

Can asthma be prevented? Evidence from epidemiological studies of children in Australia and New Zealand in the last decade

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Introduction

In the last 5 years, there have been impressive advances in the study of the epidemiology of childhood asthma. However, the question that remains is 'can we prevent asthma by use of the information that we have now acquired about risk factors?'. A surveillance of prevalence rates of childhood asthma since 1982 suggests that it should be possible. Standardized studies of rates of wheeze and of airway hyperresponsiveness (AHR), measured serially between 1982 and 1992 in several large random populations of children in Australia and New Zealand, show that the prevalence of asthma doubled over the decade [1]. The short time period over which this occurred infers that environmental factors have been responsible [2]. Given that recent studies have provided much more information about the risk factors associated with childhood asthma, we are now in a position to use this information to test methods for prevention which, hopefully, will begin to reverse the trend in prevalence.

In planning interventions to prevent asthma, we need to target the factors for which there is enough information to be confident of their effect and for which exposure levels can be controlled. For childhood asthma, we now have enough information to begin primary prevention by targeting exposure to indoor allergens, parental smoking, breastfeeding and diet [3]. Although there is good evidence that infections, outdoor allergens and air pollutants are also involved in the aetiology of asthma, we are not yet in a position to control their exposure levels.

There is accumulating evidence that the earlier interventions are begun, the more effective they will be [4]. Thus, we expect that interventions which begin in infancy will prevent the asthmatic process from being 'switched on' in the first instance or, at the very least, will 'downregulate' the processes of sensitization, and subsequent associated airway inflammation and symptoms. We expect that preventive strategies will not only prevent asthma developing in

some children but will also lead to less severe disease than would otherwise have developed in others. We also expect that the same interventions will be effective in moderating asthma in those who have already developed sensitization and/or resultant symptoms.

House dust mite allergen exposure

The single largest risk factor for asthma that has been identified, at least in humid regions, is sensitization and exposure to house dust mite allergens [5]. Our data show that the odds ratios for children to have current asthma, that is both AHR and wheeze, if they are sensitized to house dust mites conservatively doubles with every doubling of house dust mite allergen exposure level [6]. This suggests that, in population terms, the risk of current asthma can be reduced by half if levels of house dust mite allergen exposure are similarly reduced. A similar relationship has also been demonstrated in clinical studies. In a study of house dust mite sensitized asthmatics in the UK in which exposure to other allergens such as pollens and pets was controlled, the level of AHR also doubled for every doubling in the level of house dust mite allergen exposure [7].

Exposure to house dust mites is widely recognized as an important factor which upregulates allergic sensitization or exacerbates asthma and, as result, there have been many studies which have tested the efficacy of allergen avoidance. Such studies include those in which asthmatic children have been taken to the Alps [8] or in which low allergen levels in beds have been achieved [9], both of which have achieved improvements in asthma severity. However, there have been few studies of primary prevention. The only reliable data of the efficacy of primary prevention has come from a randomized controlled trial of infants in the UK who have been followed until they are 4 years of age [10]. The intervention was complex in that it included avoidance of some food groups in addition to allergen control of floors and beds but, nevertheless, the results to date are extremely encouraging. A significant reduction in atopy and allergic symptoms was found in the active group at ages 1, 2 and 3 years and was maintained at age 4 (Fig. 1). Although the difference in the

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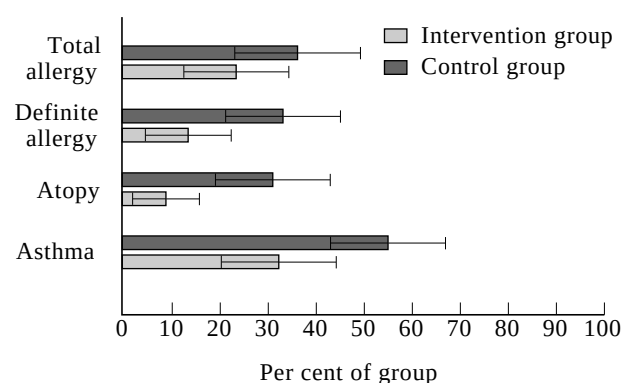


Fig. 1. Effect of allergen avoidance in the first year of life on atopic and symptomatic outcomes at age 4 years from a study in the UK by Hide *et al.* [10]. Children were randomized to the intervention group ($n=58$) or control group ($n=62$). 'Total allergy' was defined as the presence of asthma, rhinoconjunctivitis, atopic dermatitis or food allergy/intolerance, 'definite allergy' was defined as symptoms defined in total allergy plus the presence of positive skin-prick tests, 'atopy' was defined as a positive skin-prick test and 'asthma' was defined as recurrent cough or wheeze.

rate of asthma was not statistically significant at age 4, the difference in rates between the intervention and control groups was 11% with a 95% confidence interval of -5 to 27% . This difference is wide and whereas it does not rule

out that there is no difference between groups, it also does not rule out an important reduction of 27% . The results of paramount interest from this trial, that is whether the severity of atopy and asthma was reduced in the intervention group, were not reported. This is disappointing because it would be very interesting to know if the intervention not only reduced the prevalence of sensitization but, more importantly, downregulated the entire allergic and symptomatic process. This result would be a significant long-term achievement because children who develop atopy in later childhood or who have less severe atopy are at a significantly reduced risk of developing severe asthma [11,12].

The potential for the primary prevention of asthma using allergen avoidance is obviously large. Table 1 shows that if 30% of children in Australia and New Zealand become sensitized to house dust mites and 80% are exposed to house dust mite allergen levels, of whom $\approx 50\%$ have AHR [13], then we can calculate that there are over half a million children who are sensitized to house dust mites and have AHR. If we then use the conservative estimate that halving exposure halves risk, we can estimate that a reduction in exposure levels to half the amounts encountered at present could prevent AHR in 6% of children. Although allergen avoidance can be problematic in humid regions, better methods for controlling allergens and for reducing exposure are now available [14] and should be able to achieve this health goal, especially if begun in early childhood.

Table 1. Estimated effects of interventions to change exposures to environmental factors in Australia and New Zealand

	House dust mite allergens	Parental smoking	Breastfeeding	Omega-3 fatty acids
Population at risk	1.4 million children age 0–14 years who are sensitised to housedust mites	4.6 million children age 0–14 years	0.3 million newborns	4.6 million children age 0–14 years
Outcome	AHR	Wheeze	Allergic symptoms	Current asthma
Exposure rate	80% of children who live in humid regions	25% with a mother who smokes during pregnancy	50% breastfed less than 4 months	60% have a diet with predominantly omega-6 fatty acids
Odds ratio for effect	0.5 if exposure halved	1.3	0.8	0.7
Number of exposed children with condition	550 000	320 000	No data available	390 000
Number if exposure reduced	275 000	260 000		280 000
Difference	6.0%	1.3%		2.4%

Parental smoking

The evidence for the factors that lead to the development of wheeze and asthma is most complete for the effects of exposure to parental smoking. Worldwide, more than 200 studies have examined the association between exposure to parental smoking and respiratory symptoms in children and their results have been surprisingly consistent [15]. Studies which have measured the effect of parental smoking on wheeze and asthma in children under 5 years of age show that the odds ratio for children to have wheeze or asthma if their parents smoke is fairly consistent at between 1.3 and 2.4. Other studies which have measured the effect in older children also show consistent but slightly reduced association with odds ratios which range from 1.0 to 2.3. The variations in estimates highlight the methodological problems in quantifying the effect of an environmental exposure which confers a small risk and for which measurement and misclassification errors will tend to decrease the effect size estimated.

Although odds ratios below 2 are sometimes thought to be unimportant in public health terms, this is only true if the odds ratio has not been measured with precision or if exposure rates are low. However, in the case of parental smoking, the effect has now been measured with consistency and precision and there is evidence that rates of exposure, especially to maternal smoking, remain high. As a result, the potential for prevention of wheeze in children by prevention of exposure to tobacco smoke is significant. Table 1 shows that in Australia and New Zealand, the number of children who are at risk of respiratory problems if exposed to parental smoking is 4.6 million children. If 25% of parents smoke, which recent studies suggest is a conservative estimate, and if the effect is an odds ratio of 1.3 for wheeze in the last 12 months, which is also a conservative estimate, we can calculate that 320 000 children wheeze as a result of being exposed to parental smoking. Thus, the potential for prevention if we can instigate effective anti-smoking campaigns for parents is 1.3% of all children.

Although there have been a very large number of studies of the effects of parental smoking on the respiratory health of children, there have been few reports of the efficacy of anti-smoking interventions. A recent intervention in a hospital ante-natal clinic was moderately successful [16] but other studies were not [17,18]. It is clear that interventions that are able to reduce smoking rates in young women before they become pregnant or that are able to achieve a reduction in smoking rates during pregnancy are urgently needed.

Breast-feeding

A factor which is likely to protect against the development of allergic symptoms is prolonged breast-feeding. This may

have a dual effect. Human milk is rich in long chain fatty acids which are thought to prevent allergic responses by preventing inflammation developing in the airways. In addition, breast-feeding also prevents exposure to the ingested foreign proteins of cow's milk at an early age. To date, few studies have investigated respiratory or allergic outcomes in children who have been breast-fed and although the estimates differ in magnitude, all show a protective effect [19–22]. The exception is the results from a study of atopic children in whom the effects of allergen exposure may have dominated the smaller, beneficial effects of breast-feeding demonstrated in non-atopic children [23].

It is hard to estimate the potential benefits of prolonging breast-feeding because we do not yet have sufficient data. However, 300 000 babies are born each year in Australia and New Zealand and recent data show that only 50% of infants are breast-fed for more than 4 months and 25% for more than 6 months. This suggests a large potential for improvement. If we estimate that the odds ratio for the protective effect of breast-feeding is 0.8 then the situation is the same as for parental smoking, that is we have a factor (feeding by cow's milk) which confers a small risk but to which a large number of children are exposed. Thus, the promotion of prolonged breast-feeding may, in all likelihood, be a significant factor in preventing allergic symptoms in infancy and subsequent respiratory symptoms throughout childhood.

Diet

The data from epidemiological studies of the association between diet and asthma are difficult to summarize because measurements of exposure or outcome have not been standardized. However, a number of studies have related the presence or severity of asthma to dietary intake of antioxidants, salt and fatty acids [3,24,25]. A recent study of children in the UK found that children who ate a 'westernized' diet had significantly more asthma than those who ate an 'Asian' diet, regardless of race [26]. This is consistent with the hypothesis that a diet which is low in antioxidants and omega-3 fatty acids and high in salt and omega-6 fatty acids may promote the development of asthma. In Australia, we have shown that children who eat fish at least once a week and who therefore consume adequate amounts of omega-3 fatty acids are protected from having AHR or current asthma after adjusting for other risk factors [27,28].

It is difficult to make estimations of the potential effects of improving diet. In a recent study, we estimated that 60% of children eat no fish or have a predominantly omega-6 fatty acid intake, which suggests a large potential for intervention but we made no estimates of salt or antioxidant

intake. A conservative estimate from our studies of 8–11-year-old children is that the protective effect of a high omega-3 diet has an odds ratio of 0.7 so that, using these figures, the potential for prevention would be 2.4% of children (Table 1). This estimate is calculated for the prevention of current asthma, that is AHR and symptoms, which defines children with asthma at the more severe end of the spectrum [29]. Thus, this would represent a significant public health benefit in terms of reduction in the rates of morbidity and use of health services and medications.

Summary

We now have excellent evidence that preventing exposure to parental smoking and to house dust mites has the potential to significantly reduce the prevalence of childhood asthma and there is accumulating evidence that promoting breast-feeding and a diet with a high antioxidant and omega-3 fatty acid content and a low salt and omega-6 fatty acid content will have health benefits for children. In Table 1, the most conservative figures available have been used to estimate potential benefits and to show that health gains could be significant. Because asthma has several phenotypic expressions, the potential outcomes have been estimated only for specific expressions of the disease which have associated morbidity. Although it could be argued that not all children who wheeze have clinically important asthma, more than 80% of such children visit a doctor and over 70% use an asthma medication [12]. Table 1 does not show the total potential benefits because not all outcomes are represented but this will be balanced by some overlap between exposures.

Avoidance of parental smoking and house dust mite allergens and the promotion of breast-feeding have been tested a study of infants (Fig. 2) in which the intervention comprised avoidance of parental tobacco smoke and house dust collecting materials plus a breast-feeding or hypoallergenic formula. Unfortunately, there was no randomization and the control group was a historical cohort with no matching for parental history or other confounders. Nevertheless, the results are encouraging in that the prevalence of atopic symptoms and wheeze was reduced by half in the intervention group and, although some of this difference could be explained by reporting bias, it is unlikely that inadequacies in the study design could account entirely for the differences found.

Future directions

It is important to recognize that we now have the strongest evidence about risk factors that will be gained from large-scale epidemiological studies for a long time. Thus, it is important that we make a decision to act on the evidence and give advice to parents, or to ignore the evidence until we

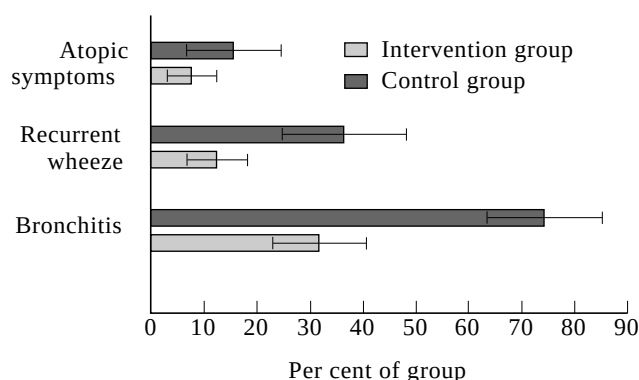


Fig. 2. Effect of diet modification, promotion of breast-feeding or use of a hypoallergenic formula, and avoidance of both parental smoking and dust collecting materials in the bedroom on symptom at 18 months of age as reported by Halken *et al.* [30]. The intervention group comprised 105 children who were studied in 1988 and the control group comprised a historical cohort of 54 children studied in 1985. 'Atopic symptoms' were defined as the presence of asthma, recurrent wheezing, atopic dermatitis, urticaria, or food allergy or recurrent, unexplained vomiting/diarrhoea and 'recurrent wheeze' was defined as two or more episodes of wheezing.

have completed long-term cohort studies or randomized trials of preventive strategies. It would seem most sensible to adopt the former approach especially since the interventions suggested have coherence with other health benefits and can do no harm.

It is also important that we continue to test intervention strategies both to evaluate their efficacy and to resolve the components which are necessary and which confer the greatest benefits. In practice, we should not advise parents to make expensive changes to their homes, such as removing carpets or installing ventilatory systems, if these components have a minimal effect on allergen avoidance. At this point in time, a number of randomized controlled trials of house dust mite allergen avoidance interventions, each with different methods, are underway around the world. In judging the results of such interventions when they become available, it will be important to keep in mind that apparently small effects may make large differences to the total amount of asthma in our communities simply because of the high levels of adverse exposures which exist at present.

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