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Environmental allergen exposure, sensitisation and asthma

Environmental allergen exposure, sensitisation and asthma: from whole populations to individuals at risk

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To prevent asthma and allergies we need to design interventions appropriate for individual susceptibilities, taking account of both genes and the environment

Sensitisation to inhalant allergens remains a major risk factor for asthma,[1] but the size of the effect is hotly debated.[2 3] Several cross sectional studies have suggested a simple dose-response relationship between dust mite allergen exposure and specific sensitisation, both within communities[4–7] and between communities exposed to differing levels of mite allergens.[8] The threshold concentration of 2 μg Group 1 mite allergen per gram of dust for developing mite sensitisation in children at high risk has been suggested, but a much higher cut off level of 80 μg/g appeared significant in low risk children.[4] For other allergens the relationship between exposure and sensitisation is less well defined. Several studies in the US inner city areas reported that children are more likely to become sensitised to cockroach with increasing cockroach allergen exposure,[9] and that high exposure to mouse allergen appears to be associated with an increased prevalence of sensitisation to mouse.[10] Some studies in older children and adults reported a close relationship between specific allergen sensitisation and current domestic exposure for mite and cockroach, but not cat allergen.[5 11] This, together with studies reporting a protective effect of high cat allergen exposure on sensitisation,[12 13] raises the question of whether the dose-response relationship between exposure and sensitisation may be different for different allergens. However, there are remarkably few published data on the longitudinal relationship between allergen exposure and the development of specific sensitisation.

EVIDENCE FROM LONGITUDINAL STUDIES

Several observational birth cohort studies investigating risk factors for the development of allergen sensitisation and asthma have measured allergen levels in dust samples collected in early life to examine the association between allergen exposure and the development of specific sensitisation. The studies were based in Germany,[14] Sweden,[15] Holland,[16] and the UK (Manchester[17] and Ashford cohorts[18]). While this is the optimal study design for conditions which manifest early in life and progress into adulthood, these studies are difficult and expensive to run and it takes many years to obtain meaningful results.

Following several reports by the German Multicenter Allergy Study (MAS-90),[19 20] in this issue of *Thorax* Cullinan *et al* become only the second birth cohort to report the exposure-outcomes relationship presenting their results for sensitisation and atopic wheeze at age 5 years in 552 children.[18] This cohort from Ashford, UK is truly population based; the investigators approached every woman presenting for antenatal care to three general practices in the area. By skin prick testing the children at the age of 5 years to three common allergens (mite, cat and pollen) they identified a rate of allergic sensitisation of 17%, a figure similar to the 19.6% reported in the Isle of Wight cohort at age 4 years.[21] A total of 7% of the children had atopic wheeze. Mite and cat allergen levels were measured in the living room floor at one time point (8 weeks after birth) and the levels were similar to other contemporaneous data from the UK. For the whole population there was no linear dose-response relationship between mite and cat allergen levels and the respective specific sensitisations. For mite, there was an increase in the proportion of sensitised children on moving from the 1st to the 2nd quintile of exposure, after which rates of sensitisation appeared to tail off. For cat, sensitisation increased steadily from the 2nd to the 4th quintile and then tailed off. While this pattern was not significantly altered when children with paternal atopy were considered separately, there was a significant interaction between paternal atopy and mite exposure with a considerably higher proportion of high risk children being sensitised at any given quintile of exposure (except for the lowest).

These results are markedly different from those in the MAS-90 study.[19 20] The population sample in the German study was larger (939 at age 7 years) and differs from the Ashford cohort as it is enriched with high risk children. Rates of sensitisation were compared between children in the lowest and highest quartiles of mite allergen exposure. At the age of 7 those in the highest quartile were significantly more likely to be sensitised than those in the lowest quartile (~14% *v* ~4%). A similar effect was seen for cat allergen exposure and sensitisation to cat.

How do we assimilate these two apparently different sets of results? It is likely that the relationship between exposure and sensitisation differs markedly between children at high risk and those at low risk of allergic sensitisation. The MAS-90 study was weighted with high risk children and the strongest dose-response relationship was seen in this group.[19] On the other hand, the study by Cullinan *et al* is more representative of the general population with allergen exposure likely to be of little relevance for the majority of subjects. In a population of this composition and size with a modest (by Australian

standards) range of mite allergen levels, the dose-response relationship is likely to appear flat. Thus, a dose-response relationship between mite allergen exposure and sensitisation is easier to demonstrate in larger populations weighted with high risk children.

How about the relationship between allergen exposure and asthma development? The Poole cohort described by Sporik *et al*[22] is the only longitudinal study to date to report a significant relationship between early life exposure to dust mite allergen and asthma at the age of 11 years in a small group of 69 high risk children. Most other studies were unable to reproduce these results. Burr *et al*[23] reported no relationship between physician diagnosed asthma or wheezing at age 7 years and dust mite allergen levels in the first or seventh year of life in a prospective study of 453 children. Similarly, in the MAS-90 study, despite a strong association between sensitisation to mite and cat allergens and wheezing and the significant relationship between mite and cat allergen exposure and specific sensitisation, there was no consistent dose-response relationship between allergen exposure and doctor diagnosed asthma, wheezing within the last 12 months, or wheezing ever.[20]

LESSONS FROM INTERVENTION STUDIES

Intervention studies focusing on high risk children that use environmental control aimed at reducing allergen exposure from or before birth may help to explain the relationship between allergen exposure and clinical outcomes. Six ongoing studies have published results to date.

Isle of Wight Study

This study implemented an intervention designed to reduce exposure to inhalant and food allergens as part of a primary prevention programme. At the age of 1 year there was a reduction in sensitisation and in wheeze in the intervention group,[24] but the differences in respiratory symptoms disappeared by age 2 and 4 years.[25 26] At the age of 8 sensitisation to mite in the intervention group was reduced by more than 50%.[27] Furthermore, children in the active group were significantly less likely to have current wheeze, nocturnal cough, and wheeze with bronchial hyperresponsiveness.

Canadian Asthma Primary Prevention Study (CAPPS)

A multifaceted intervention including measures to reduce exposure to inhalant and food allergens was used.[28] At the age of 1 year there was a significant reduction in probable asthma and rhinitis in the active group.[29] At the age of 2 years significantly fewer children had asthma in the intervention group than in the control group (16.3% *v* 23%) but there was no difference in sensitisation.[30]

Study on the Prevention of Allergy in Children in Europe (SPACE)

In this study the multifaceted intervention was directed towards both inhalant and food allergens. Results reported at the age of 1 year showed a reduction in mite sensitisation but no difference in the proportion of children who had wheezed (21% both groups).[31]

Childhood Asthma Prevention Study (CAPS)

The Childhood Asthma Prevention Study in Sydney, Australia reported no effect of mite allergen avoidance on sensitisation rates at the age of 18 months.[32] However, by 3 years of age mite sensitisation was significantly reduced in the active mite allergen avoidance group.[33] Respiratory symptoms were not affected by mite allergen avoidance but there appeared to be more eczema in this group.

Prevention and Incidence of Asthma and Mite Allergy Study (PIAMA)

The Prevention and Incidence of Asthma and Mite Allergy Study in the Netherlands achieved significantly lower mite allergen levels in the active group than in the control group 1 year after the introduction of intervention measures, but the baseline exposure was very low.[34] Children in the active group appeared less likely to have had recurrent wheeze during the first year of life, but the only significant difference between groups was a reduction in night time cough without a cold in the active group at age 2 years.[35] There was no difference in sensitisation between the groups.

Manchester Asthma and Allergy Study (MAAS)

This study used a much more stringent environmental control regime than other primary prevention studies.[36] A significant and sustained reduction in allergen exposure was achieved in the active group.[36 37] At 1 year of age there was slightly more sensitisation in the active group (17% *v* 14%) but this did not reach statistical significance.[38] Asthma-like symptoms were consistently lower in the intervention group, and this reached significance for attacks of severe wheeze with shortness of breath, prescribed medication for wheezy attacks, and wheeze after playing or exertion. However, counter-intuitive results were reported at the follow up at 3 years of age, suggesting that stringent environmental control was associated with *increased* risk of sensitisation to dust mite but *better* lung function.[39]

How did the children become sensitised to mite allergens if they had low exposure at home? Even with a complex intervention there remains a residual mite allergen exposure within the home. Additional exposure in the homes of relatives or outside the home may lead to intermittent exposure, which may favour sensitisation in comparison with continuous exposure.[39]

CONCLUSIONS

Clinical outcomes reported from different observational and intervention studies appear inconsistent and often confusing. What are the implications of the study by Cullinan *et al* for the design of primary prevention strategies? These results emphasise the point that any single primary prevention strategy will not be applicable to the whole population, but only to individuals within the population with a particular susceptibility. This raises the important question of how one determines susceptibility. To date most investigators have used parental history of allergic disease and allergen sensitisation to assign risk. There is an ongoing debate about the relative role of maternal and paternal disease, with most studies (but, interestingly, not the Ashford cohort[18]) finding an increased influence of maternal disease. However, assigning risk based on parental history of allergy is insufficiently precise and unsatisfactory, and we have to find more specific markers. Many research groups are trying to identify genetic polymorphisms which confer an increase in risk for allergen sensitisation and for asthma with limited success. This is partly due to the difficulties in phenotype definition and the fact that genetics research has rarely taken account of the relevant environmental exposures. A particular genetic polymorphism may only be associated with an increase (or decrease) in risk in those exposed to a specific environmental factor. In order to understand risk factors for asthma and allergies, one needs to study the interaction between the inherited risk and the environment by measuring both. Future primary prevention studies aimed at prevention of asthma and allergies will be informed by studies of gene–environment interactions. We need to move away from the concept of blanket advice aimed at the whole population to tailor made individualised measures targeting individuals with specific susceptibilities who will benefit from a particular intervention.

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Lung Alerts: Call for Contributors

Lung Alerts were introduced in *Thorax* in January 2003. We aim to increase the educational content of the journal by providing rapid, concise (approximately 250 words) summaries of papers published in general medical or non-respiratory specialist journals that are of interest to the readership of *Thorax*. Articles are selected by the Editors and commissioned from a database of contributors. To remain topical, completed submissions must be returned to us quickly, usually within seven working days.

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