitisation preceded virus-induced wheezing, which led them to conclude that preventing sensitisation may reduce the risk of developing asthma [47]. Although rhinovirus-induced wheezing is an independent risk factor for developing asthma, studies have shown that infants under 1 year of age with rhinovirus-induced wheeze and aeroallergen sensitisation are more than twice as likely to be affected with asthma by the age of 6 years [48]. The CCAPPS group analysed exposure to common childhood viruses during the first two years of life, finding that children exposed to respiratory syncytial virus (RSV) and parainfluenza virus (PIV) in the first 12 months were more likely to be diagnosed with new-onset asthma in the second year of life [49]. Indeed, PIV and RSV exposure in the first year of life were independently associated with increased odds of developing asthma, and exposure to PIV was associated with increased risk of persistent asthma. The association between viral exposures and new-onset and persistent asthma was not modified by allergen avoidance [49], and thus the data remain conflicting. The COPSAC 2010 birth cohort may provide additional evidence as to the utility of vitamin D supplementation and the benefits of macrolide antibiotics and administration of influenza vaccine in the development of asthma [50].

In conclusion, there is only limited evidence that primary allergen avoidance is useful in preventing asthma in later years. Further work is needed to determine whether the relationship is causal or casual. The efficacy of allergen avoidance in established asthma was further brought into question by the recent high-altitude data for atopic and non-atopic disease. Viral infections remain the major triggers for exacerbations, but allergens may work synergistically to worsen symptoms. Finally, it is important to remember that asthma is not one disease, and there is no gold-standard definition for diagnosis. Future studies may benefit from better diagnostic criteria and interventions targeted to specific asthma groups in order to better interpret the data that are accumulating.

Compliance with Ethics Guidelines

Conflict of Interest
Nicola J. Gray and Anthony J. Frew declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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