

The National Asthma Campaign Manchester Asthma and Allergy Study

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The ^{NAC}Manchester Asthma and Allergy Study is a prospective study of the development of asthma and allergies in childhood. The subjects (995 children at age 3 years) were recruited *in utero* by screening parents in the antenatal clinic using skin prick testing and a questionnaire regarding allergic diseases. Children were assigned to risk groups according to parental atopic status (high risk, both parents atopic; medium risk, one parent atopic; low risk, neither parent atopic). A subgroup of those at high risk (with no pets in the home) was randomized to stringent environmental control (allergen impermeable covers for the parental and infant bed, hot washing of bedding weekly, HEPA vacuum cleaner, hard floor for the nursery), and the remainder followed a normal regime. The children have been followed prospectively. The environmental influences are very clearly defined. Measurements of environmental exposures include levels of house dust mite; cat and dog allergens during pregnancy and early life; pet ownership and exposure; childcare arrangements; number of siblings; vaccination uptake; thorough dietary questionnaire; and endotoxin exposure. Further unique *objective* outcome in the cohort is the assessment of lung function in preschool children using specific airways resistance, which at age 3 years clearly reflects both genetic and environmental influences.

**Adnan Custovic,
Bridget M. Simpson,
Clare S. Murray,
Lesley Lowe and
Ashley Woodcock, on behalf of the
NAC Manchester Asthma and Allergy
Study Group**

North West Lung Centre, Wythenshawe Hospital,
Manchester, UK

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Adnan Custovic, MD, PhD, North West Lung Centre,
Wythenshawe Hospital, Manchester M23 9LT, UK
Tel.: +44 161 291 2398
Fax: +44 161 291 5020
E-mail: acustovic@fs1.with.man.ac.uk

Asthma and other allergic disorders are the most common chronic diseases in childhood and a major health burden on primary care services. Wheeze is one of the commonest causes of emergency hospital admissions and one of the most frequent medical reasons for time off school and work. Asthma is considered incurable and may persist through the lifetime of many patients. Furthermore, exacerbations need treatment with oral steroids, with potential long-term morbidity.

Asthma consumes a large share of economic resources. It is estimated that asthma costs between 1% and 2% of the total healthcare budgets in direct costs in terms of provision of medical care, and there are equally large indirect costs incurred by time lost from work and reduced productivity. The National Asthma Campaign estimates that the total cost of asthma to the UK is now in excess of £2,000 million per year

(based on figures for 1995/96), with the cost to the NHS being £672 million. Potential savings from a reduction in childhood asthma and other allergic disorders are enormous. A successful, simple and widely applicable intervention towards primary prevention of allergic disease would have major benefits. Whilst prevention of the disease should be the primary aim of such an intervention, it is also possible that one of the outcomes may be the shift in pattern of the disease from moderate/severe towards mild.

Information about the risk factors for different diseases has been used in public health interventions (e.g. ischaemic heart disease and cholesterol). As direct evidence is lacking of the primary risk factors that have led to the increase in asthma prevalence, the only way forward is to test the hypothesis of changing the exposure to risk factors for which there is a good evidence of their

association with asthma (1). In addition, they have to be appropriate for use in a public health intervention. Therefore, although genetic factors may be very important in the development of asthma, it is highly unlikely that in the foreseeable future this knowledge will be used to manipulate the genetic make-up in order to prevent asthma and other allergic diseases. Similarly, although gender and ethnicity may identify individuals at risk, this cannot be used in terms of primary prevention. One of the aspects of the National Asthma Campaign Manchester Asthma and Allergy Study (^{NAC}MAAS) is to investigate whether a very stringent environmental control can prevent sensitization and allergic disease in children at high risk of atopy.

The National Asthma Campaign Manchester Asthma and Allergy Study

We have identified a cohort of infants, which will provide comprehensive data on the interaction between genes and environment in the development of allergic disorders. This is a prospective study, following-up more than 1,000 children.

Screening and recruitment

All parents were screened at 'Booking' antenatal visits (during the first 8–10 weeks of pregnancy) by using skin-prick testing and a structured questionnaire. Recruitment started on 1 October 1995 and finished on 1 July 1997. Six hundred and fifty-four antenatal clinics were attended and a total of 3,618 mothers and 2,172 fathers were skin-prick tested. The data on the prevalence of and the risk factors for asthma and other allergic diseases in parents have been described in detail previously (2).

Allocation to risk groups

Children were allocated to the risk groups outlined below, according to parental atopic status.

High-risk infants (both parents atopic, i.e. skin-prick test positive; no pets)

This group was entered into a prospective, prenatally randomized, parallel-group study investigating whether living in a low-allergen environment reduces the risk of primary sensitization and the development of asthma and other atopic diseases. Infants were randomly allotted to house-dust mite-allergen avoidance [high-risk active group (HRA)] or a control group [no intervention: high-risk control group (HRC)].

The following allergen-avoidance measures were implemented.

1 Prenatal (completed by the 16th week of pregnancy):

- parental bed (pillow, mattress and quilt) covered with mite-proof bedding through pregnancy and after delivery;
- parents provided with a high-filtration vacuum cleaner; and
- bed linen subjected to hot washing (55°C cycle) fortnightly.

2 Infant's bedroom:

- at 36 weeks of pregnancy, carpets were removed and replaced by vinyl flooring;
- the new cot mattress was encased in the mite allergen-proof material supplied;
- the new carrycot mattress was encased in the mite allergen-proof material supplied;
- any bed linen was subjected to hot washing (55°C cycle) fortnightly;
- washable soft toy was supplied.

3 Rest of the house:

- acarosan (benzyl benzoate) was applied to carpets/sofas.

The stringent environmental control regimen used in the ^{NAC}MAAS was highly effective in achieving and maintaining a very low allergen environment in homes of children at high risk of allergic disease, which we described in detail previously (3). Briefly, *Dermatophagoides pteronyssinus* (*Der p 1*) levels in parental beds were reduced by 98.5% in the active group (519 ng to 8 ng), with no change in the controls. In addition, there was a highly significant reduction in *Der p 1* in carpets in the active compared with the control group. Mite-allergen levels in the infants' rooms in the active group were extremely low (total recovered *Der p 1* from infants mattresses was 7 ng, and from the nursery floor 2 ng). Furthermore, in order to estimate the possible sources of exposure outside homes, we determined that mite-allergen levels are very low outside the domestic environment in the area (day-care centres, schools, etc.).

Once all the measures were in place, there was very little additional effort required from the families in maintaining a low-allergen environment. The practical acceptance of this stringent environmental control was excellent. The participating families in the Active group are encouraged to continue to use these measures long-term (e.g. children's beds are covered in mite-impermeable covers).

'High risk' infants with pets in the home (HRP) (both parents are skin-prick test positive; family history of atopy)

Comparison of the outcomes in this group will enable us to determine the influence of pet

ownership in early life on the expression of atopic phenotype, and to establish the threshold levels for the exposure to airborne *Canf* 1 and *Fel* d 1, which represent the risk for specific sensitization. This puts us in a position to be able to prospectively compare the relative significance of the exposure to either of the three most relevant indoor allergens in the UK, and whether the presence of pets in early life reduces or increases the risk of atopy.

'Low risk' infants' (both parents skin-prick test negative; no family history of atopy)

Comparison of the outcomes in this risk group with those in other groups will enable us to determine the influence of genetic predisposition and environmental exposures in early life on the expression of the atopic phenotype.

'Medium risk' infants (one parent skin-prick test positive; family history of atopy)

This group forms the recruitment basis for the IFWIN study (Inhaled fluticasone in wheezy infants). This is a single-centre, double-blind, placebo-controlled, randomized parallel-group study comparing the effect of fluticasone propionate delivered by a metered-dose inhaler (MDI) spacer (Babyhaler including facemask; 100 µg twice daily) with the effect of placebo.

Children are followed up prospectively and included in the study between the ages of 6 months and 5 years:

- after their second period of physician-verified wheeze; and/or
- after a first wheezy episode if the wheeze is continuous for longer than 4 weeks (provided that it is not caused by bronchiolitis).

Patients are stratified to treatment by:

- 1 exposure to passive smoking;
- 2 exposure to pets;
- 3 maternal asthma; and
- 4 age of onset of wheeze.

Primary outcome measures are asthma prevalence at 6 years of age, and lung function and airway reactivity at 6 years of age.

Follow-up

A total of 1,916 couples met the criteria for inclusion in this study and 1,499 gave informed consent to follow-up for the first 5 years of their child's life. Figure 1 outlines the study population from recruitment to 3 years of age.

Prenatal recruitment

Three hundred and twenty-seven (327) couples were suitable for inclusion in the randomized allergen-avoidance trial (mother atopic to at least one indoor allergen, father atopic, no pets). Of

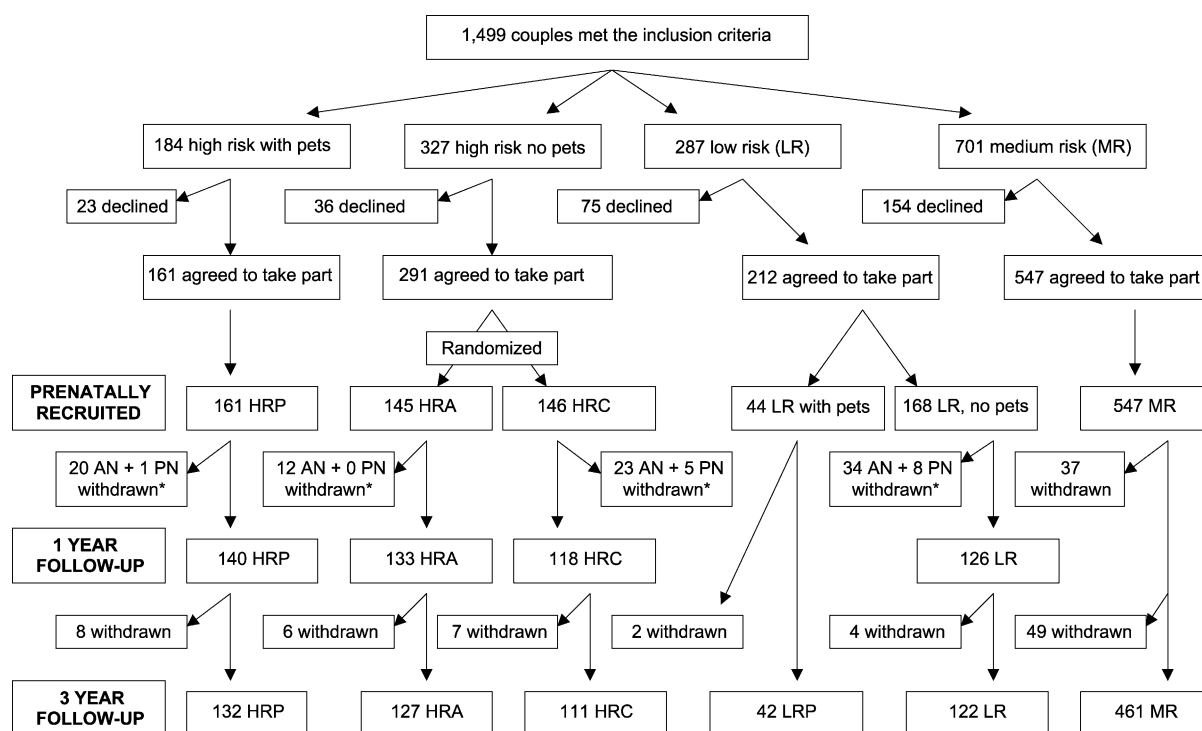


Fig. 1. Schematic representation providing an audit trail from population to sample.

these, 291 (89%) agreed to take part in the study and were randomized (145 HRA, 146 HRC). Four couples declined to be randomized because they found the proposed allergen-avoidance measures too stringent and unacceptable. Four couples had already decided that they would be getting a pet, four were moving out of the area before the delivery of their baby, two felt that they would be unable to give the commitment necessary in terms of time, and the remainder gave no recorded reason for their decision not to take part.

A total of 184 high-risk couples (mother atopic to at least one indoor allergen, father atopic) with pets (cat and/or dog) in the home were identified, of whom 161 (87.5%) consented to take part in the follow-up and were recruited into the HRP group.

Of the 287 low-risk couples (neither parent atopic, no history of allergy) identified, 212 (74%) agreed for their child to take part in the study. Of these, 168 did not keep cats or dog in their home (LR), and 44 were cat and/or dog owners (LRP).

As expected, medium-risk couples (MR; one parent atopic) was the largest group identified, and in total 701 couples who met the entry criteria for this group agreed to be followed up. The outcomes in this study group were not assessed until the children were 3 years of age.

Follow-up at 1 year of age

HRA group

Twelve participating families (8.3%) in the active group were lost to follow-up between the recruitment and the birth of the baby, for the following reasons:

- two miscarriages;
- one intrauterine death;
- one case of a twin pregnancy;
- six discontinued because of the avoidance measures that had to be implemented;
- one moved abroad (to Belgium); and
- one family withdrew without giving a specific reason.

A total of 133 infants were due to be reviewed at 1 year of age, and all attended the clinic (100% follow-up rate).

HRC group

Twenty three families (15.7%) dropped out between the recruitment and the birth of the baby. The following reasons were given for the withdrawal:

- two families moved abroad (one to Belgium before the birth of a child, and one to the USA when the child was 3 months of age);

- one child had an extended stay in the Special Care Baby Unit, and the parents were unwilling to continue with the study;
- two stillbirths;
- one intrauterine death;
- one miscarriage;
- one child was born prematurely, and died at 29 weeks of gestational age;
- 14 gave no specific reason for the withdrawal; and
- one family decided to get a cat.

One hundred and twenty-three infants were due to be reviewed at 1 year of age. Of these, 116 attended the clinic, and in a further two cases the questionnaire was completed over the telephone (95.9% follow-up rate). One family moved abroad (USA) and four did not attend at least three appointments, did not respond to at least three letters, and were subsequently withdrawn.

HRP group

Of the 161 high-risk couples with pets in the home, 20 (12.4%) dropped out between the recruitment and the birth of the baby. The following reasons were stated for the withdrawal:

- one miscarriage;
 - two terminations of pregnancies;
 - one maternal death;
 - one withdrawal as a result of maternal illness;
 - four moved out of the area; and
 - 11 gave no specific reason for the withdrawal.
- Of 141 infants due to be seen at 1 year of age, 140 (99%) attended the follow-up clinic. One mother did not want to attend the 1-year follow-up clinic and was subsequently withdrawn.

LR group

In the low-risk group, 168 couples without pets agreed to take part. Thirty-four (20.3%) withdrew before the birth of a child owing to the following reasons:

- three miscarriages;
- one termination of pregnancy;
- one intrauterine death;
- three premature babies;
- one congenital dislocation of the hip – mother decided not to proceed;
- one severe maternal post-natal depression;
- six moved out of the area; and
- 18 gave no reason.

Of 134 infants due to be seen, six mothers declined to attend a 1-year follow-up clinic. A further two mothers were pregnant again, and unable to

attend, giving a total of 126 sets of data for analysis.

One-year follow-up summary

A total of 517 mothers/fathers completed respiratory questionnaires about their children at 1 year of age (133 HRA, 118 HRC, 140 HRP, and 126 LR). Of these, 501 were evaluated at the 1-year follow-up clinic, 13 were visited at their homes, and in three cases the questionnaire was completed over the telephone.

Follow-up at 3 years of age

Between the follow-up at 1 year of age and 3 years of age, eight children were withdrawn from the HRP group, six from the HRA group, seven from the HRC group, and four from the LR group. The loss to follow-up in the MR group from birth to 3 years of age was 10%.

Summary of follow-up

A total of 1,085 children were born into the study (of 1,211 prenatally recruited). Of these, only a very small proportion was lost to follow-up during first 3 years of life ($n = 92$, i.e. 8.5%) and 995 children were reviewed at 3 years of age (91.7% follow-up rate; Fig. 1).

Effects of environmental control on symptoms

We have recently reported the outcomes in terms of symptoms and sensitization at 1 year of age, showing lower estimates of relative risks for a range of respiratory symptoms during the first year of life for infants in the Active group compared with infants in the Control group (4). At the same time, the findings in the Control group and in the group of children with pets in their homes were similar. The apparent protective effect of environmental control was limited to respiratory symptoms, which at this early age may or may not relate to the subsequent development of allergic asthma.

We emphasize that it would be premature to use these early results as the basis for advice on clinical management, and that further follow-up is essential to determine whether living in a low-allergen environment reduces allergy and asthma in later childhood.

Some other aspects of the ^{NAC}MAAS

Assessment of environmental allergen exposure

Visits have been made to the homes of all participating children, where levels of exposure to dust

mite (*Der p 1*) cat (*Fel d 1*) and dog (*Can f 1*) were determined in dust and air samples.

Lymphoproliferative responses at birth and at 1 year of age

We have recently reported on the relationship between lymphoproliferative responses at birth and 1 year of age with maternal and 1-year infant house-dust mite-allergen exposure (5). There was no relationship between *Der p 1* levels in maternal bed and cord blood mononuclear cell immunoproliferative responses, despite the 21,000-fold range of maternal *Der p 1* exposure. No significant differences in magnitude, or in proportion of positive responses to any stimulant, were observed between the neonates at low, medium or high tertiles of allergen exposure. However, the proportion of positive proliferative responses in infants at 1 year of age significantly increased with increasing exposure of the infant to *Der p 1* at 1 year of age (5). These data support the concept of sensitization to inhalant allergens occurring in early life, but not *in utero*.

Lung function measurement in early life

The diagnosis of airway disease in preschool children has always been based on clinical evaluation, as no objective measurement has been available. Measurement of lung function through childhood would be exceptionally valuable in the study of asthma development. To date, lung function assessment could not be achieved in preschool children using standard lung function tests. Forced expiratory volume in 1 s (*FEV₁*) and peak expiratory flow (*PEF*) measurements require active co-operation from the subject and these tests are not suitable for children younger than 6 years of age. We have used a novel method developed by Professor H. Bisgaard (Copenhagen) for the measurement of specific airway resistance by whole-body plethysmography in young children (3 and 5 years of age) (6,7), and are successfully performing this in all children in our cohort at age 3 years (8). We plan to continue with this measurement and in addition assess non-specific airway reactivity using dry-air challenge, which provides objective outcomes at age 5 and 7 years.

Genetic epidemiology of asthma and allergy

Asthma and allergy are complex diseases whose aetiology clearly has important genetic as well as environmental components. The described cohort makes an ideal framework in which to study the genetic epidemiology of these conditions, and in particular gene-environment interactions

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