

Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study – 24 months results of the Study of Prevention of Allergy in Children in Europe

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Summary

Background Sensitization to house dust mite (HDM) is an important risk factor for the development of asthma and allergic disease in childhood. Higher levels of HDM allergen are linked to increased sensitization to HDM.

Objective To study the effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a newborn cohort.

Methods Six hundred and ninety-six newborns at high risk of developing allergies were enrolled in three European countries (Germany, Austria, UK) in a prospective, randomized, controlled birth-cohort study. Children were randomly assigned to an intervention and control group. Intervention measures included the use of mite-impermeable mattress encasings for the child's bed and a simple educational package on allergen avoidance. The control group received basic information about allergies. Children were followed up at age 6, 12, 18 and 24 months.

Results 80.9% of the children were followed up to the age of 24 months. No difference in the prevalence of sensitization to HDM (control vs. intervention group: 8.4% vs. 6.1%, $P = 0.33$) or the development of symptoms (recurrent wheezing 10.3% vs. 10.7%, nocturnal cough 12.5% vs. 12.5%) or allergic diseases (asthma 3.5% vs. 5.1%, eczema 20.0% vs. 19.6%, rhinitis 28.9% vs. 25.8%) could be found between the control and intervention group.

Conclusion In this study, HDM avoidance did not show a protective effect on the development of sensitization to HDM or symptomatic allergy in children at age 24 months.

Keywords allergy, birth cohort, dust mite, newborn, primary prevention

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Introduction

The prevalence of allergic disease in childhood has increased considerably in developed countries over the last 30 years [1]. Sensitization to house dust mite (HDM) has been established as an important risk factor for the development of asthma [2, 3]. Furthermore, in the German Multicenter Atopy Study (MAS) children exposed to higher levels of HDM allergen in their first 3 years of life were more likely to develop sensitization to HDM between the ages of 3 and 7 years [2, 4]. These studies suggest that avoidance measures introduced at a very early stage of life could possibly prevent the development of allergic disease and asthma in later childhood.

To date, only a small number of randomized, controlled, prospective intervention studies have been performed. While some have used very expensive intervention measures (mattress encasings, acaricides, new mattresses, high-filtration vacuum cleaner, new vinyl floor [5, 6]), others required a strict dietetic regimen [7–9] or change of lifestyle (avoid use of day-care centers, pets removed or kept outside [10]).

The Study of Prevention of Allergy in Children in Europe (SPACE) was carried out by research teams in five European countries (UK, Austria, Germany, Lithuania, Greece) to evaluate the effect of simple HDM avoidance measures. Three cohorts of children at high risk of developing allergic disorders were recruited into the study: newborn, toddlers (2–4 years) and schoolchildren (5–7 years). The study was designed to prevent sensitization to HDM as well as the development of allergic symptoms in children at high risk. Measures were intended to be easily implemented, inexpensive and socially acceptable in different countries, cultures and lifestyles. The newborn cohort was recruited and

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followed up in Vienna (Austria), The Isle of Wight (UK) and Freiburg (Germany). Analysis of the 12 months follow-up of the newborn cohort [11] showed a trend for a reduced prevalence of sensitization to HDM in the intervention group compared with the control group. We now report results of the 24 months follow-up of this cohort.

Methods

Study design

The protocol for this prospective, randomized, controlled study was written in collaboration with participants from all centres. The local ethics committee of each centre gave approval and parents gave informed written consent for participation in the study. The study procedures were similar and comparable between centres and care was taken to avoid selection bias.

Subjects and recruitment

Recruitment of study subjects has been previously reported [11]. Briefly, over a 12-month period all pregnant women (5601) at the three centres were screened. The majority of women were approached at routine visits to obstetric wards or antenatal clinics during pregnancy.

To determine the family history of atopic disorders in parents or siblings, questions from the International Study of Asthma and Allergies in Childhood [12] and German MAS [13] were selected.

If a positive answer to any of these questions was given for a parent or sibling, a skin prick test (SPT) or blood test for specific IgE was carried out, on at least one parent, to determine their allergic sensitization.

SPT was carried out using standardized equipment and technique [14]. Standardized allergen extracts (ALK Scherax, Hamburg, Germany) were used in all three centres to test for HDMs (*Dermatophagoides pteronyssinus* (D pter), *Dermatophagoides farinae* (D far)), six grass mixture and cat dander. A positive test required a mean weal diameter of at least 2 mm larger than the negative control (sodium chloride 9 g/L) and at least half of the diameter of the positive control (histamine hydrochloride 10 mg/mL) as previously described [11].

In Germany and Austria, pregnant women and those who preferred not to have an SPT had their blood tested for IgE against the core allergens. Levels of specific IgE were determined by means of the Magic Lite system (Chiron Diagnostics, Fernwald, Germany). The test was considered to be positive above a level of 1.43 MLU/mL. Using the same methodology, correlation between specific IgE and SPT for HDM, grass pollen, cat and birch pollen, has previously been shown to be high [15].

The newborn infant was considered to be at high risk of developing atopy, and therefore eligible for the study, if there was a positive history of allergic symptoms in a parent or sibling, and a parent was sensitized to at least one of the panel of aero-allergens.

Randomization was in 2-week periods. Infants were assigned to prophylactic or control group according to the

expected date of delivery or the actual date of delivery if recruited post-natally as previously reported [11].

Parents were informed that there would be two study groups, both containing high-risk children, but following different advice.

Allergen avoidance measures

Intervention group At birth, special mite-impermeable mattress encasings (ACB Allergy Control barrier, Dr Beckmann GmbH, Seefeld, Germany) were applied to the baby's cot and also to other beds in the infants room and other areas where the infant may sleep, such as the parents' bed. Parents were encouraged not to take the baby into a bed, which does not have the mattress encased.

In addition, parents were given a booklet explaining allergy and giving advice on allergy prevention. This advice involved recommending exclusive breastfeeding for at least 3 months or otherwise use a hypo-allergenic formula (not recommended in UK). Cow's milk formula should not be given before 6 months (not recommended in UK). Cow's milk, other than formula, as well as egg and fish should not be introduced until 12 months. Introduction of solid foods should be delayed until 4–6 months and wheat should not be introduced until 6 months of age. Products containing cow's milk should be excluded until 6 months unless a cow's milk formula has been used. Peanuts and tree nuts should not be introduced until 3 years. One to two weeks should be allowed between the introduction of each new food. Carpets should be removed in the baby's room, and curtains selected that could be washed at 55 °C. Furthermore, parents were asked to avoid soft toys or, if this was not possible, to hot wash them with the bedding at 55 °C or freeze them once a week. Frequent ventilating rooms, usage of a damp cloth when dusting and vacuuming rooms at least once a week when the baby is absent was recommended. Finally, we encouraged parents not to allow smoking in the house and to avoid having pets.

Control group Parents of children randomized to the control group were given a booklet at randomization, identical in outward appearance to that given to the prophylactic group.

The advice inside the booklet was more basic. It included exclusive breastfeeding for at least 3 months as well as the delayed introduction of solids until 4–6 months, wheat for 6 months and cow's milk, other than formula, for 12 months. Parents were asked to ventilate the rooms frequently, protect the baby against passive smoking in their house and not allowing pets in the bedroom.

Outcome measures and follow-up

Parents and children were either visited at home or contacted by telephone when the children were aged 6, 12, 18 and 24 months. Parents were asked to complete a questionnaire on allergic symptoms in the child, pet ownership, smoking at home, presence of carpet in the child's bedroom and ventilation of the home since the last visit. In addition, the prophylactic group was asked questions on compliance with the intervention measures. Both groups were asked if they had taken any additional allergy prevention measures.

An SPT or blood test for specific IgE to D pter and D far was performed on all children at age 12 and 24 months.

The primary outcome was sensitization to HDM at 12 and 24 months. The secondary outcome was the development of allergic disorders (recurrent wheeze, nocturnal cough, asthma, eczema, rhinitis) in the first 24 months of life.

Definition of primary outcome Either a positive SPT for D pter or D far or a specific IgE ≥ 1.43 kU/L for D pter or D far.

Definition of secondary outcomes Asthma: ever asthma since last visit (Question: Has your child ever had asthma in the last 6 months?).

Recurrent wheeze: at least three episodes of wheezing in the last 6 months (Question: How many attacks of wheezing has your child had in the last 6 months? None, 1–2, 3–12, more than 12).

Nocturnal cough: any episode of nocturnal cough apart from a cold in the last 6 months (Question: Has your child had a dry cough at night, apart from a cough associated with a cold or chest infection? Yes/No).

Eczema: A doctor's diagnosis of eczema in the last 6 months (Question: Was a doctor's diagnosis made in your child of atopic dermatitis or eczema? Yes/No).

Rhinitis: any episode of rhinitis in the last 6 months (Question: Has your child had a problem with sneezing, or a runny, or a blocked nose when he/she did not have a cold or the flu? Yes/No)

'Any allergic symptom in the first 24 months': asthma or nocturnal cough or recurrent wheeze or eczema or rhinitis in the first 24 months of life.

Statistics

All statistical analyses were performed using the SAS software package V6.12 (SAS Institute, Inc., Cary, NC,

USA). Comparisons of proportions in two groups were done via continuity adjusted χ^2 -tests at 5% level. Differences in parental education were analysed using Mantel–Haenszel χ^2 -test.

Prevalences of sensitization and symptoms were analysed for each investigation separately and in a cumulative way, e.g. 'cumulative sensitization to mites' as the occurrence of sensitization to mites in any of the two investigations. The main analysis is an 'intention to treat' analysis. In a sensitivity analysis, children were excluded that did not stick to the protocol (children from the intervention group that have not used mattress covers, children from the control group that reported use of mattress covers or allergy bedding).

Results

Of 5601 families that were initially approached, 696 children could be recruited and randomized to the intervention or control group (Fig. 1). Six hundred and thirty nine (91.8%) of the infants were seen on at least three occasions. Five hundred and sixty-three (80.9%) children could be followed up to the age of 24 months. 80.8% of the intervention group and 74.4% of the control group were seen at all four occasions. Demographic and socio-economic data (Table 1) did not differ between the two groups.

Children who dropped out were more likely to have parents who smoked in pregnancy (drop out 25.4% vs. non-drop out 15.0%, $P = 0.007$) or usually smoke at home (30% vs. 16.7%, $P = 0.0001$). They did not differ in parental education, dual heredity for allergies or gender (data not shown).

Adherence to the main intervention (mattress encasings) was generally good, and just slightly dropped over the study period from 95.1% to 90.0% (Table 2). Recommendations

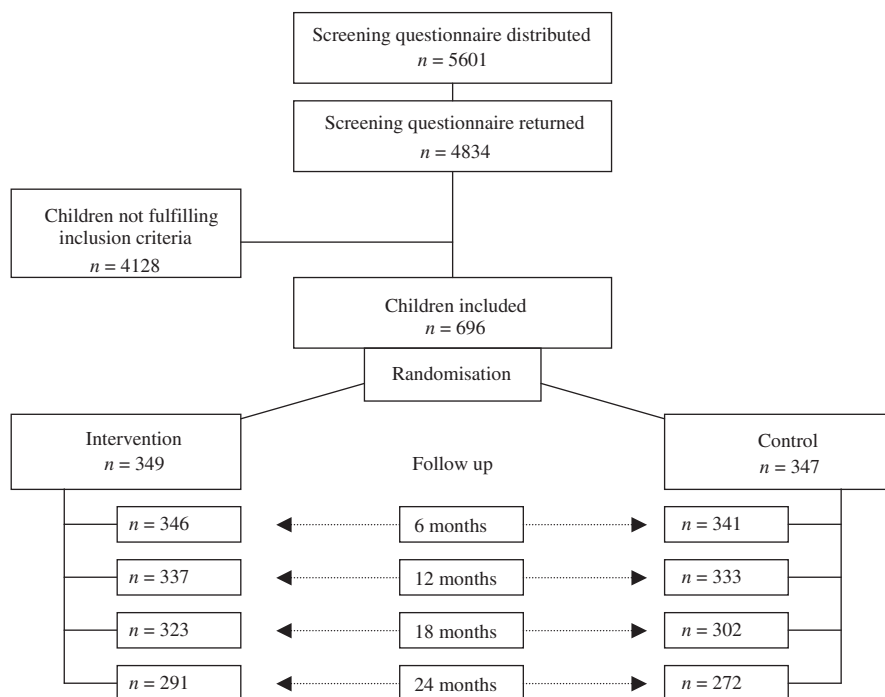


Fig. 1. Trial profile.

for avoidance of milk or egg were well accepted in the first 6 months but dropped until the age of 1 year. Apart from frequent ventilation of the child's bedroom there was poor acceptance of the other recommendations concerning lifestyle changes. After 24 months, 73.3% of the children still had a carpet in their bedroom, while only 8.1% carpets were removed.

Table 3 gives the results of the bivariate analyses of sensitization and symptoms in the control and intervention group at follow-up at 12, 18 and 24 months. The tendency for a decreased prevalence of sensitization to HDM in the intervention group at 12 months could not be confirmed at the age of 24 months. Recurrent wheezing, asthma, doctors diagnosis of eczema, nocturnal cough or rhinitis symptoms were not different in the two groups. In addition, symptoms of eczema (itchiness, scratching) or any wheezing episodes did not show a difference (data not shown). There was no difference in the

cumulative prevalence of sensitization or symptoms in the first 24 months of life (Table 4). Furthermore the variable 'any allergic symptom in the first 24 months' was not different between the control group (43.5%) and the intervention group (44.7%; $P = 0.822$).

In a sensitivity analysis, we excluded children that did not stick to the protocol concerning use of mattress encasings (children from the intervention group that have not used mattress covers, children from the control group that reported use of mattress covers or allergy bedding). The difference in sensitization to mites between control and intervention group got slightly more pronounced (control 8.8%, intervention 5.5%) but did not reach statistical significance ($P = 0.154$). The other outcome parameters remained unchanged (data not shown).

Discussion

Over the last decade, different studies have looked at the possibility of preventing allergic sensitization to HDM and associated allergic symptoms with different intervention measures. The interventions described in the studies consisted of either environmental measures (including mite-allergy prevention) [5, 16] or a combination of a dietary regimen and environmental measures [7, 10, 17].

The first of these studies, published in 1992 [7], combined the use of mattress encasings and acaricides. One hundred and twenty mothers of infants at very high risk (family history of atopy and cord blood IgE > 0.5 kU/L) of developing asthma and allergic disease were recruited into this randomized, controlled study. In the prophylactic group, lactating mothers followed a strict dietary regimen. The infants' diet was also free of allergenic food. Follow-up at 12 months showed a lower prevalence of sensitization to HDM as well as lower prevalence of allergic disorders. The effect on sensitization and prevalence of any allergy and eczema was confirmed at 24 months and 4-year follow-up, while the effect on asthma was no longer significant [8, 9]. Eight-year follow-up showed that asthma and sensitization on SPT to HDM were still significantly reduced in the prophylactic group [18].

In a Canadian study [10] comparable intervention measures were used in a high-risk cohort of 545 infants. These included mattress encasings, acaricides and a strict educational

Table 1. Population characteristics at time of randomization

	Control (<i>n</i> = 349) (%)	Intervention (<i>n</i> = 347) (%)
Sex (male)	52.2	48.6
Smoking in pregnancy	16.7	17.2
Smoking at home	19.3	18.9
Parental education:		
High	32.6	34.7
Medium	48.4	46.4
Normal	18.7	18.3
Older siblings		
0	59.7	63.0
1	29.7	26.7
2	7.8	7.5
≥ 3	2.9	2.9
Dual heredity for allergies	47.2	52.8
Heating at home		
Central	70.9	69.1
Single room	13.5	14.0
Single story	15.3	15.2
Heating with coal/oil/gas	51.8	53.8
Mould	30.3	28.9

Parental education: high, university; medium, additional non-academic training; normal, compulsory school $\pm$ apprenticeship (highest graduation of both parents count).

Table 2. Compliance with intervention measures (intervention group)

	6 Months (%) (<i>n</i>)	12 Months (%) (<i>n</i>)	18 Months (%) (<i>n</i>)	24 Months (%) (<i>n</i>)
Child sleeping on a covered mattress most of the time or always	95.1 (325)	92.8 (333)	90.6 (319)	90.0 (289)
Soft toys washed $> 55^{\circ}\text{C}$ or frozen at least once in the last 6 months	52.4 (294)	63.8 (282)	57.7 (286)	57.5 (268)
Bed linen washed $> 55^{\circ}\text{C}$ at least every second week	76.9 (337)	69.5 (334)	68.1 (320)	66.8 (289)
Carpet				
No carpet	Not asked	20.9	18.4	18.6
Carpet	Not asked	73.7	74.8	73.3
Carpet removed	Not asked	5.4 (335)	6.9 (321)	8.1 (285)
Ventilation of the child's bedroom				
At least once a day	Not asked	91.0 (335)	88.9 (307)	90.6 (287)
Food prevention				
No egg during last 6 months	96.8 (344)	67.2 (335)	—	—
No milk during last 6 months	88.4 (344)	52.4 (336)	—	—

Table 3. Bivariate analysis: sensitization and symptoms in the intervention and control group in the first 24 months of life

	12 Months			18 Months			24 Months		
	CO (%) (n)	IV (%) (n)	P	CO (%) (n)	IV (%) (n)	P	CO (%) (n)	IV (%) (n)	P
Sensitization to mites	5.3 (300)	2.5 (322)	0.102	NA	NA	NA	5.9 (236)	5.6 (268)	1.000
Nocturnal cough	NA	NA	NA	6.4	5.6 (321)	0.816	10.9 (247)	11.1 (252)	1.000
Recurrent wheezing	7.0 (331)	7.5 (333)	0.898	5.7 (300)	5.4 (318)	1.000	3.4 (269)	2.1 (289)	0.506
Asthma	1.8 (330)	2.7 (334)	0.618	2.7 (302)	4.1 (319)	0.447	2.2 (270)	4.5 (291)	0.217
Eczema	10.1 (328)	10.0 (330)	1.000	11.3 (293)	13.4 (314)	0.505	11.0 (263)	13.1 (275)	0.547
Rhinitis	NA	NA	NA	16.7 (299)	16.8 (322)	1.000	20.6 (272)	15.5 (290)	0.146

CO, control group; IV, intervention group; P, probability for continuity adjusted χ^2 -test; recurrent wheezing, at least three episodes of wheezing since the last visit; eczema, doctors diagnosis of atopic dermatitis or eczema since the last visit; asthma, asthma since the last visit; rhinitis, sneezing, runny/blocked nose apart from cold. NA, not applicable.

Table 4. Bivariate analysis: sensitization and symptoms in the intervention and control group in the first 24 months of life (cumulative prevalence)

	Control		Intervention		P
	%	n	%	n	
Sensitization to mites	8.4	311	6.1	330	0.330
Nocturnal cough	12.5	313	12.8	327	0.978
Recurrent wheezing	10.7	337	10.5	342	1.000
Asthma	3.6	334	5.3	340	0.377
Eczema	21.1	342	18.8	346	0.516
Rhinitis	28.3	315	25.6	328	0.505

package (encouragement to stop smoking, the removal of pets, avoidance of use of day-care facilities) as well as a diet for the mothers during the last trimester of pregnancy and lactation. This study found a reduced risk of asthma (34%) and rhinitis (49%) in the intervention group at 12 months of age. In our study, we could not find any difference in the prevalence of asthma between the study groups. However, as the definition of asthma in the Canadian study was based on respiratory symptoms instead of parental reporting, the overall prevalence of asthma was much lower in our study compared with Canada (2.3% vs. 17.6%) at 12 months of age, with possibly little potential for further reduction. The Manchester Asthma and Allergy study (MAAS) involved a cohort of 291 infants that were pre-natally randomized to a HDM allergen avoidance or normal regimen. The intervention measures started at the 16th week of pregnancy including mattress encasings for parental bed, cot-mattress and a portable cot-mattress, high-filtration vacuum cleaner, vinyl floor in infant's bedroom, acaricides applied to carpets and soft furniture, bed-linen hot-washed weekly and a washable soft toy. These quite expensive measures showed to maintain a low mite allergen environment during pregnancy and in the first year of life [5]. Furthermore, children in the intervention group had a reduced risk to develop attacks of severe wheeze, wheeze after playing or exertion and prescribed medication for wheezy attacks than the control group [6]. As in our study, no group differences could be found concerning wheeze, asthma, eczema or sensitization to HDM.

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study followed a cohort of 1282 [16] infants of allergic mothers in a placebo-controlled trial using active mite-impermeable mattress encasings and cotton placebo

covers from the third trimester of pregnancy. Follow-up at 2 years of life revealed a reduction of nocturnal cough but no effect on other respiratory symptoms or sensitization of the infants.

A very recent study [17], the Childhood Asthma Prevention Study (CAPS), used a combination of dietary supplementation (Ω -3 fatty acid) and/or HDM avoidance measures (acaricides and mite-impermeable mattress encasings). While the dietary intervention showed some protective effect on the development of wheeze in the first 18 months of life, HDM avoidance measures did not show a benefit either on the development of sensitization or on allergic symptoms. The authors postulated that they probably could not reduce their mite concentrations sufficiently to show a protective effect of HDM avoidance. Nevertheless the levels of HDM allergens found in the homes of the intervention group were comparable with the Isle of Wight study [9] that found a significant reduction of allergies, asthma and eczema at 1 year of age.

In the present study, HDM levels were not measured. Therefore, we do not know if our intervention measures did actually reduce allergen levels in the dust. However, it has been previously shown that reduction of HDM levels can be achieved by the use of mite-impermeable mattress encasings [19–22], with no additional effect from the use of acaricides [10, 23, 24]. Furthermore, compliance with the use of mattress encasings was generally good in our cohort.

Interestingly, in both the PIAMA and CAPS study, atopic dermatitis was more prevalent in the active group than in the control group at the age of 12 months. Thus, it can be speculated, that either the material of HDM encasings can worsen eczema or that there is a protective substance in the dust (possibly bacterial endotoxin) that can prevent eczema. Another explanation may be that in the placebo group, mothers with children suffering from eczema introduced other avoidance measures (cleaning of bedding, etc.) to reduce dust and HDM concentrations. However, it is possible that these observations were simply artefactual. In our study, the prevalence of eczema was much lower compared with the CAPS (13.4% vs. 33.5%), and showed no difference between the two groups. The MAAS study [6] observed a higher prevalence of eczema that was not different in the intervention (40%) and control group (37%).

It is interesting that the two studies that, in addition to environmental intervention, used a low-allergenic diet for either pregnant women [10] or the infant as well [7] seem to be more beneficial for the prevention of atopic disorders than

environmental measures alone (or the use of Ω -3 fatty acid). The main interventions of the SPACE study were the use of mattress encasings with additional information provided for the parents about low-allergenic diet but not with a strict controlled dietary regimen. It can only be speculated if a stricter dietary regimen would have resulted in a better outcome concerning the prevention of allergies.

The use of different SPT criteria could potentially alter observed results. In a study of Meinert et al. [14] the use of different SPT criteria was investigated. The author found that a combination of a 2 mm criterion + 0.5 of the histamine weal was preferable to the use of a 3 mm criterion. In our study, we used the published 2 mm + 0.5 histamine criterion. Reanalysing our data with a 3 mm criterion marginally reduced the prevalence of a positive SPT. This effect was comparable in both groups (mite sensitization 12 months 2 mm criterion: CO 5.3%, IV 2.5%; 3 mm criterion: CO 5.0%, IV 2.5%; 24 months 2 mm criterion: CO 5.9%, IV 5.6%; 3 mm criterion: CO 5.1%, IV 4.9%).

In summary, in the present study conducted in three European countries ($n = 696$ high-risk infants), HDM avoidance measures had no protective effect up to the age of 2 years. These infants will be followed up until the age of 4 years to determine any possible benefits in later childhood. Current research studies suggest that HDM allergen levels can be reduced by simple avoidance measures such as mite-impermeable mattress encasings, but the outcome of such avoidance measures varies across countries. At this stage no global recommendation for the use of HDM avoidance measures as a primary intervention can be given. Socio-economic, genetic and environmental factors differ between countries and it seems that each has to set up its own strategy to reduce allergic diseases in the future.

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