

Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial

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Summary

Background Asthma places huge demands on health-care services, and its prevalence is increasing. Reduction of exposure to environmental allergens could offer a realistic chance for primary prevention. Our aim was to ascertain whether or not living in a low-allergen environment reduces the risk of asthma and atopic diseases in infants.

Methods We assigned infants to four risk groups according to parental atopic status. We enrolled 291 high-risk couples (both parents atopic, no pets) into a prospective, prenatally randomised, cohort study, and allocated them to environmental manipulation, in which measures to reduce prenatal and postnatal allergen exposure were undertaken (active HRA) (n=145) or no intervention (control HRC) (n=146). Two further prospective groups were studied: 161 high-risk infants with pets in the home (HRP group) and 168 low-risk infants, whose parents were both non-atopic (LR group). The main outcome measures were signs and symptoms of atopic disease at 1 year of age.

Findings 103 families dropped out or were lost to follow up. At age 1 year we followed-up 133 HRA, 118 HRC, 140 HRP, and 126 LR infants. Children in the HRA group were less likely to have respiratory symptoms during the first year of life than those in the HRC group. The most pronounced differences were in the relative risks for severe wheeze with shortness of breath (relative risk 0.44 [95% CI 0.20–1.00]), prescribed medication for the treatment of wheezy attacks (0.58 [0.36–0.95]), and wheezing after vigorous playing, crying, or exertion (0.18 [0.04–0.79]). Probability of respiratory symptoms in HRC and HRP infants was similar, whereas it was much lower in the LR than in the HRC group. Cat ownership was significantly associated with sensitisation to cats (24.6 [3.04–199.05]; p=0.003).

Interpretation Environmental manipulation reduces some respiratory symptoms in the first year of life in high-risk infants. Further follow up is needed, however, to ascertain whether living in a low-allergen environment reduces allergy and asthma in later life.

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Introduction

Sensitisation to indoor allergens is a major risk factor for asthma,¹ and there is a dose-response relation between allergen exposure and sensitisation.^{2,3} Although the importance of exposure in progression from sensitisation to asthma is less certain,⁴ reduction of exposure to allergens might offer a realistic opportunity for primary prevention of atopy and asthma.^{5,6} The National Asthma Campaign Manchester Asthma and Allergy Study (^{NAC}MAAS) is investigating whether or not stringent environmental manipulation can prevent sensitisation and allergic disease in children at high risk of atopy. We previously reported that practical acceptance of this regimen was excellent, and that it achieved and maintained exposure to low-allergen concentrations during pregnancy and in the first year of life.⁷ Here, we present data on the effect of environmental manipulation on symptoms during the first year of life. For comparison, we also include data from two non-randomised but similar groups of infants—ie, those at high risk with pets and those at low risk without pets.

Methods

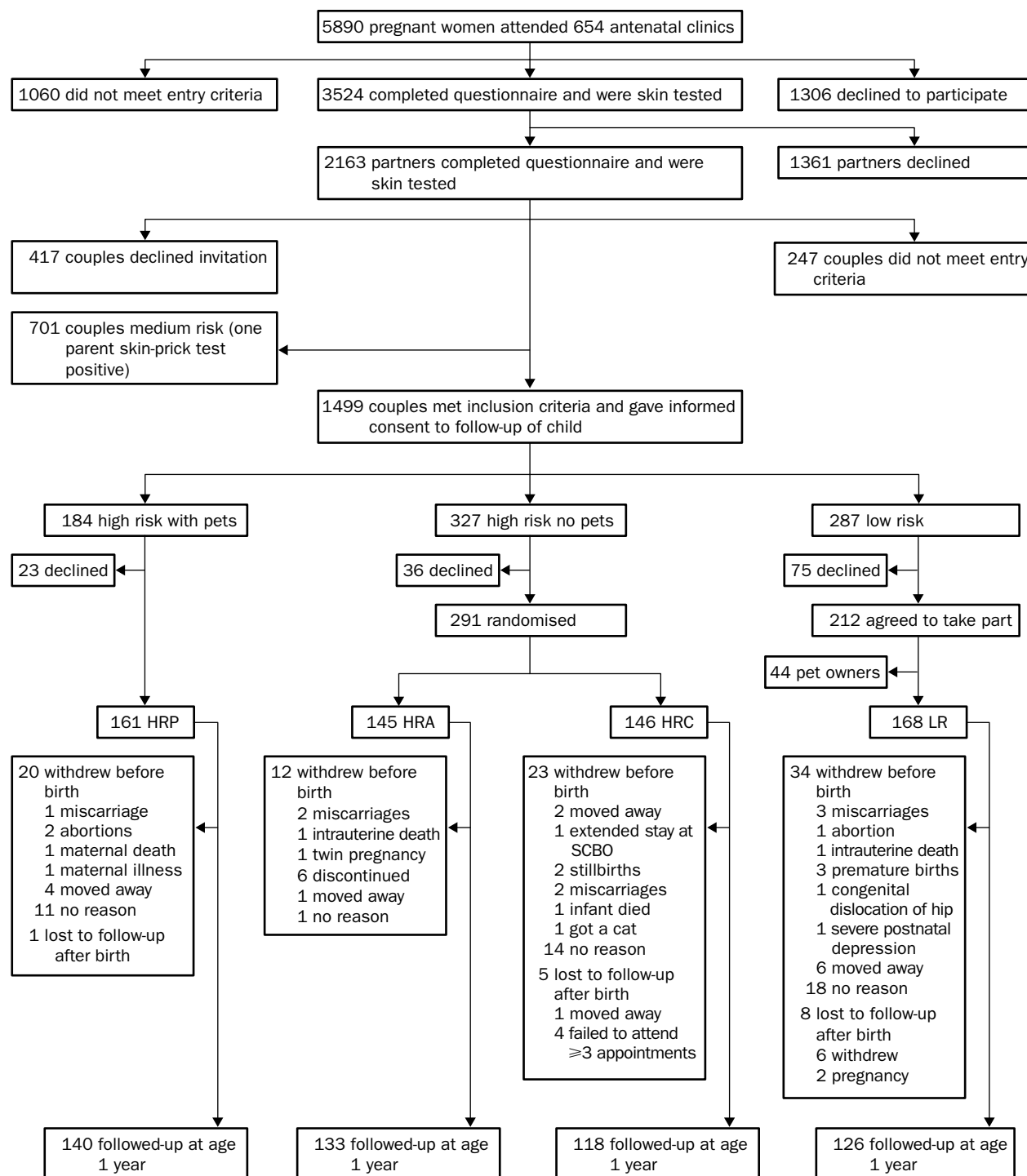
Study population

^{NAC}MAAS is a prospective, prenatally randomised, cohort study. Detailed description of screening and recruitment is provided elsewhere.⁸ Briefly, all pregnant women and their partners were screened at “booking” antenatal visits. Both parents completed a questionnaire and had skin testing. Couples who agreed to take part were allocated to risk groups according to their atopic status, history of allergic disease, and pet ownership.

Couples were randomly allocated (stratification by maternal smoking) into a stringent environmental manipulation (high risk active [HRA]) or control group (high risk control [HRC]) if both parents were atopic (skin-test positive), the mother was sensitised to indoor allergens, and there was no cat or dog in the home. We also prospectively followed participants at high risk (both parents skin-test positive) with a cat or dog, or both (HRP), and couples whose child would be at low risk of developing allergic disease (both parents skin-test negative, no history of atopic disorders, no pets [LR]).

Study protocol

Environmental manipulation measures are described in detail elsewhere.⁷ Briefly, prenatal (completed by the 16th week of pregnancy) interventions comprised covering the maternal bed (pillow, mattress, and quilt) with allergen impermeable bedding (Intervent, WL Gore, Surrey, UK) during pregnancy and after delivery, and provision of a high-filtration vacuum cleaner (Nilfisk, Brøndby, Denmark). At 36 weeks of pregnancy, we removed carpets in the infant's room and laid a vinyl floor (Forbo-Nairn, Fife, UK). We gave couples a new custom-made cot and carrycot mattresses that had been encased in allergen-proof material during the manufacturing process



Trial profile

(Slumberland, Oldham, UK). A washable soft toy was supplied. We asked participants to hot-wash their infant's bed linen (55°C) once a week. Throughout the rest of the house, we applied benzyl benzoate (Allergopharma, Reinbek, Germany) to carpets and soft furnishings.

We invited parents and children into the clinic within 2 weeks of the child's first birthday. The follow-up (clinical and home visits) was identical in all four groups of infants. A standard questionnaire⁹ was interviewer-administered and a physical examination done to identify the presence of respiratory symptoms or eczema, or both, in children, and the use of medication. The specific diagnosis of asthma was

not made at this early age. We asked several questions to assess the severity and frequency of wheeze—eg, wheeze with shortness of breath, medication for the treatment of wheezy attacks. Medication was prescribed by infants' primary or secondary care physicians, who were unaware of the study group. We measured concentrations of cotinine in cord blood (98 HRA, 90 HRC, 104 HRP, 110 LR) and 1-year serum samples (63 HRA, 56 HRC, 69 HRP, 47 LR) with a capillary column gas liquid chromatography.

We did skin-prick tests with standardised allergen preparations of six common allergens (*Dermatophagoides pteronyssinus*, cat, dog, mixed grasses, milk, and egg) with

Characteristic	Group			
	High risk, active (n=133)	High risk, control (n=118)	High risk, pets (n=140)	Low risk, no pets (n=126)
Sex				
Male	62 (47%)	63 (53%)	81 (58%)	75 (60%)
Female	71 (53%)	55 (47%)	59 (42%)	51 (40%)
Delivery				
Normal	104 (78%)	110 (93%)	108 (77%)	108 (86%)
Caesarean section	29 (22%)	8 (7%)	32 (23%)	18 (14%)
Needed oxygen after birth	9 (7%)	11 (9%)	15 (11%)	11 (9%)
Breast fed	81 (61%)	80 (68%)	84 (60%)	69 (55%)
Older siblings	80 (60%)	72 (61%)	94 (67%)	87 (69%)
History of asthma				
Maternal	40 (30%)	47 (40%)	52 (37%)	0
Paternal	43 (32%)	30 (25%)	35 (25%)	0
Current asthma				
Maternal	35 (26%)	36 (31%)	31 (22%)	0
Paternal	26 (20%)	13 (11%)	23 (16%)	0
Sibling	16 (12%)	22 (19%)	27 (19%)	14 (11%)
Asthma medication				
Mother	36 (27%)	36 (31%)	39 (28%)	0
Father	26 (20%)	15 (13%)	24 (17%)	0
Eczema				
Maternal	31 (23%)	31 (26%)	37 (26%)	0
Paternal	25 (19%)	19 (16%)	23 (16%)	0
Siblings	25 (19%)	27 (23%)	31 (22%)	11 (9%)
Hayfever				
Maternal	63 (47%)	53 (45%)	59 (42%)	0
Paternal	54 (41%)	51 (43%)	61 (44%)	0
Siblings	5 (4%)	9 (8%)	7 (5%)	2 (2%)
Smoking				
Maternal	23 (17%)	16 (14%)	33 (24%)	22 (18%)
Paternal	33 (25%)	20 (17%)	47 (34%)	32 (25%)
Cotinine				
Cord blood cotinine (median, IQR)	0.2 (0.05–0.8)	0.2 (0.05–0.6)	0.4 (0.05–1.7)	0.4 (0.05–1.85)
1 year cotinine ($\mu\text{g/L}$) (median, IQR)	0.2 (0.05–0.8)	0.2 (0.05–0.6)	0.2 (0.05–1.3)	0.2 (0.05–1.4)
Detectable (cord)	60/98 (61%)	61/90 (68%)	73/104 (70%)	72/110 (66%)
Detectable (1 year)	41/63 (65%)	30/56 (54%)	40/69 (58%)	27/47 (57%)

Table 1: Demographic characteristics

negative and positive (histamine dihydrochloride 10 g/L) controls (Bayer Corporation, Elkhart, USA). Weal diameter at least 2 mm greater than negative control was judged a positive response. Everyone involved in the study procedures was unaware of group allocation.

Statistical analysis

Our aim was to identify the size of effect of environmental manipulation on development and severity of wheeze and atopy in infants, and the size of difference in measured outcomes between different risk groups. Outcome data are

presented as relative risk and 95% CI.^{10–12} We estimated the outcome probabilities for each risk group of children in relation to the HRC group. Statistical analyses were done with a Confidence Interval Analysis computer programme¹⁰ and SPSS version 9.0.

Results

The figure shows the trial profile. 89 families withdrew before the birth of a child, and 14 were lost to follow-up after the birth of a child. 517 participants completed the follow-up at age 1 year: 133 HRA, 118 HRC, 140 HRP

	Group			
	High risk, active (n=133)	High risk, control (n=118)	High risk, pets (n=140)	Low risk, no pets (n=126)
Symptoms				
Wheeze	51 (38%)	56 (48%)	61 (44%)	34 (27%)
Wheeze with colds	49 (37%)	51 (43%)	59 (42%)	34 (27%)
Wheeze apart from with colds	12 (9%)	18 (15%)	20 (14%)	4 (3%)
Attacks of severe wheeze with shortness of breath	8 (6%)	16 (14%)	16 (11%)	10 (8%)
≥3 episodes of severe wheeze with shortness of breath	3 (2%)	6 (5%)	6 (4%)	1 (1%)
Prescribed medication for wheezy attacks	21 (16%)	32 (27%)	35 (25%)	21 (17%)
Wheeze after playing or exertion	2 (2%)	10 (9%)	8 (6%)	1 (1%)
Cough apart from with colds	18 (14%)	22 (19%)	25 (18%)	12 (10%)
Cough after exertion	5 (4%)	10 (9%)	13 (9%)	5 (4%)
Congested in chest apart from with colds	4 (3%)	10 (9%)	12 (9%)	3 (2%)
Current doctor diagnosed asthma	6 (5%)	11 (9%)	10 (7%)	3 (2%)
Taking asthma medication	5 (4%)	10 (9%)	6 (4%)	3 (2%)
Eczema	53 (40%)	44 (37%)	55 (39%)	24 (19%)
Allergies to foods or medicines	18 (14%)	12 (10%)	20 (14%)	5 (4%)

Table 2: Symptoms suggestive of allergic disorders

Outcome	Risk ratio (95% CI)		
	High risk, active (n=133)	High risk, pets (n=140)	Low risk, pets (n=126)
Wheeze	0.81 (0.61–1.10)	0.92 (0.70–1.20)	0.57 (0.40–0.80)*
Wheeze with colds	0.85 (0.63–1.16)	0.98 (0.73–1.29)	0.62 (0.44–0.89)*
Wheeze apart from with colds	0.59 (0.30–1.18)	0.94 (0.52–1.69)	0.21 (0.07–0.60)*
Attacks of severe wheeze with shortness of breath	0.44 (0.20–1.00)*	0.79 (0.41–1.51)	0.59 (0.28–1.24)
Prescribed medication for wheezy attacks	0.58 (0.36–0.95)*	0.92 (0.61–1.39)	0.62 (0.38–1.00)*
Wheeze after playing or exertion	0.18 (0.04–0.79)*	0.67 (0.28–1.65)	0.09 (0.01–0.72)*
Cough apart from with colds	0.73 (0.41–1.29)	0.96 (0.57–1.61)	0.51 (0.27–0.99)*
Cough after exertion	0.44 (0.16–1.26)	1.10 (0.50–2.41)	0.47 (0.16–1.33)
Congested in chest apart from with colds	0.36 (0.11–1.10)	1.01 (0.45–2.26)	0.28 (0.08–1.00)*
Current doctor diagnosed asthma	0.48 (0.19–1.27)	0.77 (0.34–1.74)	0.26 (0.07–0.89)*
Eczema	1.07 (0.78–1.46)	1.05 (0.77–1.44)	0.51 (0.33–0.79)*
Allergies to foods or medicines	1.33 (0.67–2.65)	1.40 (0.72–2.75)	0.39 (0.14–1.07)

*p≤0.05.

Table 3: Different outcomes in risk groups compared with the high-risk control group

(66 cat owners, 60 dog owners, 14 owned cats and dogs), and 126 LR. Table 1 shows demographic data for these infants.

Table 2 shows the frequency of signs and symptoms suggestive of atopic diseases in the four groups. Table 3 shows the relative risks and 95% CI for different outcomes in different groups of children compared with the HRC group. The estimates of relative risks for the range of respiratory symptoms during the first year of life are consistently lower for the HRA group than for the HRC group. The most pronounced differences were seen for attacks of severe wheeze with shortness of breath, prescribed medication (bronchodilators and inhaled corticosteroids) for the treatment of wheezy attacks, and wheezing after vigorous playing, crying, or exertion.

A trend was seen for all other respiratory symptoms unrelated to viral infections. Additionally, the probability of all respiratory symptoms in HRC and HRP infants was similar (table 3). In the HRP group, the proportion of symptomatic children was almost identical in cat and dog owners—eg, wheeze 45% versus 41%, wheeze apart from with colds 15% versus 16%, and attacks of severe wheeze with shortness of breath 12% versus 10%, for dog and cat owners, respectively.

An estimate of the relative risk for virtually all respiratory symptoms was significantly lower in LR compared with HRC infants. In the group of high-risk infants, the estimates of relative risks for several symptoms were significantly lower in HRA than in HRC and HRP—eg, prescribed medication for wheezy attacks (relative risk 0.18, 95% CI 0.39–0.95), wheeze after playing, crying, or exertion (0.22, 0.05–0.92), and congestion in chest apart from with colds (0.35, 0.12–1.00). A different pattern of the estimates of relative risk for eczema than for respiratory signs and symptoms was recorded. The probability of having eczema in HRA and HRP compared with those in the HRC group was almost identical, whereas LR infants had a significantly lower estimate of having eczema than HRC children.

501 (97%) infants were successfully skin tested. The results are presented in table 4. Very few infants developed a positive skin test to inhalant allergens at this early age. However, the proportion of infants with a positive skin test to cat was much higher in HRP children than in other groups. Furthermore, of 66 HRP infants with only cats in their home, ten were skin-test positive to cats (compared with only one in the dog owners in HRP, zero in HRC, and four of 126 in HRA). In a multivariate regression analysis of infants in HRC and HRP, cat ownership was significantly associated with sensitisation to cats (odds ratio 24.6 [95% CI 3.04–199.05]; p=0.003). Dog ownership was not associated with either sensitisation to cats or dogs.

Sensitisation to egg was the most common in this infant cohort at age 1 year. An estimate of the relative risk of having a positive skin-test reaction to egg seemed higher in high-risk infants than in LR children (relative risk 2.07 [95% CI 0.90–4.79]). An estimate of the relative risk of being atopic (at least one positive skin test) was significantly higher in high-risk than in LR infants (2.60, 1.23–5.73).

Discussion

Our results suggest that environmental manipulation can reduce respiratory symptoms in infants aged 1 year or younger, who are at high risk of allergic disease. These are preliminary results, however, and should not be used as the basis for advice on clinical management, since further follow up is needed to ascertain whether or not living in a low-allergen environment reduces frequency of allergy and asthma in later childhood.

The stringent environmental manipulation regimen that we used was effective in achieving and maintaining a low-allergen environment.⁷ At age 1 year, children in the active group (HRA) were less likely to have respiratory symptoms unrelated to viral infection than those in the control group (HRC). Furthermore, infants living in homes with pets and children in the control group were at a closely similar

Allergen	Group			
	High risk, active (n=126)	High risk, control (n=113)	High risk, pets (n=139)	Low risk, no pets (n=123)
<i>Dermatophagoides pteronyssinus</i>	3 (2%)	1 (1%)	3 (2%)	1 (1%)
Cat	4 (3%)	0	11 (8%)	0
Dog	3 (2%)	2 (2%)	4 (3%)	0
Mixed grasses	0	2 (2%)	0	0
Milk	3 (2%)	0	0	0
Egg	17 (14%)	12 (11%)	12 (9%)	7 (6%)
Atopic	21 (17%)	16 (14%)	22 (16%)	8 (7%)
Sensitised to mite, cat, or dog	6 (5%)	3 (3%)	16 (12%)	1 (1%)

Table 4: Sensitisation to dust mites, cat, dog, mixed grasses, milk, and egg assessed by skin-prick testing at age 1 year

risk of developing respiratory symptoms. Since HRA and HRC infants were randomly assigned to the active and control groups comparisons between them are the most valid. However, the prospective data obtained from the group of pet owners are of value, even though it is not possible to completely exclude bias. The comparisons with low-risk infants strengthen the findings of our study.

In the Isle of Wight Study,¹³⁻¹⁵ even modest reductions in mite allergen amounts (from 25 to 6 µg/g by use of an acaricide) in homes of infants at risk of allergy reduced the prevalence of sensitisation to mites and overall manifestation of atopy during the first year of life. Additionally, some benefits on allergic disease (but not asthma) were recorded at age 4 years. In our study, the concentrations of dust-mite allergens in the homes of the active group, measured in comparable dust reservoirs, were 30–150-fold lower than those measured in the prophylactic group of the Isle of Wight study. However, one has to be careful in attributing the potential benefits of environmental manipulation only to reduction in mite or other allergens. A whole range of other potentially harmful exposures (eg, volatile organic compounds) could also have been reduced simultaneously.

The heterogeneity of wheeze in early life^{16,17} and difficulties in distinguishing between different causes of wheezy illness are reasons why the specific diagnosis of asthma was not made in our study. Early transient wheeze and viral-associated wheeze might be characterised with apparently less severe and less frequent symptoms during the first few years of life than the symptoms seen in children whose recurrent episodes of airway obstruction persist into the school years.¹⁸ Therefore, the questions of particular interest are related to severity and frequency of wheezy attacks (eg, attacks of severe wheeze, the prescription of medication for wheezy attacks) and the possible indicators of the increase in non-specific airway reactivity (eg, wheeze apart from colds). The most pronounced differences between the active and control groups in our study were in the attacks of severe wheeze with shortness of breath, prescription of medication for wheezy attacks, and wheeze after exertion. However, one has to be cautious in the interpretation of these data, particularly in view of the relatively low number of events (table 2) and the relatively wide CI (table 3). Furthermore, some questions (eg, “cold” or “exertion” in young infants) required subjective judgments to be made by the mothers. Nevertheless, the fact that the size of the apparent protective effect was much the same across the groups and remained consistent for different outcomes is reassuring.

Environmental tobacco smoke exposure is an important risk factor for wheeze in infancy. Our groups were well balanced in terms of exposure to parental smoking, assessed both by questionnaire and measurement of cotinine in cord and 1-year blood samples. The possibility of responder bias cannot be discounted. All participants were aware of their respective study groups, which is inevitable when such an intensive environmental intervention is used, and when the analysis focuses on subjectively reported symptoms. However, we cannot see how this bias could have affected prescribing patterns or diagnostic labelling by primary or secondary care physicians not associated with the study (the pronounced differences between study groups in prescribed medication for the treatment of wheezy attacks is worth noting). The other possibility is a chance imbalance in the trial allocation groups, although this occurrence is unlikely in a trial of this size. These concerns can only be resolved by testing objective measures, such as bronchial reactivity, at later follow-ups, and by monitoring the natural history of respiratory symptoms.

Our findings should not be overinterpreted, since the children studied were of a very young age. The results suggest that the overall prevalence of wheeze was similar between the groups, whereas certain types of wheezing (which at this early age might or might not relate to the subsequent development of airway hyper-responsiveness and asthma) were lower in the intervention than in the control group. This protective effect of environmental manipulation was limited to respiratory symptoms, and the relative risks for other symptoms suggestive of atopic disorder (eg, eczema and allergies to food) were almost identical in the three groups of high-risk infants. This result is perhaps not surprising, since atopic dermatitis during the first year of life is usually associated with sensitisation to food,³ and environmental manipulation would probably have little effect.

As expected, very few infants developed positive skin-test reactions to inhalant allergens at this early age, and we identified no relation between sensitisation to inhalant allergens and symptoms. The overall frequency of sensitisation to dust mites was 1·4%, but is expected to rise as children grow older.³ Therefore, the effects of environmental manipulation on IgE-mediated sensitisation to dust mites will become clear in the years to come.

Intriguing and often conflicting data on the effect of pet ownership in early life on the subsequent development of sensitisation and atopic disease have been reported. Some study results indicate that exposure to cats and dogs in early infancy is associated with later sensitisation and allergic disease.^{19,20} Others, however, report a protective effect.²¹⁻²³ Most of these studies were cross-sectional and retrospective. In a prospective study, Wahn and colleagues³ have shown a dose-response relation between exposure to cat allergen and specific sensitisation during the first 3 years of life. The frequency of specific sensitisation to cats in our study was 3·4%, and is higher than that seen in the German Multicentre Atopy Study (1·3%).³ Our findings support a dose-response relation between exposure to cat and specific sensitisation, at least in early life. Results of a study by Platts Mills and colleagues²⁴ suggested that many children who are exposed to high concentrations of cat allergen made a modified Th2 response characterised by the presence of IgG4 antibody to cat proteins without becoming allergic (ie, no IgE response), which could be seen as a form of tolerance.²⁴ Can these apparently irreconcilable differences between studies be reconciled? Prospective studies indicate that, at least in early life, there seems to be a dose-response relation between exposure to cat allergen and sensitisation.³ Cat allergen is ubiquitous, and exposure outside the domestic environment might lead to specific IgE responses. If cumulative exposure to allergens is important for the development of sensitisation, then clear-cut differences with respect to pet ownership are likely to be seen only in early life. The cumulative passive exposure of non-pet owners in homes without pets and in public places might induce sensitisation in later childhood and adolescence, confounding the effect of pet ownership. Furthermore, those exposed to very high amounts of cat allergen might initially mount an IgE response (high cumulative exposure in early life), which as a consequence of continuous high exposure might be replaced by a modified Th2 response (ie, tolerance).

Contributors

A Woodcock and A Custovic conceived the idea, designed the protocol, and wrote the report. B M Simpson coordinated the study. B M Simpson, A Simpson, and A Custovic recruited participants. P Kissen collected data at 1 year follow up. All authors were involved in interpretation of data and final approval of the report.

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