Environment and development of atopy
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Purpose of review
Asthma and other atopic disorders are the result of complex interactions between genetic predisposition and multiple environmental influences. However, the marked increase in asthma prevalence over recent decades is unlikely to be due to genetic changes, highlighting the contribution of environmental factors to the process of allergic sensitization.

Recent findings
This article reviews recent information on environmental influences on the development of atopy in children. Both observational and interventional studies continue to shed new light on the critical influence of early life events – such as events in pregnancy, exposure to allergens and endotoxin, pet ownership, infections, family size – and have highlighted important gene–environment interactions that modify the relationships between environmental exposures and atopic outcomes.

Summary
The future is likely to see a concerted effort to further define the role that these environmental exposures play in allergic sensitization and the expression of atopic diseases, in order to provide a rational platform on which to develop new methods of allergy prevention that can be targeted at high-risk children.

Keywords
allergen avoidance, atopy, endotoxin, primary prevention

Introduction
Asthma and other atopic disorders are thought to be due to complex interactions between genetic and environmental factors. The prevalence of atopy, asthma and allergic rhinitis has dramatically increased over the last 30 years, though Australian data suggest that this increase may now be levelling off [1]. In many developing countries, increasing Westernization is associated with a rapid rise in the prevalence of previously uncommon atopic disorders. Notwithstanding the importance of genetic factors, the time frame over which these increases have occurred makes it implausible that they could be the result of genetic changes, highlighting the importance of environmental factors in the pathogenesis of allergic sensitization and the expression of atopic diseases.

The importance of early life events in the natural history of atopy has long been recognized. This view is further reinforced by recent findings from a population-based birth cohort, which clearly demonstrates that persistent asthma in young adults is associated with early age at onset of wheezing and impaired lung function during childhood, confirming that these important outcomes in adult asthma are determined early in childhood [2].

The hygiene hypothesis: endotoxin exposure, infections and large family size
The hygiene hypothesis has focused attention on the notion that exposure to microbes and their products in early life can modify the risk for development of allergic disorders. Thus, exposure to farm animals or domestic pets, day care attendance and large family size all appear to protect against allergic sensitization [3–6].

Recent studies have shed further light on these effects. In a large cross-sectional study, De Marco and colleagues [7] reported that early childhood respiratory infections were associated with an increased asthma risk, whereas early contact with older children was linked to permanent protection against asthma and increased the chances of remission of childhood asthma. These patterns of association were independent of the presence or absence of allergen-specific IgE, suggesting that exposure to microbial infections can partially interfere with an acquired predisposition to asthma. Similarly, otitis media and other infections in infancy may protect against allergic sensitization in older children and teenagers [8,9]. Household endotoxin levels appear to be inversely associated with a subsequent diagnosis of eczema, even after adjusting for income, season of birth and gender [10].
Having older siblings and day care attendance has usually been thought to protect against wheezing and asthma \cite{3,11}. However, recent studies suggest that the protective mechanisms involved may be more complex than previously recognized. It appears that the protective influence of day care against eczema and asthma may be restricted to those individuals without a family history of asthma \cite{12}. In contrast, in those with a maternal history of asthma, day care was instead associated with increased asthma by age 6 years \cite{12}. Thus, the relationship between day care exposure and asthma outcomes is influenced by family history—a further example of the importance of gene–environment interactions.

The protective influence of large family size has traditionally been interpreted as evidence in support of the hygiene hypothesis. However, a recent publication reported that successive pregnancies may diminish maternal skin test reactivity \cite{13}. The authors speculate that this apparent reduction in maternal atopy might affect the atopic status of successive children and provide an additional explanation for the observation of reduced atopy in large families.

Pets and other animals

The effect of family pets on the development of atopic disease remains controversial. While many would argue with the recommendation that sensitized patients should minimize exposure to cats and dogs, it is becoming increasingly clear that avoidance of such exposures is ineffective in preventing sensitization in young children, and may indeed be counterproductive \cite{14}. Early exposure to cats appears to protect against cat allergy and subsequent asthma \cite{15–17}, and may also reduce sensitization to other allergens \cite{15}, while other investigators report no relationship between cat allergen exposure and atopy or asthma outcomes \cite{11}. Interestingly, Polk and co-workers \cite{18} reported that while Fel d 1 levels in household dust within the first year protected against early wheezing, high levels of Fel d 1 were associated with increased wheezing at 4 years of age, but only if the child’s mother had asthma. The notion that high levels of cat allergen exposure has differential effects on wheezing outcomes, depending on maternal asthma, is consistent with findings reported previously \cite{19}.

Dog ownership in early life also appears to be associated with reduced allergic sensitization and atopic dermatitis \cite{16,20}. Whether levels of cat and dog allergens are a surrogate for another biologically relevant exposure such as endotoxin, or whether they are causally related to sensitization can be difficult to determine from observational studies. However, Gern and colleagues showed evidence of an important gene-by-environment interaction involving CD14, part of the receptor complex for bacterial endotoxin. The $CD14\ -159TT$ genotype appears to protect against atopic dermatitis only in those children with a dog at home, suggesting that the beneficial effect of dogs in the home may be mediated, at least in part, by increased endotoxin exposure \cite{20}.

The available information on exposure to other animal allergens does suggest a direct relationship between sensitization and exposure to high levels of rodent and cockroach allergens, even when adjustments are made for socio-economic status \cite{21–23}.

House dust mite exposure

The relationship between house dust mite allergen exposure and sensitization is unclear at this stage. Previous investigators have reported that exposure to domestic levels of Der p 1 in excess of 10 $\mu g/g$ of dust in infancy is a risk factor for asthma in older children \cite{24}, but only in those with a family history of allergic disease. Higher mite allergen exposure is associated with a greater risk of sensitization in children with a positive family history, but a lower risk of sensitization in children without a history of parental atopy \cite{25}. Cullinan and co-workers \cite{26} reported no overall relationship between early mite allergen exposure and IgE sensitization or atopic asthma at the age of 5 years. However, closer examination of the exposure–response relationships showed an increase in sensitization and wheeze at low levels of allergen exposure, and a reduction in both outcomes at high levels of allergen exposure \cite{26}. These relationships were modified by birth order and paternal atopy \cite{26}. It remains unclear whether the apparent protective effects of high allergen exposure can be attributed to high-dose immunological tolerance \cite{14,27}, to concurrent endotoxin exposure, or to a combination of both mechanisms. This issue is highly relevant to the development of primary prevention strategies, as discussed below.

Other environmental risk factors

Prolonged delivery was associated with the development of atopy in a prospective birth cohort followed to the age of 20 years, whereas prenatal smoke exposure and childhood pets decreased the risk of atopy \cite{28}, suggesting that events in pregnancy or at birth may have an enduring effect on atopy many years later. Exposure to urban traffic and environmental tobacco smoke may be associated with allergic sensitization, though such associations may be confounded by socio-economic status \cite{29}. Psychological stress in caregivers is reportedly associated with larger T-cell responses to allergens and higher total IgE levels in the first two years of life \cite{30}, while elevated body mass index and an early onset of puberty may be linked to persistence of asthma from childhood into adolescence \cite{31}. Use of skin creams containing peanut oil, and intake of soymilk or soy-based formula, are associated with the development of peanut allergy.
Primary prevention of atopy and asthma

Because the increase in asthma and other atopic disorders is likely to be due to changing environmental exposures, identification and reduction of these exposures should be an effective measure to prevent asthma and other atopic diseases in children at high genetic risk for these conditions. Moreover, such intervention studies should provide important insight into cause-and-effect relationships between environmental exposures and the development of disease.

Primary prevention: allergen avoidance

There are strong associations between allergic sensitization and asthma, and there is good evidence that allergen avoidance can be an effective strategy for children with established asthma [33]. Hence, it is important to determine whether reducing allergen exposure in early life is a worthwhile primary prevention strategy. Environmental intervention studies typically employ a multifaceted strategy that includes not only reduction of inhalant allergen exposure and delayed introduction of solid foods, but also advice about environmental tobacco smoke, breast feeding and diet. Several randomized controlled trials (RCTs) have reported interim findings in the period since January 2003. In these studies it is usually impossible to blind the parents as to whether their child has been allocated to the active intervention group or the control group, so it is particularly important that studies include objective outcome measures. It is also impossible in many cases to determine which precise environmental factor is responsible for the perceived changes in outcomes. This is particularly the case in intervention studies involving attempts to reduce exposure to indoor allergens such as mites, in which avoidance strategies such as frequent cleaning or removal of furnishings that harbour dust will also have the effect of reducing exposures to other environmental factors such as endotoxin.

The principal findings from these recent studies can be summarized as follows. Halmerbauer and colleagues [34] reported that allergen avoidance led to a reduction in the proportion of mite allergic children at 1 year, but no change in the percentage of children with a history of wheezing. Using a multifaceted intervention, including allergen avoidance, the Canadian Asthma Primary Prevention Study showed a reduction in both asthma and persistent asthma at age 2 years, but no difference in skin test reactivity between active and control groups [11]. In the Australian Childhood Asthma Prevention Study, mite avoidance was associated with reduced mite sensitization at 3 years, but did not affect wheezing [35], and increased eczema was reported at the 18-month follow-up [36].

The Isle of Wight birth cohort study is the longest running RCT of allergen avoidance. Reduction of exposure to aeroallergens and food allergens from birth led to a reduction in wheeze, wheeze with bronchial hyperresponsiveness, night cough, and atopic sensitization at the age of 8 years, as compared with children in the control group [37].

The most stringent allergen avoidance regimens employed in these trials were those used in the Manchester Asthma and Allergy Study. Woodcock and colleagues [38] reported that 3-year-old children in the active intervention group were more frequently sensitized to indoor allergens than in the control group. This difference remained significant even after controlling for likely confounding variables. In contrast, children in the active group had better airway resistance than children in the control group [38]. There was no significant difference in respiratory symptoms or eczema between the two groups.

One plausible explanation for the paradoxical finding of increased sensitization to house dust mite resulting from reduced exposure is that resistance to atopic sensitization is an active process, driven by exposure to the allergen itself. In this regard, an extensive experimental literature has demonstrated that repeated exposure to Aeroallergen in the nanogram to microgram range elicits a form of Th2-selective immunological ‘tolerance’, involving inhibition of IgE antibody production, but preservation of ongoing low to moderate IgG antibody production [39–41]. This pattern of modified immunological responsiveness is analogous to that reported by Platts-Mills and colleagues [14] as the hallmark of exposure to high levels of cat allergen, whereas low level exposure is more consistently associated with atopic sensitization. This biphasic dose–response relationship between cat allergen exposure and sensitization has also been reported by the Custovic group [42] and by others [27]. Interim analyses from the ISAAC study also suggest an inverse relationship between early life pollen exposure and sensitisation [43], and as mentioned earlier, recent findings suggest that high levels of mite allergen exposure may inhibit sensitization and wheeze [26]. Hence, this biphasic dose–response relationship may not be restricted to cat allergen.

Primary prevention: probiotics

Perinatal administration of probiotics reduced the incidence of atopic eczema in 2-year-old children [44], and the same investigators have now reported on the 4-year follow-up [45]. The beneficial effect of probiotics may extend into the preschool age group, with a continued reduction in the number of children with eczema. There
was no difference in skin test reactivity between the placebo and active treatment groups, suggesting that the mechanisms by which probiotics prevent eczema is independent of any influence on allergic sensitisation [45**]. It has been hypothesized that changes in bowel flora may be causally linked to the increase in atopic disease seen over recent decades [46]. The beneficial effects of probiotics provide circumstantial evidence in support of this hypothesis, though there is still much to be learnt regarding probiotics, and their mechanisms of action.

Primary prevention: dietary intervention

Maternal fish oil supplementation during pregnancy reduced the severity of atopic dermatitis, associated with reduced sensitization to egg at age 1 year and alterations in neonatal cytokine responses in vitro [47]. Fish oil supplementation of infants from the age of 6 months onwards led to reduced cough in atopic children at 3 years of age, but no change in wheeze, asthma, eczema or allergic sensitisation [35]. The extent to which the changing prevalence of atopic disease can be attributed to alterations in diet, and the mechanisms by which fish oil supplements exert their effects, remains the focus of much current research.

It is becoming increasingly clear that the benefits or otherwise of intervention will often only become apparent with long periods of follow-up. This is especially true in asthma, where it may take many years to disentangle the various wheezing phenotypes that present in early childhood and determine which children will develop chronic persistent asthma [48].

Conclusion

There is thus increasing evidence that controlled modification of environmental factors has potential as preventative measures to control asthma and allergies. The progressive refinement of both experimental and intervention trial strategies over the next few years can confidently be predicted to unmask an increasing range of testable new approaches.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


This long-term follow-up of a cohort of Australian children suggests that the trajectory of increasing asthma prevalence may not be continuing.


Population based, longitudinal birth cohort. Those with persistent or relapsing wheezing at age 26 years tended to have impaired lung function during childhood, suggesting that these outcomes are often determined early in childhood.


Early childhood respiratory infections were associated with increased asthma risk, whereas early contact with older children linked to permanent protection against asthma and increased the chances of remission of childhood asthma. Pet keeping had a protective effect only in childhood. These associations were independent of allergen-specific IgE.


Otis media in infancy may protect against allergic sensitisation in primary school children.


This was a cohort study from the Philippines. Infectious morbidity and indices of nutrition and growth during infancy were associated with a reduced total IgE at age 14–15 years.


Endotoxin levels in the living room at age 2–3 months were inversely associated with eczema diagnosis within the first year of life, even after adjusting for income, season of birth and sex.


This large RCT employed multi-faceted intervention during the first 12 months of life. Fewer children in the intervention group had asthma than in the control group. Intervention did not alter sensitization rates at 2 years, although day care was associated with reduced atopy.


The relationship between day care exposure and asthma outcomes is influenced by a maternal history of asthma.


Women were studied at enrolment and again 7 years later. Fifteen percent of mothers were no longer skin test positive, and this was more likely in those with higher numbers of pregnancies in the intervening years.


Exposure to cats before the age of 2 years was associated with less skin test reactivity to any allergen in adults, whereas current exposure was unrelated to skin test reactivity.


Cat and dog ownership were inversely associated with prevalence of allergy in a large prospective study.
Prolonged delivery was associated with the development of atopy by age 20 years, and may induce tolerance. This is consistent with previous work showing that high-dose exposure to cat allergen is associated with clinical tolerance: a modified Th2 immune response? Clin Exp Allergy 2003; 33:1681–1685.

This birth cohort was followed to age 5 years. There was an increase in sensitization and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. Thorax 2003; 58:489–493.

This describes the longest running RCT of allergen avoidance. Authors report reduced wheeze, bronchial hyperresponsiveness, night cough, and atopic sensitization in the intervention group at age 8 years.

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Paediatric asthma and development of atopy


This was a RCT of fish oil supplementation given during pregnancy. Active intervention reduced the severity of atopic dermatitis.