Asthma, allergy and the hygiene hypothesis

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ABSTRACT

Recent studies have shown high prevalence rates of asthma symptoms in developed countries, including New Zealand, compared with developing countries. The *hygiene hypothesis* was evolved in the late 1980s as a potential explanation for the rise in asthma prevalence worldwide. It is hypothesised that early childhood infections may protect against the acquisition of atopy. Evidence suggests that in recent years reduced exposure to infections because of 'westernisation', reduced family size, improvements in hygiene and increased medical interventions such as antibiotics and vaccinations, may be contributing to the observed increase in atopic diseases.

This article outlines the *hygiene hypothesis* and the evidence available to support the view that the rising prevalence of asthma can be ascribed to reduced infections and increased 'cleanliness'.

Key words

Asthma, allergy, hygiene hypothesis

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Over the past three decades there has been an increase in asthma observed in most countries. The increase in prevalence cannot be explained by changes in genetic factors or by improvements in diagnosis alone. Environmental factors, particularly those associated with a Western lifestyle, are believed to play an important role.

In the late 1980s, Strachan found that repeated infections in early life may prevent the development of hayfever.[1] He suggested that an important factor related to the increase in atopic diseases in Western countries is the decreased exposure to cross-infections among younger siblings as a result of decreased family size.[2]

This *hygiene hypothesis* challenged the immunological opinion prevailing at the time which was that early childhood infections might promote, rather than protect against, allergic sensitisation.[3] Recent advances in our understanding of T-lymphocyte differentiation, however, support a possible mechanism for a protective effect from early exposure to infections.[4]

> Reduced exposure to infections because of 'westernisation'...may be contributing to the observed increase in atopic diseases

The early years of life are recognised to be very important in the development of the immune system. Human T-helper cells diverge into two separate subsets – T-helper 1 (Th-1) cells and T-helper 2 (Th-2) cells. Th-1 cells are effective in eliminating certain viruses and intracellular pathogens and regulate delayed-type hypersensitivity reactions. Overproduction of Th-1 cells are implicated in some autoimmune diseases. Th-2 cells are effective in eliminating extracellular pathogens such as helminthic parasites and are responsible for immune responses to persistent antigens, including environmental allergens. Th-2 cells recruit eosinophils and activate mast cells, leading to allergic and inflammatory conditions. The two T-helper subsets cross-regulate each other and the balance between the two determines whether or not an immune response is appropriate or detrimental.[4,5]

It has been proposed that the fetal immune system is weakly skewed toward the preferential development of Th-2-type immune responses.[6] Early infection, whether with viruses or bacteria, will tend to stimulate a Th-1 immune response which will switch any Th-2 biased allergic immune responses to a Th-1 immunising pattern. The time period that is critical for the reversal of the Th-1/Th-2 balance is not clear, but maturation of the immune system continues up to five to seven years of age.[7] As the peak incidence of asthma is in the first four years of life, in-utero and early childhood exposure to infecting organisms may be expected to have a greater impact on the development of asthma than later infections.

What is the evidence to support the *hygiene hypothesis* and the view that the rising prevalence of asthma can be ascribed to reduced infections and increased 'cleanliness'?

Family size/sibling numbers

The average family size in developed countries has decreased over the past century. In New Zealand the birth rate was 1.98 births per woman in 2001, compared to 4.2 births per woman in 1960 and 3.1 in 1920. In 1966 there was an average of 2.5 children per family, falling to 1.95 children per family in 1996. There has also been a two- to three-fold reduction in the proportion

of New Zealand families with four or more children in the past four decades.[8]

Sibship size has been shown to be a strong determinant of atopic conditions in children, adolescents and adults.[9] The structure as well as the size of the family also appears to be influential. Older siblings have been found to provide a greater protective effect against the development of atopic disorders than younger siblings,[1] this effect is more pronounced with brothers than sisters.[10] Furthermore, sharing a bedroom as a child provides a protective effect which is independent of family size.[11] Some studies have indicated that a low birth order is a risk factor for the development of atopic disease although results are conflicting. Overall these studies are consistent with the hypothesis that repeated infections in early childhood transmitted by contact with older siblings prevent the development of atopic immune responses.

The 'sibling effect' has mainly been shown for atopy. However a recent study by Ball et al[12] examined the exposure to siblings during infancy in relation to the subsequent development of asthma and frequent wheezing in over 1 000 children. The presence of one or more older siblings at home was found to protect against the development of asthma (adjusted relative risk for each additional older sibling, 0.8; 95% confidence interval [CI], 0.7-1.0). Although the children with older siblings had more frequent wheezing during the preschool years compared to children with no older siblings, this ratio reversed in later childhood.

The same sibship effect has been shown in New Zealand families. A case-control study based on the New Zealand arm of the International Study of Asthma and Allergies in Childhood (ISAAC) found that, after controlling for confounders (including infections, atopy and socioeconomic status), family size was inversely related to the prevalence of asthma.[13] Having no or one sibling was associated with an increased risk of asthma compared with having more than one sibling.

Day-care attendance

While sibling numbers may have declined in recent decades, day-care attendance has increased. If the presence of older siblings protects children against the subsequent development of allergic disease by exposing them to more infections in early childhood, then attendance at day-care should have a similar effect. Day-care attendance is lowest among children from low-income families, a group in which asthma morbidity is high.[14]

Atopic sensitisation occurs considerably more frequently in West German children than their peers in East Germany (37% versus 18% respectively), as does asthma, hayfever and bronchial hyperreactivity.[15] The high frequency of early day-care use in East Germany prior to unification has been proposed as an explanation for these differences. Day-care attendance was characteristic of the former East German lifestyle where the majority of women worked and up to 71% of East German children aged one to three years attended day-care. In comparison only 7% of West German children in this age group accessed day-care.[15]

> Older siblings have been found to provide a greater protective effect against the development of atopic disorders than younger siblings

Results from studies examining the issue of day-care attendance and subsequent risk of asthma have been conflicting however. Some of this confusion may arise from the multiple causes of wheezing during childhood. Wheezing in preschool children is primarily associated with infections, whereas in school-age children atopy and bronchial hyperresponsiveness is more important.[16] It follows therefore that early exposure to other children (either at home or in day-care) puts preschool children at greater risk from wheezing associated with respiratory infections, but this may also help protect them from IgE-associated wheezing in later childhood.

Attendance at day-care was found to be a risk factor for wheezing and asthma in children less than five years of age,[17,18] but among children 5–14 years old the frequency of asthma was inversely associated with previous day-care attendance.[19]

The Tuscon Children's Respiratory Study[12] also showed that attendance at day-care in the first six months of life protected against the development of asthma (adjusted relative risk 0.4; 95% CI 0.2-1.0). Although these children were found to have more frequent wheezing at the age of two years they were less likely to have frequent wheezing from the age of 6–13 years.

In a cross-sectional study of 669 German children aged 5–14 years from small families (up to three peo-

Key points

- Recent studies have shown high prevalence rates of asthma symptoms in developed countries compared with developing countries.
- Early childhood infections may protect against the acquisition of atopy.
- The hygiene hypothesis suggests that the rising prevalence of asthma can be ascribed to reduced infections and increased 'cleanliness'.
- Some reports have suggested a lower prevalence of allergic disease, including asthma, among young people raised on farms.
- Childhood exposure to pets seems to protect against allergy.

ple), those who entered a day-care centre between the age of six and 11 months had fewer allergies later in childhood than children who first attended day care at an older age. In 1 761 children from larger families (more than three people) age of entry to day-care had no effect on atopy.[19] Possibly those children from larger families had already been exposed to cross-infection and hence there was no additional benefit from day-care exposure.

Early viral and bacterial infections

The role of viral infections in the development of asthma has been the subject of considerable research and debate. Most wheezing lower respiratory tract infections in the first years of life are caused by respiratory viruses, particularly respiratory syncytial virus (RSV).[20] RSV infection has been associated with more rather than less allergy[21] – a finding which would appear to conflict with the *hygiene hypothesis*.

Stein et al however have reported that while children with a history of RSV lower respiratory tract infections were at increased risk of recurrent wheezing at the age of six years, this risk markedly decreased by the age of 13 years.[22] Furthermore, children with a history of RSV infection were less likely to have raised total IgE levels or be sensitised to local aeroallergens compared to children without a history of infection.

A study of West African children has shown an inverse relationship between measles infection and atopy. Of 133 participants who had had measles, 17 (13%) were atopic, compared with 33 (26%) of the 129 who had not been infected with measles.[23] Infection with measles virus therefore appears to prevent the development of atopy in African children.

These results have not been reproduced in other studies. A British 1970 birth cohort of over 13 000 children showed no evidence of a protective effect from wild measles.[24] In a Finnish study of over half a million children, those with a history of measles illness had an increase in the prevalence of asthma, hay fever and eczema.[25]

The prevalence of atopy and respiratory allergies has been found to be inversely related to the level of exposure to orofaecal or foodborne pathogens such as Toxoplasma gondii, hepatitis A virus and Helicobacter pylori.[26] The same relationship was not seen with viruses transmitted through other routes, that is, mumps, rubella, chickenpox, herpes simplex virus type 1 or cytomegalovirus. These results suggest that orofaecal and foodborne microbes may be better than airborne respiratory viruses for providing a 'protective' effect against atopy. Hence hygiene and a westernised, semi-sterile diet may be facilitating atopy by influencing the overall pattern of gut commensals and pathogens that stimulate the gut associated lymphoid tissue.

> Studies examining the relationship between vaccinations and the development of atopic disorders have shown inconsistent results

A strong Th-1 response in the form of delayed-type hypersensitivity to Mycobacterium tuberculosis has been associated with relative protection against the development of atopy and allergic symptoms. A study of 867 Japanese schoolchildren found that 36% manifested atopic symptoms at some time.[27] A strong inverse association was found between positive tuberculin responses at both six and 12 years of age and atopic symptoms and IgE levels. In positive tuberculin responders the rate of current atopic symptoms was one-third the rate in negative responders. Asthma was one-half to one-third as likely in positive responders as in negative responders. Moreover, remission of atopic symptoms between seven and 12 years of age was six to nine times as likely in positive tuberculin responders. These data are consistent with the hypothesis that atopic responses are limited by Th-1 immune mechanisms. Further research is being carried out to assess the effect of M. tuberculosis immunisation in deviating immunity away from atopy.

The probable protective effect of certain infectious agents against asthma and atopy is also supported by the clinical observation of asthma and atopy remissions during infectious illnesses with viral hepatitis, measles, chickenpox and herpes zoster.[28-30]

Infant immunisation

There has been concern raised that immunisation may be contributing to the development of allergic disease, whether through reducing clinical infections in infancy[31] or by direct IgE-inducing effects of the vaccines.[32] Studies examining the relationship between vaccinations and the development of atopic disorders have shown inconsistent results.

Pertussis vaccination has been reported in two separate practices to be associated with an increased risk of diagnosed asthma or atopy.[33,34] In one report[34] the vaccination was associated with a 75% relative increase in the risk of atopic disorders.

Data from the Christchurch Health and Development study, which comprises 1 265 children born in 1977, suggest a similar effect.[35] The 23 children who received no diptheria/pertussis/tetanus (DPT) or polio immunisation had no recorded asthma episodes or consultations for asthma or allergy before the age of 10 years. In the immunised children, 23% had asthma episodes and 30% had consultations for other allergic illnesses. An important limitation is this study is the very small non-vaccinated group. It is also possible that non-atopic families were choosing not to vaccinate.

Several large studies have not confirmed these findings however. Butler and Goldberg,[24] in a study of over 13 000 children from the 1970 British birth cohort, found no association

between pertussis vaccination and wheeze at five years, but a lower risk of eczema. The later British cohort study of nearly 9 500 children born in the early 1990s[36] and a Swedish study of 9 829 children[37] have also found no association between this vaccine and asthma. Approximately half of the children from the 1970 British birth cohort study were vaccinated against measles and no substantial difference was seen in the prevalence of hayfever or eczema at age five years between immunised and non-immunised children.[24]

In New Zealand children the lifetime prevalence of asthma was increased fourfold in those children who had received antibiotics in the first year of life

Childhood exposure to a farming environment

A number of reports have suggested a lower prevalence of allergic disease, including asthma, among young people raised on farms.[38-41] These reports have raised the possibility that animal exposure and/or zoonotic infections may offer important protection against allergic sensitisation.

A study of 1 199 Quebec students showed that those raised on a farm had less asthma (odds ratio [OR] 0.59; 95% CI 0.37-0.95) and atopy (OR 0.58; 95% CI 0.46-0.75), as well as less wheeze and airway hyperreactivity.[41] This difference was most pronounced in girls and remained even after controlling for the number of siblings and current smoking.

A Finnish study of 10 667 University students confirmed a similar pattern.[11] A childhood farm environment independently reduced the risk for allergic rhinitis and/or allergic conjunctivitis (OR 0.63; 95% CI 0.5-0.79), as well as diagnosed asthma and episodic wheezing (OR 0.71; 95% CI 0.54-0.93), independent of family size. There was little to suggest that eczema is less common in farmers' children.

Children raised in farming environments might be exposed to larger quantities of allergens, toxins and irritants than their urban peers. Environmental exposure to immune modulating agents such a environmental mycobacteria and actinomycetes, favouring manifestation of a non-atopic phenotype, could explain the lower prevalence of asthma and allergic disorders in this population. There is no evidence of selection bias from atopic individuals moving from rural environments in these studies to account for the differences in allergic diseases.

Childhood exposure to pets

A major difference between rural and urban children is their exposure to livestock. For many years exposure to animals, especially 'furry' ones, was felt to be a risk factor for allergy. In fact, a protective effect has been found in relation to childhood exposure to dogs[11] and pigs[23]. Results from the European Community Respiratory Health Survey involving over 13 900 subjects, found that a dog within the home in childhood was negatively associated with adult atopy (OR 0.85; 95% CI 0.78-0.92).[11] This effect remained after adjustment for parental and sibling allergy and adult pet ownership.

A recent study of 226 school children in the USA[42] confirmed that high exposure to cat allergen was associated with decreased sensitisation. The mechanism appears to be by induction of IgG antibody to the cat allergen Fel d1. If sensitised to cat allergen however there was a significant risk of asthma in the children at all levels of exposure. The proportion of atopic children was similar in all exposure groups, arguing against the possibility that allergic families had chosen not to keep cats.

Intestinal flora and antibiotics

Studies comparing infants in Sweden and Estonia[43,44] have shown marked differences in the types of faecal bacteria found in the infants, broadly matching the differences seen between atopic and non-atopic infants in each country. Lactobacilli are present in larger numbers in the faeces of Estonian and non-atopic infants. This raises the possibility that differences in intestinal bacterial colonisation in early childhood may contribute to both the international variations and the individual risk of allergy within countries.

In New Zealand children the lifetime prevalence of asthma was in-

Large rural families are less common now than 50 years ago. Is this related to the rising prevalence of asthma?

creased fourfold in those children who had received antibiotics in the first year of life, with a dose-response relationship shown to the number of courses.[45] A retrospective review of records in a UK general practice found a doubling of the risk of hayfever and eczema among children who had received any antibiotics by the age of two years, independent of the clinical indication for the antibiotic. Cephalosporins and macrolides were associated with a greater risk than penicillins.[34] These observations may be linked to the effects of early antibiotic treatment on the bacterial colonisation of the child's gut, with antibiotics possibly resulting in a loss of the 'protective' pattern of bacterial colonisation.

Contrary to earlier opinions, both exposure to animals and early day-care have been found to protect against the development of asthma and allergy.

Conclusions

The *hygiene hypothesis*, which postulates that early childhood infection protects against atopy, is considered immunologically plausible and has been supported by a number of epidemiological observations. Family size, birth order and early childhood day-care are unlikely to be the direct determinants of allergy prevalence. Rather they are likely to be indirect measures of some other biologically relevant factor, which increases with family size and early infection, that confers protection against allergic sensitisation. The role of immunisation in altering the prevalence of allergic disease remains unresolved. So while the *hygiene hypothesis* may not be able to provide all the answers to explain the observed 'allergic' epidemic, it provides us with a new perspective on mechanisms of asthma and allergic diseases, as well as potential treatments.

References

1. Strachan DP. Hayfever, hygiene and household size. Br Med J 1989; 1989:1259–60.
2. Strachan DP. Is allergic disease programmed in early life? Clin Exp Allergy 1994; 24:603–605.
3. Busse WW. The relationship between viral infections and onset of allergic diseases and asthma. Clin Exp Allergy 1989; 19:1–9.
4. Romagnani S. Human TH1 and TH2 subsets: regulation of differentiation and role in protection and immunopathology. Int Arch Allergy Immunol 1992; 98:279–285.
5. Broide DH. Molecular and cellular mechanisms of allergic disease. J Allergy Clin Immunol 2001; 108:S65–71.
6. Prescott SL, Macaubas C, Holt BJ, Smallacombe TB, et al. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. J Immunol 1998; 60:4730–4737.
7. Holt PG. A potential vaccine strategy for asthma and allied atopic diseases during early childhood. Lancet 1994; 344:456–458.
8. Department of Statistics, Wellington, New Zealand.
9. Von Mutius E. The influence of birth order on the expression of atopy in families: a gene-environment interaction? (Editorial) Clin Exp Allergy 1998; 28:1454–1456.
10. Strachan DP, Harkins LS, Golding J, ALSPAC Study Team. Sibship size and self-reported inhalant allergy among adult women. Clin Exp Allergy 1997; 27:151–155.
11. Svanes C, Jarvis D, Chinn S, Burney P. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. J Allergy Clin Immunol 1999; 103:415–420.
12. Ball TM, Castro-Rodriguez JA, Griffith KA, et al. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. N Engl J Med 2000; 343:538–543.
13. Wickens KL, Crane J, Kemp TJ, et al. Family size, infections, and asthma prevalence in New Zealand children. Epidemiology 1999; 10:699–705
14. Wissow LS, Gittleson AM, Szklo M, et al. Poverty, race and hospitalisation for childhood asthma. Am J Public Health 1988; 78:777–782.
15. Von Mutius E, Martinez FD, Fritzsche C, et al. Prevalence of asthma and atopy in two areas of West and East Germany. Am J Resp Crit Care Med 1994; 149:358–364.
16. Silverman M. Out of the mouths of babes and sucklings: lessons from early childhood asthma. Thorax 1993; 48:1200–1204.
17. Marbury MC, Maldonado G, Waller L. Lower respiratory illness, recurrent wheezing, and day-care attendance. Am J Respir Crit Care Med 1997; 155:156–161.
18. Nafstad P, Hagen JA. Oie L, Magnus P, Jaakkola JJK. Day care centers and respiratory health. Pediatrics 1999; 103:753–758.
19. Kramer U, Heinrich J, Wjst M, Wichmann H-E. Age of entry to day nursery and allergy in later childhood. Lancet 1999; 353:450–454.
20. Wright AL, Taussig LM, Ray CG, et al. The Tucson Children's Respiratory Study: II. Lower respiratory tract illness in the first year of life. Am J Epidemiol 129; 1232–1246.
21. Sigurs N, Bjarnason R, Sigurbergsson F, et al. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. Pediatrics 1995; 95:500–505.
22. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 year. Lancet 1999; 354:541–545.
23. Shaheen SO, Aaby P, Hall AJ, et al. Measles and atopy in Guinea-Bissau. Lancet 1996; 347:1792–1796.

24. Golding J, Peters T. Eczema and hay fever. In: Butler N and Golding J, eds. From birth to five. A study of the health and behaviour of Britain's five-year-olds. Oxford: Pergamon Press, 1986:171–186.
25. Paunio M, Heinonen OP, Virtanen M, et al. Measles history and atopic disorders: a population-based cross-sectional study. JAMA 2000; 283:343–346.
26. Matricardi PM, Rosmini, Riondino S, et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. BMJ 2000; 320:412–417.
27. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. Science 1997; 275:77–79.
28. Serafini U. Long-term asthma remission. Eur J Intern Med 1996; 7:5–12.
29. Gorin N. Temporary relief of asthma by jaundice JAMA 1949;141:24.
30. Kondo N, Fukutomi O, Ozawa T, et al. Improvement of food-sensitive atopic-dermatitis accompanied by reduced lymphocyte responses to food antigen following natural measles virus infection. Clin Exp Allergy 1993; 23:44–50.
31. Shaheen SO. Changing patterns of childhood infection and the rise in allergic disease. Clin Exp Allergy 1995; 25:1034–1037.
32. Pauwels R, Van Der Straeten M, Platteau B, Bazin H. In vivo effects of Bordetella pertussis vaccine on IgE synthesis. Allergy 1983; 38:239–246.
33. Odent MR, Culpin EE, Kimmel T. Pertussis vaccination and asthma: is there a link? JAMA 1994; 272:592–593.
34. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. Thorax 1998; 53:927–932.
35. Kemp T, Pearce N, Fitzharris P, Crane J, et al. Is infant immunisation a risk factor for childhood asthma or allergy? Epidemiology 1997; 8:678–680.
36. Henderson J, North K, Griffiths M, et al. Pertussis vaccination and wheezing illness in young children; prospective cohort study. BMJ 1999; 318:1173–1176.
37. Nilsson L, Kjellman NI, Bjorksten B. A randomised controlled trial of the effect of pertussis vaccines on atopic disease. Arch Pediatr Adolescent Med 1998; 152:734–738.
38. Braun-Fahrlander CM, Gassner M, Grize L, Neu, U, et al. Prevalance of hayfever and allergic sensitisation in farmer's children and their peers living in the same rural community. Clin Exp Allergy 1999; 52:936–937.
39. Aberg N. Asthma and allergic rhinitis in Swedish conscripts. Clin Exp Allergy 1989; 19:59–63.
40. Ernst P, Cormier Y. Relative scarcity of asthma and atopy among rural adolescents raised on a farm. Am J Respir Crit Care Med 2000;161:1563–1566.
41. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Farm environment in childhood prevents the development of allergies. Clin Exp Allergy 2000; 30:201–208.
42. Platts-Mills T, Vaughan J, Squillace S, et al. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. Lancet 2001; 357:752–756.
43. Sepp E, Judge K, Vasar M, et al. Intestinal microflora of Estonian and Swedish infants. Acta Paediatr 1997; 86:956–961.
44. Bjorksten B, Naaber P, Sepp E, et al. The intestinal microflora in allergic Estonia and Swedish two-year-old children. Clin Exp Allergy 1999; 29:342–346.
45. Wickens K, Pearce N, Crane J, et al. Antibiotic use in early childhood and the development of asthma. Clin Exp Allergy 1999; 29:766–771.