

Epidemiology of atopic dermatitis

H. C. Williams

Department of Dermatology, University Hospital, Queen's Medical Centre, Nottingham, UK

Summary

Although research into atopic dermatitis (AD) has been dominated by the study of cells and chemical mechanisms over the last 40 years, the last 7 years has witnessed a respectable growth within the field of AD epidemiology. Significant advances include valid disease definitions that can be used in epidemiological studies, global prevalence studies, and studies which quantify the morbidity and economic cost of the disease. These have all helped to argue the case for more research into AD. Epidemiological studies demonstrating that AD is commoner in wealthier families, linkage with small family size, increased prevalence in migrant groups, and the increasing prevalence of the disease all argue strongly towards an important role for the environment in determining disease expression. Future research gaps include evaluation of gene–environment interactions, better studies of the natural history of AD, and better clinical trials that answer questions that are important to physicians and their patients.

Introduction

Research into atopic dermatitis (AD) over the last 40 years has been dominated by exploration of the cellular and molecular mechanisms (Fig. 1). Much of this work has produced interesting breakthroughs such as the discovery of the role of different T-lymphocyte cell subsets and markers of skin barrier function. Yet, if I ask myself, how have these interesting developments helped me to educate and treat the families I see with AD: the honest answer has to be 'not very much'. That is apart from a few drug treatments, which at best, only partly modify disease symptoms. We still do not know the genetic basis for AD, and we do not know what makes it appear for the first time and whether genetic predisposition is a prerequisite for disease expression. It is unclear which factors consistently cause flare-ups in established cases, and it is not understood why some children clear of the disease and others apparently do not. It is also unclear why some children with AD go on to develop asthma,

and more importantly whether the long-term natural history of AD can be modified by any early interventions.

Only epidemiology offers the methodological framework to answer these questions, yet it is only during the last 7 years that research into the epidemiology of AD has started in earnest. Thanks to such studies, far more is now known about the prevalence, morbidity, cost and risk factors of AD in populations. This short account summarizes important developments and gaps in our knowledge of the epidemiology of AD.

What is atopic dermatitis?

Even as recently as the late 1970s, at least 14 synonyms for AD were in widespread use, and it is quite unclear whether these names depicted the same clinical concept to all workers.¹ The consensus criteria developed by Hanifin, Lobitz and Rajka in 1980 represented an important milestone in listing the main clinical features of AD. Although they have been useful for describing clinical participants in studies, they have been unsuitable for epidemiological studies due to their complexity and unknown validity and repeatability. These criteria therefore served as building blocks for a more refined

Correspondence: H. C. Williams, Department of Dermatology, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK. Tel.: + 44 (0)115 9249924 extn 42697. Fax: + 44 (0)115 9709003.
E-mail: hywel.williams@nottingham.ac.uk

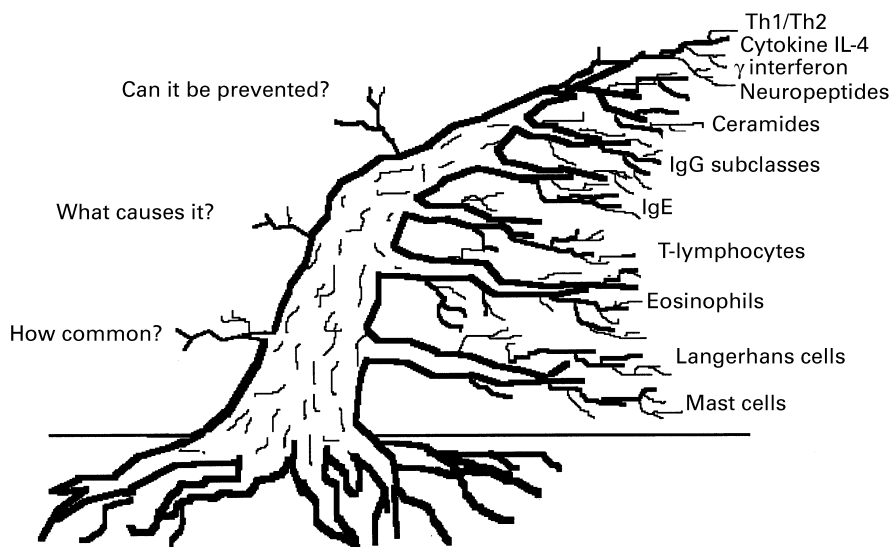


Figure 1 The tree of AD research over the last 30 years has been a very lop-sided one.

and easy to use set of criteria developed by a UK Working Party of 16 physicians (Table 1).

These criteria have been shown to have good repeatability and have been validated extensively in many populations, although more validation work is required in infants and adults. Any definition which uses subjective responses will always be prone to inaccuracies,² but the simplified refined criteria offer a standardized approach towards defining AD in a way that allows comparison of studies from different countries all over the world.

It is likely that the genetic basis of AD will be understood far better within the next 20 years, and it may well be that there are different subtypes of AD such as intrinsic or extrinsic, chronic or intermittent AD, or AD associated with discoid patterns, or subtypes which

are strongly associated with asthma. Some genes may predict disease severity or susceptibility to infection with *Staphylococcus aureus* whereas others may predict the development of additional mucosal atopy. The current diagnostic criteria for the classical AD phenotype may well have to change in the light of these developments.

This does not mean, of course, that our current criteria are wrong, only that they will give way to better and more objective descriptions of disease phenotype when we have a better way of classifying disease in terms of genetic or causative factors. Until more is known about the genetic and environmental causes of AD, it is perhaps wiser not to consider reclassifying AD into several subtypes based on biological phenomena such as IgE, unless such reclassification markedly increases our clinical predictive ability in terms of treatment responsiveness or natural history.³ It is possible that markers such as IgE are epiphenomena of disease severity rather than markers of specific disease subtypes. Providing that it is recognized that the terms 'atopic' within the disease label of 'atopic dermatitis' is simply an indicator of the phenotype of flexural dermatitis, which may include up to 40% of nonatopic individuals, then there is little harm in persisting with such a term.

Who gets it?

Age and sex

Although AD is often thought of as a condition of early infancy, some prevalence surveys have suggested that

Table 1 The UK refinement of the Hanifin and Rajka Diagnostic Criteria for AD for use in epidemiological studies.

To qualify as a case of atopic dermatitis with the UK Diagnostic Criteria, the child must have:

An itchy skin condition in the last 12 months

Plus three more of:

- (i) onset below the age of two years*
- (ii) history of flexural involvement
- (iii) history of a generally dry skin
- (iv) personal history of other atopic disease**
- (v) visible flexural dermatitis as per photographic protocol

*Not used in children under 4 years of age. **In children under 4 years, history of atopic disease in a first-degree relative may be included.



Figure 2 The disability caused by AD is among the highest for skin diseases.

the decline in AD prevalence throughout childhood is not as steep as generally assumed. Prevalence appears to fall substantially in the teenage years. A slight increase in females is noted in prevalence studies of childhood.⁴

Ethnic group

Based on a prevalence study which used the UK Diagnostic Criteria, a study in London has suggested that black Caribbean children are at increased risk of AD when compared with their white counterparts.⁵ It is difficult to say whether these differences were due to factors affecting disease chronicity or disease incidence between the groups. Another study of Asian children in Leicester has not shown any difference in the prevalence of AD between ethnic groups, although Asian children were three times more likely to be seen in the local dermatology Department, perhaps reflecting lack of parental familiarity with the condition.⁶

Socio-economic factors

There is a strong link between AD and socio-economic advantage (as measured by occupation of parents or household tenure) and also with smaller family size. These have been shown for both reported and examined dermatitis in several countries. Similar trends have been seen in surveys of skin test reactivity. These suggest that environmental factors correlated with a 'Western' lifestyle may account for a large part of the variation in the prevalence of AD.⁷

Occupational groups

Several reports have suggested that those with a previous history of AD are at increased risk of developing irritant hand dermatitis due to wet exposures in certain occupations such as domestic cleaning, hairdressing and nursing. Although severe AD can be associated with marked disability, studies suggest that the majority of AD patients manage to remain in working life, and that once they are employed, do not appear to change their occupations more frequently when compared with nonatopics.⁴

How does it affect people?

Most doctors caring for AD patients immediately recognize the suffering caused by the intractable itching (Fig. 2), yet only recently have studies attempted to quantify such effects on sufferers and their families. Such studies have suggested that the morbidity is comparable to other 'important' noncommunicable diseases. Given that health care systems have finite resources, economic studies on AD are extremely important in helping to raise public health awareness and help prioritization. Recent studies suggest that the direct economic costs of AD to the state in the UK, Australia and the USA are very high indeed. Additional personal financial costs to families with AD include special clothing, bedding, laundry and extra visits to the doctor. It is this product of low to moderate morbidity times the high prevalence of AD that makes it an important disease in public health terms in view of its large absolute burden.⁸

Will it clear?

The natural history of AD has recently been reviewed in detail.⁹ Although at least 25 studies have been published on the subject, the quality of these studies is generally poor in terms of small sample size, lack of

disease definition at inception and follow-up, length of follow-up being too short, heavy losses to follow-up, lack of adjustment for recurrent disease and selection bias in the initial cohort. Most of the larger studies of well defined and representative AD cases suggest that around 60% of childhood dermatitis cases are clear or free of symptoms in early adolescence.⁹ Many such apparent cases are likely to recur in adulthood. The strongest and most consistent factors which appear to predict more persistent AD are early disease onset, severe widespread disease in early life, concomitant asthma or hayfever and a family history of AD.

Where does it occur?

There is reasonable evidence to show that the prevalence of AD varies considerably from one country to another, and also within countries. Perhaps the most comprehensive geographical study of AD is the International Study of Asthma and Allergies in Childhood (ISAAC).¹⁰ This study used standardized definitions of AD based on questions on disease symptoms, similar to those used in the UK Diagnostic Criteria for epidemiological studies. Data on around half a million children from the ISAAC study suggests a band of low prevalence in low latitudes, and high prevalences in Northern Europe, Australasia and also some cities in developing countries undergoing rapid demographic change.

Differences within countries have also been noted, e.g. much lower prevalence has been noted in the UK both in the 1958 and the 1970 cohort studies in Scotland compared with the south of England. Marked regional variations in AD have also been reported in a study of over 3000 children in northern, eastern and southern Finland.¹¹ A decreased prevalence in AD has been noticed in rural compared with urban areas of Sweden.¹¹ Further spatial analyses are required to see whether these regional variations are related to environmental factors, such as water supply, pesticide residues and proximity to urban highways. A recent ecological study in the Nottingham area has found that children living in harder water areas are more likely to have AD compared to those living in soft water areas.¹² This does not mean to say that water softeners are an effective treatment for AD unless a randomized controlled clinical trial shows this to be the case.

Migrant studies have also been helpful in suggesting a strong role for the environment in AD.¹³ Three studies have shown that populations from countries where there is a low prevalence of AD assume rates which are similar or higher than those in the adopted country. Thus, approximately 15% of black Caribbean children

living in London had AD according to the UK criteria, compared with 5.6% of similar children living in Kingston, Jamaica, when administered the same criteria by the same investigator.¹³ This difference persisted for other measures for defining AD such as simply examining for flexural dermatitis, or using doctor-diagnosed 'eczema'. Possible 'risk factors' worthy of further explanation in such a migrant study include differences in exposure to aeroallergens, differences in diet, climate, microbial colonization and health-rated behaviour (i.e. appropriate use of treatment).

When does it occur?

Seasonality

One study has suggested that in those with existing AD, deterioration of symptoms was experienced in 33–88% of patients during autumn and winter.⁴ However, no major seasonal difference in the point prevalence of AD was seen in a large survey of schoolchildren in northern Sweden.⁴ Similarly, no seasonal variation in the proportion and absolute number of endogenous cases of eczema referred to a region of UK dermatology centre was noted.⁴

Secular trends

There is reasonable direct and indirect evidence to suggest that the prevalence of AD has increased between two- and three-fold over the last 30 years.¹⁴ Some of these changes probably reflect fashions in recognizing the disease by both parents and doctors, but the magnitude and consistency of these trends support a genuine increase. The trends are also present for asthma, and also for more objective measures of allergic disease such as skin prick tests and bronchial hyper-reactivity. Reasons for this increase in AD are less clear, but an increased susceptibility to sensitization induced by environmental factors associated with a western lifestyle seems to be a more plausible explanation than an increase in specific allergens or a sudden increase in the pool of genetically susceptible people.

Why does it occur?

Genetics

There is strong evidence to suggest that genetic factors are important in the predisposition to AD.¹⁵ In addition to family studies, twin studies have shown much higher disease concordance for monozygotic (85%), when

compared with dizygotic twins (21%).¹⁵ AD is probably a complex disease caused by several genes and environmental triggers. The genetic variance of serum IgE constitutes about 50% of the phenotypic variance. One of the loci influencing the IgE level is located on chromosome 5. A nonconfirmed report suggests that another locus is located on chromosome 11 (high-affinity receptor for IgE). Maternal atopy causes a greater risk of atopic disorders in the offspring than paternal atopy; the reasons for this are still unclear.¹⁵

Fetal predictors

Because the vast majority of AD cases present in the first year of life, and heritability is more strongly linked to the maternal side, it seems logical to suggest that environmental influences operating *in utero* or in early infancy may be critical in determining disease expression. These have recently been reviewed by Godfrey.¹⁶ Effects of the intrauterine environment may have resulted in classical twin studies overestimating the genetic contribution to many diseases including AD. Some studies have suggested a weak association between increased birth weight and AD. Recent studies have also found associations between disproportionate foetal growth and adult IgE concentration. Such associations could reflect effects on essential fatty acid metabolism or an inability of the maternal supply line to match foetal nutrient requirements during a critical period of thymic development. Other studies have suggested that increased maternal age and prior contraceptive use may be linked to later AD in the offspring.

Environment

Several factors such as the rapid increase in disease prevalence over the last 30 years, the positive social class gradient, the marked geographical variation, and migrant studies showing higher rates in newly adopted countries, all strongly point to the critical role that environmental factors play in determining expression of the AD phenotype.¹⁷ It is still unclear whether predisposition to atopy is a prerequisite to developing such AD and recent studies looking at atopic dermatitis 'score' suggest that this might be normally distributed in the population rather than in two distinct peaks.¹

Studies of disease mechanisms and intervention studies have suggested that various allergens such as house dust mite play an important part in the course of AD exacerbations, at least in a subset of people. The role of dietary factors in preventing disease is still unclear, although it probably plays a small effect if present.¹⁸

There is clear evidence however, from double-blind placebo-controlled food challenges, that some children with AD have food allergies. There is as yet no reliable simple test for the identification of individual food triggers or for the prediction of outcome after dietary elimination in AD.¹⁸

It is possible that exposure to infections in early life may be an important determinant of AD expression. Thus the 'hygiene' hypothesis forwarded by Strachan,¹⁹ whereby children living with many other siblings are 'protected' from expressing allergic disease because of continuous exposure to other infections, could be the explanation of the link between AD and small family size. Other studies have documented decreased expression of atopy following measles infection, and such work needs to be repeated specifically in AD.

The role of environmental pollution in AD has recently been reviewed by Schäfer and Ring.²⁰ Although biologically plausible, information linking AD with air pollutants is still weak and if real, probably only accounts for a small proportion of cases.

Risk factors for disease exacerbation

Irritants may be more important than allergens in triggering skin inflammation in AD.⁴ Low humidity, excessive exposure to soaps and hard water may be important by indirectly increasing vulnerability to sensitization as well as direct chemical irritation. The dry skin that is characteristic of AD also favours colonization by *Staphylococcus aureus*, an organism which may be important in directly causing secondary inflammation and also by causing widespread inflammation through superantigen formation. The degree to which such colonization is primary or secondary to existing dermatitis is still unclear as studies suggest that treatment of the underlying AD alone reduces such colonization drastically.²¹

Can AD be prevented and treated effectively?

Primary prevention typically deals with preventing the disease from appearing for the first time in unaffected individuals, which some have considered to include prevention of sensitization to allergens. Secondary prevention refers to preventing expression of disease in already sensitized individuals, whereas tertiary prevention refers to the traditional role of treating established AD cases.

Given that factors operating early in life may be critical in determining subsequent AD, manipulation of the early environment offers a promising way to prevent

Table 2 Ten recent advances in our understanding of the epidemiology of AD.²⁴

1.	Simple, valid and repeatable definitions for AD for use in epidemiological studies.
2.	Prevalence studies, such as the ISAAC study, which document the burden of AD throughout the world.
3.	Economic studies that have documented the high patient and health service costs of AD compared with other diseases.
4.	Geographical studies that suggest there is a distinct pattern of AD which cannot easily be explained by current risk factors.
5.	Ecological studies which suggest a possible link between water hardness and AD in younger school children.
6.	Migrant studies which suggest a strong role of the environment for disease expression.
7.	A consistent link between AD and socio-economic advantage, suggesting that environmental factors are important in disease.
8.	Progress in understanding the skin immune system in AD.
9.	Studies which point to the role of genetics and the early environment in programming subsequent AD.
10.	Studies suggesting that a substantial proportion of AD might be preventable.

AD, especially since pregnant mothers with a family history of atopic disease are highly motivated to do what they can to prevent disease in their offspring. A number of attempts at disease prevention have been done and are summarized elsewhere.²² Various 'allergy prevention programmes' in these studies suggest large magnitudes of decrease in disease in the intervention groups, although these intervention studies have rarely distinguished between maternal avoidance of allergenic foods and measures for reducing house dust mite. It is also unclear whether or not such intervention programmes are best conducted on children born to 'high risk' parents, i.e. those with existing atopic disease, or whether they could be applicable to all newborns. A reduction in disease severity rather than prevalence may be a more acceptable aim for those attempting to lessen the burden of AD in the community by public health measures.

A systematic review of all randomized controlled trials (RCTs) of prevention and treatment for AD has recently been conducted.²³ In that study, around 600 RCTs had to be discarded because of unclear disease definition, or because many different sorts of inflammatory skin diseases were grouped together in the results section. The quality of reporting of the remaining 283 RCTs was generally poor, with inadequate description of randomization or concealment of allocation, lack of blinding of observers and a virtual absence of intention-to-treat analysis. Most of the RCTs for AD have been sponsored by pharmaceutical industry. These are geared towards establishing 'me too' products, such as new topical corticosteroids or different formulations of existing ones, in a market that already has scores of products available. There is a virtual absence of randomized controlled trials on products such as emollients, despite their almost universal use in AD. Studies on disease prevention and on simple cheap interventions such as salt water for infected AD, bandaging for moderate AD, and oral steroids or oral azathioprine for severe AD are nonexistent. Most of the RCTs have been of very short

duration in AD, i.e. 6 weeks or less, which is inappropriate in a chronic intermittent disease which can last many years. There are however, exciting new drug developments for both topical and systemic therapy for AD which now need to be compared against the best current treatments using analyses of cost-effectiveness.

Which are the research advances and gaps?

Progress

Areas of notable progress in the epidemiology of AD are summarized in Table 2.

Current research gaps

Undoubtedly, one of the current obstacles for further research is the lack of definition for a new (incident) case of AD in epidemiological studies,¹ and also the lack of simple measures of AD disease severity for use in large scale epidemiological studies which do not require a dermatologist to examine the patient.²⁴ There is also a case for conducting a prospective population-based study for the natural history of AD as none have been specifically set up for this purpose in the past.⁹ Given the early onset of AD, such studies could produce useful results in a relatively short time period, and also point to risk factors which could determine disease incidence, chronicity or development of subsequent asthma or hayfever. Although much research has looked at allergic factors in AD, nonallergic mechanisms may also be important in AD, and these require investigation in future epidemiological studies. Other research gaps include investigating the relationship between AD and other types of dermatitis such as the nummular or dyshidrotic patterns. There is a virtual absence of studies on the epidemiology of adult AD.

The patchy nature of studies which evaluate the treatment of AD has already been mentioned. Although new and possibly powerful treatment modalities exist

around the corner, the mainstay of treatment for the majority of AD is still topical steroid preparations and emollients. Yet, although these have been used for over 30 years, their evidential basis is quite weak. We still do not know how effective emollients are in AD or which ones are best. We still do not know if the benefit : risk ratio is better for potent preparations of topical corticosteroids applied for a few days as opposed to weaker preparations used for longer periods, and it is difficult for any clinician to make an evidence-based choice when faced with the 30 or so preparations currently available. Future trials need to include long-term outcome measures and incorporate patients views of disease activity, rather than so-called 'objective' measures such as surface area which are measured unreliably by even experienced physicians.²⁵

Conclusion

We have moved from a position of relative ignorance on the epidemiology of AD to one where there is promising foundation in a relatively short time. AD is no longer the poor third cousin of allergic disease epidemiology research. We now have good working definitions for disease occurrence and disease severity. It is clear that AD is a common and troublesome problem worldwide, and that it is a costly one. This has provided researchers with the ammunition to argue more effectively for resources for future AD research. There is now overwhelming evidence that environmental factors are at least as important as genetic factors in determining disease expression. The challenge ahead is to identify those factors which can be manipulated easily at a population level so that the current epidemic of AD that is currently evident worldwide can be curbed. The potential that epidemiology holds in improving our understanding of the distribution, causes and prevention of AD has never been better.

Further reading

Williams HC (ed.) *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000.
Schäfer T, Ring J. Epidemiology of atopic eczema. *Allergologie* 1998; **21**: 259–71.

References

- 1 Williams HC. What is atopic dermatitis and how should it be defined in epidemiological studies? In: Williams HC, ed.

- Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 3–24.
- 2 Williams HC. Defining atopic dermatitis – where do we go from here? *Arch Dermatol* 1999; **135**: 583–6.
- 3 Williams HC. Defining cases. In: Williams HC, Strachan DP, eds. *The Challenge of Dermato-Epidemiology*. Boca Raton: CRC Press Inc., 1997: 13–24.
- 4 Williams HC. Atopic dermatitis. In: Williams HC, Strachan DP, eds. *The Challenge of Dermato-Epidemiology*. Boca Raton: CRC Press Inc., 1997: 125–144.
- 5 Williams HC, Pembroke AC, Forsdyke H, Boodoo G, Hay RJ, Burney PGJ. London-born black Caribbean children are at increased risk of atopic dermatitis. *J Am Acad Dermatol* 1995; **32**: 212–7.
- 6 Neame RL, Berth-Jones J, Kurinczuk JJ, Graham-Brown RAC. Prevalence of atopic dermatitis in Leicester: a study of methodology and examination of possible ethnic variation. *Br J Dermatol* 1995; **132**: 772–7.
- 7 McNally N, Phillips D. Social factors and atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 139–47.
- 8 Herd RM. The morbidity and cost of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 85–95.
- 9 Williams HC, Wüthrich B. The natural history of atopic dermatitis. Chapter 3. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 41–59.
- 10 Williams HC, Robertson CF, Stewart AW, on behalf of the ISAAC Steering Committee. Worldwide variations in the prevalence of atopic eczema symptoms. *J Allergy Clin Immunol* 1999; **103**: 125–38.
- 11 McNally N, Phillips D. Geographical studies of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 71–84.
- 12 McNally NJ, Williams HC, Phillips DR *et al*. Atopic eczema and domestic water hardness. *Lancet* 1998; **352**: 527–31.
- 13 Burrell-Morris C, Williams HC. Atopic dermatitis in migrant populations. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 169–82.
- 14 Diepgen T. Is the prevalence of atopic dermatitis increasing? In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 96–112.
- 15 Schultz Larsen F. Genetic epidemiology of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 113–24.
- 16 Godfrey K. Fetal and perinatal origins of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 125–38.
- 17 Williams HC. Atopic eczema – why we should look to the environment. *Br Med J* 1995; **311**: 1241–2.
- 18 David TJ, Patel L, Ewing CI, Stanton RHJ. Dietary factors in established atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 193–204.

- 19 Strachan DP. Hay fever, hygiene, and household size. *Br Med J* 1989; **299**: 1259–60.
- 20 Schäfer T, Ring J. The possible role of environmental pollution in the development of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 155–68.
- 21 Stalder JF, Fleury M, Sourisse M, Rostin M, Pheline F, Litoux P. Local steroid therapy and bacterial skin flora in atopic dermatitis. *Br J Dermatol* 1994; **131**: 536–40.
- 22 Mar A, Marks R. Prevention of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 205–20.
- 23 Hoare C, Li Wan Po A, Williams HC. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; in press.
- 24 Williams HC. The future research agenda. In: Williams HC, ed. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 247–61.
- 25 Charman CR, Venn AJ, Williams HC. Measurement of body surface involvement in atopic eczema: an impossible task? *Br J Dermatol* 1999; **140**: 109–11.