

EDITORIAL

Allergy and family size: a riddle worth solving

George Bernard Shaw urged his readers to choose their parents wisely. When it comes to allergy, it appears prudent also to choose the number, and perhaps the age, of one's siblings. Children from large families are at reduced risk of developing hay fever [1–3], eczema [1,2], and allergic sensitization to common aeroallergens [3–5]. This observation, first published 10 yr ago [1] was subsequently elaborated into an aetiological hypothesis [2] which attributed the emergence of allergic disease as a 'post-industrial revolution epidemic' [6] to the decline in cross-infection within young families.

This 'hygiene' hypothesis [2] challenged the immunological opinion prevailing at the time, which proposed that early infection might promote, rather than protect against, allergic sensitization [7]. However, more recent advances in our understanding of T-lymphocyte differentiation [8,9] have suggested a possible mechanism for such a protective effect. The 'natural' immune response to infections occurring in early life, perhaps specifically at the time of first exposure to the relevant allergen, may inhibit the proliferation of Th2-cell clones, and thereby prevent allergy [10]. An alternative hypothesis is that a stable state of Th1-type or Th2-type predominance is not reached for some 5–7 yr after birth [11], and may be influenced by the cytokine environment prevailing at each of multiple exposures to a specific allergen [9]. Despite these immunological advances, epidemiological evidence directly relating early infection to the subsequent development of allergy is sparse and far from convincing [3,12–14].

The relationship of family size to allergy thus remains unexplained, but is it a riddle worth solving? Before addressing this question, it is timely to review the evidence in more detail, considering not only the size but also the structure of the household in childhood.

An inverse association between manifestations of allergy and sibship size has been consistently found from an early age [1,2] through childhood [4] and adolescence [3]. In this issue of the journal, Jarvis *et al.* [15] provide further evidence, this time in adults. Two other recent studies of adults corroborate these findings [5,16]. Four studies [3–5,15] have reported inverse correlations between objective measures of allergic sensitization and sibship size, arguing strongly against a spurious relationship attributable to differential recognition, reporting or diagnosis of allergic symptoms in smaller and larger families.

Jarvis *et al.* [15] report that some symptoms of asthma were inversely related to family size. The incidence and prevalence of all forms of wheezing illnesses throughout

childhood varies little with birth order or family size [17,18]. A possible explanation for this discrepancy is that an inverse correlation between sibship size and the prevalence of allergic asthma is counterbalanced, particularly in younger age groups, by the tendency of children from larger families to experience viral infections triggering wheeze by non-allergic mechanisms [7].

The structure as well as the size of the family may be influential. After adjustment for family size, position within the sibship [1–3,5], birth spacing [3], sibling gender [16] and maternal age [3,19] have been related to hay fever or allergic sensitization. These associations are less consistent than for total sibship size and require further confirmation. Nevertheless, they may offer useful clues to a solution of the conundrum.

Jarvis *et al.* [15] found slightly stronger associations of hay fever and specific IgE with sibship size than with birth order, suggesting that family size is of greater importance than position within the household. However, large sample sizes are required to distinguish with confidence the effects of older and younger siblings, and two studies of over 10 000 subjects [2,3] are consistent in finding a significantly steeper decline in prevalence of hay fever with the number of older brothers and sisters than with the number of younger siblings. This is confirmed by skin prick tests to common aeroallergens at age 35 in one study [5]. In contrast, another large study of self-reported allergy among adult women [16] found no independent effect of birth order, after adjustment for maternal age and total sibship size. The intriguing finding in the latter study was that the number of brothers was much more influential than the number of sisters. Whether this reflects a protective effect of brotherly love, or exposure to siblings of the opposite sex, remains to be resolved.

Taken individually, these effects of family size and structure are subtle and are detected at a high level of statistical significance only in large datasets. Nevertheless, they are of considerable epidemiological and scientific importance, for two reasons.

Firstly, they are unlikely to arise from genetic variation. In theory, the inverse association between allergy and family size could reflect a genetic link between fertility and atopy, but such a link could not explain the associations with birth order within families of similar size. If parents deliberately limited their family size as a result of bearing a child with allergic disease, it would tend to be the last born, rather than the first born, who would experience the highest prevalence. Thus, although genetic factors are undoubtedly important in determining the risk of allergy, we have a

strong indication that there are environmental exposures which vary sufficiently within modern families to generate measurable differences in risk of atopic sensitization and allergic disease.

Secondly, it is almost certain that family size and structure are imprecise surrogate measures for some more influential exposure. If so, the effect of this unknown factor must be substantial. Consider a hypothetical protective agent to which 10% of single child families are exposed, the prevalence of exposure increasing by 10% with each additional child in the family to 50% among families with five children. If exposure to this factor reduced the risk of allergy by a factor of 10 (relative risk 0.1) then the prevalence of allergy would be reduced by about 10% in relative terms for each additional child in the family (relative risk 0.9 per sibling). This is typical of the gradient observed in large epidemiological studies [2,3,15,16]. A similar relationship between sibship size and allergy could be generated by a protective factor with relative risk 0.2 and prevalence ranging in a graded fashion from 30% in single child families to 70% in families with five children.

Such hypothetical calculations become even more remarkable when we consider that the penetrance of genotype to phenotype is likely to be 'elastic' in only a portion of the population. Many, perhaps the majority, will not carry the necessary genes, and there may be a small proportion whose genetic predisposition is so strong that it will be expressed in almost all environmental circumstances. Studies of the association of allergic manifestations with sibship size and structure in families known to be at higher than average risk, for example due to parental history of allergy, have yet to be conducted, but they may demonstrate steeper risk gradients with increasing numbers of siblings than surveys of the general population.

The influence of family size is potentially the most important clue to the causes and prevention of allergic disease which has emerged from epidemiological studies over the last decade. It remains a riddle with several lines, many of them barely legible and few, at least at present, ending in rhyme. Nevertheless, the phenomenon to be explained seems to be real and the solution to the riddle is certainly well worth seeking. Although a protective effect of infection is attractive as a unifying explanation for many of the epidemiological features of allergic sensitization [19], other exposures which vary with family size and structure also deserve further investigation.

References

- 1 Golding J, Peters T. Eczema and hay fever. In: Butler N, Golding J, eds. *From birth to five. A study of the health and behaviour of Britain's five-year-olds*. Oxford: Pergamon Press, 1986: 171–86.
- 2 Strachan DP. Hay fever, hygiene and household size. *Br Med J* 1989; 299:1259–60.
- 3 Strachan DP, Taylor EM, Carpenter RG. Family size, neonatal infection and hay fever in adolescence. *Arch Dis Child* 1996; 74:422–6.
- 4 von Mutius E, Martinez FD, Fritzsch C et al. Skin test reactivity and number of siblings. *Br Med J* 1994; 308:692–5.
- 5 Strachan DP, Harkins LS, Johnston IDA, Anderson HR. Childhood antecedents of allergic sensitisation in young British adults. *J Allergy Clin Immunol* 1997; 99:6–12.
- 6 Emmanuel MB. Hay fever, a post industrial revolution epidemic: a history of its growth during the 19th century. *Clin Allergy* 1988; 18:295–304.
- 7 Busse WW. The relationship between viral infections and onset of allergic diseases and asthma. *Clin Exp Allergy* 1989; 19:1–9.
- 8 Romagnani S. Human TH1 and TH2 subsets: regulation of differentiation and role in protection and immunopathology. *Int Arch Allergy Immunol* 1992; 98:279–85.
- 9 Holt PG. A potential vaccine strategy for asthma and allied atopic diseases during early childhood. *Lancet* 1994; 344:456–8.
- 10 Martinez FD. Role of viral infections in the inception of asthma and allergies during childhood: could they be protective? *Thorax* 1994; 49:1189–91.
- 11 Hattevig G, Kjellman B, Björkstén B. Appearance of IgE antibodies to ingested and inhaled allergens during the first 12 years of life in atopic and non-atopic children. *Pediatr Allergy Immunol* 1993; 4:182–6.
- 12 Backman A, Björkstén F, Ilmonen S, Juntunen K, Suoniemi I. Do infections in infancy affect sensitization to airborne allergens and development of allergic disease? *Allergy* 1984; 39:309–15.
- 13 Shaheen SO. Changing patterns of childhood infection and the rise in allergic disease. *Clin Exp Allergy* 1995; 25:1034–7.
- 14 Shaheen SO, Aaby P, Hall AJ et al. Measles and atopy in Guinea-Bissau. *Lancet* 1996; 347:1792–6.
- 15 Jarvis D, Chinn S, Luczynska C, Burney P. The association of family size with atopy and atopic disease. *Clin Exp Allergy* 1997; 27:240–5.
- 16 Strachan DP, Harkins LS, Golding J, ALSPAC Study Team. Sibship size and self-reported inhalant allergy among adult women. *Clin Exp Allergy* 1997; 27:151–5.
- 17 Strachan DP, Butland BK, Anderson HR. The incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *Br Med J* 1996; 312:1195–9.
- 18 Lewis S, Butland B, Strachan D, Bynner J, Britton J. Study of the aetiology of wheezing illness at age 16 in two national British birth cohorts. *Thorax* 1996; 51:670–6.
- 19 Strachan DP. Epidemiology of hay fever: towards a community diagnosis. *Clin Exp Allergy* 1995; 25:296–303.

DAVID P. STRACHAN
Department of Public Health Sciences
St George's Hospital Medical School
Cranmer Terrace
London SW17 0RE
 UK