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Prevention of sensitization to house dust mite by allergen avoidance in school age children: a randomized controlled study

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Summary

Background Sensitization to dust mites predisposes to asthma and allergic rhinitis, and prevention of this sensitization might reduce the rising prevalence of these disorders.

Objective To test the effectiveness of dust mite avoidance measures on the development of sensitization to dust mites in children.

Methods As part of a multicentre study (Study of Prevention of Allergy in Children of Europe), 242 children, aged 5–7 years, in three European countries (United Kingdom, Greece and Lithuania), were randomized to prophylactic group ($n = 127$) and control group ($n = 115$). At randomization these children were required to have a family history of atopy and positive skin test to an aeroallergen but not to house dust mite. Children in the prophylactic group were provided with dust mite impermeable mattress covers and advice on environmental measures to reduce exposure to dust-mite allergen. Control group children were given non-specific advice. After 12 months a standardized questionnaire was completed and skin prick tests were performed.

Results Ten children in the prophylactic group and 19 in the control group were lost to follow-up. Three of 117 (2.56%) children in the prophylactic group and nine of 96 (9.38%) in the control group developed sensitization to dust mites. Logistic regression analysis confirmed an independent effect of prophylactic measures (adjusted odds ratio (OR): 0.14, 95% confidence interval (CI): 0.03–0.79, $P = 0.03$). Fifteen children need to be treated to prevent sensitization in one child.

Conclusion Dust mite sensitization can be reduced in school age children with simple mite avoidance measures.

Keywords asthma, childhood, house dust mites, prevention, sensitization

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Introduction

Increases in the prevalence of asthma and other allergic diseases during the last few decades have focused attention on the need for primary prevention [1, 2]. There is also considerable evidence of the strong relationship between allergen sensitization and atopic disorders such as asthma, eczema and rhinitis [3–5]. Atopic disorders usually manifest for the first time in childhood, and often lead to chronic disease that may continue into adulthood. These chronic diseases may impact on the education and general well-being of the child, in addition to having an enormous economic cost [6].

Sensitization to house dust mite (HDM), a perennial allergen, has a key role in the pathogenesis of asthma [7, 8] and is often implicated in atopic eczema and perennial rhinitis. The best single predictor of asthma is allergic sensitization to HDM [8], which also plays an important role in the causation of atopic eczema [9].

HDM sensitization often occurs early in childhood and is dependent on the level of exposure [10, 11]. However, the incidence and prevalence of sensitization to inhalant allergen increases with age during the first decade of life [10]. As sensitization to HDM, which often precedes clinical disorders, depends on exposure to this allergen, it makes sense to attempt to reduce exposure before the sensitization has occurred.

Complex avoidance measures in the first year of life can significantly prevent atopic manifestation up to the age of 4 years [12, 13]. However, these measures are not easy to implement, require considerable motivation on the part of the mother and intensive monitoring by physician and dietician. Prevention, if it is to be acceptable and applicable to the 'at risk' population at a wider scale in the community, must be proven to be effective and be simple to perform.

Previously, preventive measures to reduce the development of atopy have focused on new-borns [12]. New-borns are generally not sensitized to allergens (although recent evidence indicates that *in utero* sensitization is not uncommon) and therefore

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preventive measures are suggested to start from birth. However, the usefulness or otherwise of HDM avoidance measures to prevent sensitization in older children has not been studied.

The Study of Prevention of Allergy in Children of Europe (SPACE) was designed to prevent sensitization to dust mite in children at high risk. The prevention programme was based on the use of mite allergen impermeable mattress encasing [14] and health education. The aim was to test the effectiveness of intervention measures, which were simple to implement, inexpensive and socially acceptable in a variety of different climates, cultures and lifestyles. Children were therefore selected in three European countries. This report evaluates the effect of preventive measures on HDM sensitization in school children aged 5–7 years.

Hypothesis

It is possible to prevent the development of sensitization to HDM in atopic school age children, who are not HDM sensitive at enrolment, by simple dust mite-avoidance measures.

Methods

Design

A prospective, randomized controlled, single blind study was carried out to evaluate the effect of simple HDM avoidance measures on the development of sensitization to HDM in children aged 5–7 years. Participating Centres were the Isle of Wight in the United Kingdom (UK), Athens in Greece and Kaunas in Lithuania. The protocol was written in consultation with, and with the agreement of, all the participants. The protocol, questionnaires and manual on procedures, e.g. skin prick test (SPT), were written in English and translated into the national languages. The study procedures were similar and comparable between the centres. Approval of the local ethics committee was obtained in each centre. Parents or legal guardians gave informed consent for participation in the study.

Selection criteria for high-risk children

The subjects were children aged 5–7 years, with an atopic family history and sensitization to one or more common aeroallergens on SPT, in the absence of sensitization to HDM.

Recruitment

Recruitment took place over a 12-month period, from June 1997 to June 1998. Although each country had a slightly different way of approaching the parents, and the response rate was variable depending on the local set-up, the overall study procedures remained the same. A screening questionnaire was used to determine the atopic risk of the child by asking about the history of allergic disease (asthma, eczema and hayfever) in the parents and siblings. In children with a positive family history of atopy, allergic sensitization was determined by SPT to common allergens.

Skin prick test

SPT was carried out by trained members of staff under the supervision of a physician using standardized equipment and technique [15]. At least one member from each centre was trained in the procedure at the co-ordinating centre, using practical demonstration and videotape. Uniformity of the procedure was also ensured by exchange of staff between the participating centres throughout the recruitment period. Standardized allergen extracts (ALK Scherax, Hamburg, Germany) were used. Positive (histamine hydrochloride 10 mg/mL) and negative (sodium chloride 9 g/L) controls and allergen extracts were applied to the forearm with the aid of an ALK prick needle (ALK Scherax). The weal reaction was read at 15 min. The largest diameter and the diameter perpendicular to this were measured by means of a transparent ruler and the arithmetic mean was calculated. A positive test required a mean weal diameter of at least 3 mm larger than the negative control or alternatively, a weal diameter of at least 2 mm larger than the negative control and an allergen weal to histamine weal ratio equal to or larger than 0.5. For records, the weal borders were also marked with a pen and the circle was transferred to paper using a transparent strip. Three core allergens – HDM (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), six grass mixtures and cat dander – were used in all centres. Additional allergens tested were: UK (tree pollen and dog), Lithuania (birch pollen) and Greece (parietaria and olive). Sensitization to a dust mite allergen required a positive test to *Dermatophagoides pteronyssinus* (*D pt*) or *Dermatophagoides farinae* (*D f*). However, data were also analysed using any reaction size to HDM.

Study population

The random allocation was based on the day of the first contact with the child and the parents according to a block randomization of a 2-week period. All children approached during sets of 2-week periods, randomly determined by the co-ordinating centre, were allocated to the prophylactic or control group, if found eligible. The parents of participants were informed of the rationale behind the study. They were also informed that there would be two groups taking part in the study, equally at high risk, but following different advice. However, as control parents did not receive a placebo mattress cover, they might have been able to detect that their children belong to the control arm. The assessors remained blind to the study allocation of the children. The study is therefore defined as single-blind.

A questionnaire detailing reported allergic disorders (ever asthma, ever eczema, ever hayfever) in the child was completed at this stage. The questions had been validated in large cohort studies (International Study of Asthma and Allergy in Children and German Multi-centre Atopy Study) [16, 17]. Information was also obtained on the environmental risk factors relevant to the development of allergic disorders, such as exposure to cigarette smoke, presence of pets and household conditions.

Prevention measures

Both groups were told that some 'measures' were being employed. Once the child was randomiszed, the study staff handed out the written explanation of measures assigned to the respective group, with identical cover page. The information leaflets were initially written in English and then translated into Greek and Lithuanian.

Prophylactic groups

Environmental measures primarily focused on anti-dust mite procedures. The mattress on the child's bed and on any other bed in the same room was encased in an allergen-impermeable

cover (ACb®, Dr Beckmann GmbH, Seefelden, Germany), provided by the study staff. Additionally, children were discouraged from sleeping in, or playing on, beds that were not covered, and to avoid sleeping in the bottom bed of a bunk bed.

Advice was also given to remove the carpet from the child's room and to select curtains, which could be hot washed. Hot washing of soft toys and bedding (weekly), as well as of pillows and bedding, was recommended to kill the mites (alternatively soft toys could be frozen 3 days a week). It was recommended that the child's room should be ventilated whenever possible. The use of a damp cloth was advised when dusting, and vacuum cleaning to be done once a week in the absence of the child. Storage of toys, books and clothes was recommended in cupboards, so they did not collect dust. Smoking was discouraged in the house, as well as pets. If pets were present they were not allowed in the child's bedroom. Home visits were made by a health professional, to give on-site advice appropriate to the conditions found in each home. Compliance with the preventive measures was reinforced and checked by standardized interview during the household visits at 6 months. Major deviations from the recommendations were noted.

Control group

The booklet given to control group children contained information about the study and general information about allergy and allergic disorders. The booklet also contained advice given routinely for high-risk children in each country. This included avoidance of exposure to pets in the child's bedroom, which should be well ventilated, and avoidance of smoking in the presence of the child. At 6 months a reminder was sent to inform study personnel if the family intended to move in the near future.

Follow-up

After 12 months, the parents and their child attended the clinic for completion of a standardized questionnaire, similar to the one completed at the beginning of the study, seeking information on the presence of allergic symptoms/disorders during the last 12 months. Detailed information on pet ownership, smoking in the home and ventilation and heating of rooms was obtained. The prophylactic group also completed questions on the use of mattress encasing and other intervention measures and received another home visit from the health professional for assessment of compliance. Development of sensitization to HDM was evaluated with SPT performed by personnel blinded to the group allocation.

Analysis

The primary outcome measure was the development of sensitization to HDM during the period of follow-up. The secondary outcome measure was the number of wheezy children at randomization and at follow-up. The expected cumulative incidence of sensitization in the control group was 30% over a 3-year period (total planned duration of follow-up). With 120 children in each group, a threefold reduction in sensitization (expected incidence in the prophylactic group, 10%), could be detected at the 5% level of significance with 80% power.

All data were double entered in each centre on the Epi-Info database program. Data were then transferred by e-mail to the central data facility, where complementary data checks were performed. Following the intention-to-treat principle, all randomized children were included in the analysis regardless of their compliance

All data analysis was performed using the statistical analysis program SPSS for Windows 9.0 (SPSS, Chicago, IL, USA). Proportional data were cross-tabulated and compared using chi-square test for two-sided significance. The education of the parents was grouped: medium level = finished school at age 18; high level = university. Birth weight was grouped as low (< 2.5 kg) or normal (≥ 2.5 kg). The logistic regression model was created with HDM sensitization as the dependent variable, risk factors showing trends for significance ($P < 0.2$) on univariate analysis as factors and country of origin as covariate. Stepwise backward (likelihood ratio) logistic regression was used.

Results

A total of 11 140 children were initially approached but the majority was excluded due to various reasons, so that 242 children were randomized to prophylactic and control groups (Fig. 1). The two groups were similar in demographic characteristics (age, sex), family history of asthma and environmental risk factors (Table 1). Twenty-nine children were lost to follow-up and 213 (88%) children were assessed at 1 year (Fig. 1).

Compliance with the main preventive measure (mattress covers) was good. For example, 109 (93%) children slept on the covered mattresses all or most of the time: all the time = 88 (75%); most of the time = 21 (18%). In the prophylactic group, 84 (72%) opened the windows at least once a day and 33 (28%) removed the carpet. The respective figures for the control group were 67 (70%) and 9 (9%). Advice on pets was not heeded. Although 21 (18%) prophylactic homes gave up pets during the 12 months, 24 (21%) acquired a new pet. Corresponding figures for the control group were 6 (6%) and 17 (18%), respectively.

We included all randomized children where data at 1 year were available, irrespective of the compliance (intention to treat analysis). Twelve children developed sensitization to HDM, four in the UK and eight in Lithuania (Table 2). In Greece, no child was sensitized, irrespective of the group allocation. Three of 117 (2.56%) in the prophylactic group and 9 of 96 (9.38%) in the control group developed HDM sensitization. The difference was statistically significant (OR: 0.25, CI: 0.07–0.97, $P = 0.04$). Fifteen children (95% CI: 7–160) needed to be treated to prevent sensitization in one child.

Mean skin weal size to HDM in all children was generally lower in the prophylactic group. For *Der f*, the mean (SD) in the prophylactic group was 0.03 mm (0.16), whereas in the control group, it was 0.27 mm (0.82). The difference was highly significant ($P = 0.004$, Mann–Whitney *U*-test). For *Der pt*, the mean (SD) in the prophylactic group was 0.09 mm (0.49), whereas in the control group, it was 0.26 mm (0.87). The difference failed to reach statistical significance ($P = 0.08$, Mann–Whitney *U*-test). Seven of 117 (6.00%) children in the prophylactic group had positive reaction of any size to HDM in the prophylactic group, compared with 16 of 96 (16.67%) in the control group (OR: 0.32, CI: 0.13,0.81; $P = 0.01$).

Country of origin had a profound effect on the risk of developing HDM sensitization: UK = 4/31 (12.90%); Greece = 0/93 (0%); Lithuania = 8/89 (9.00%) ($P = 0.005$). To obtain an

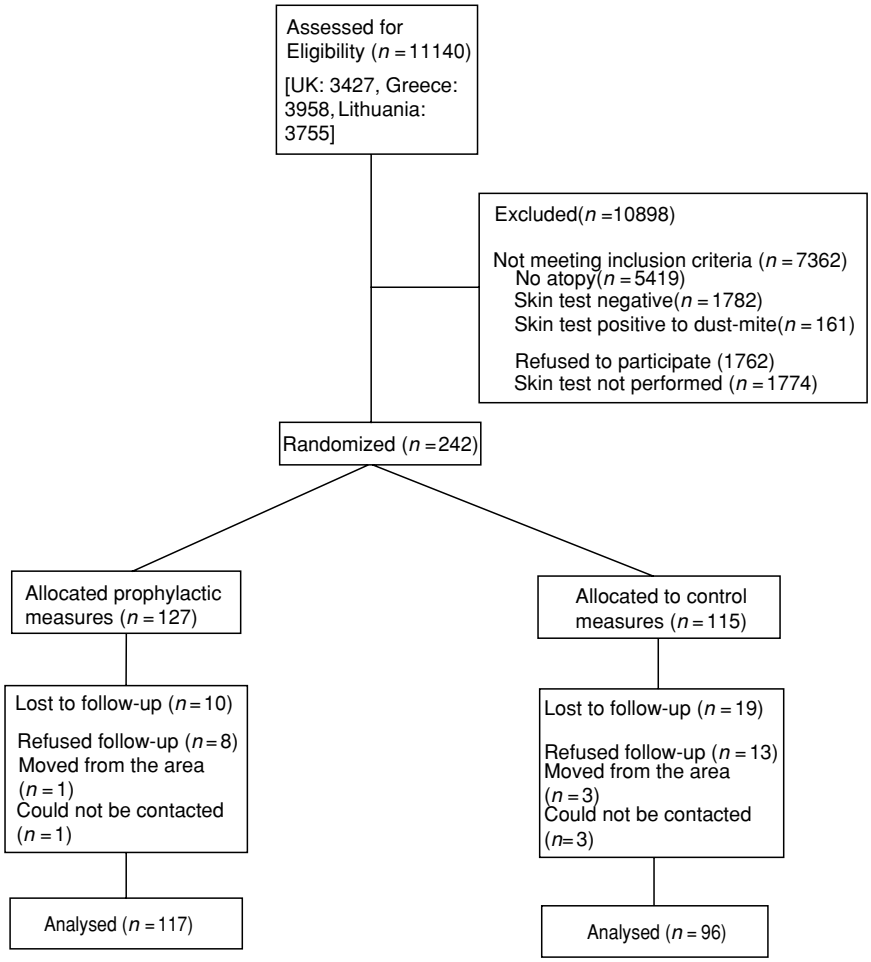

Fig. 1. Recruitment of the cohort of school children at high risk (sensitized to one or more common aeroallergens other than dust mite) of developing sensitization to dust mite.

independent effect of intervention measures, logistic regression analysis was carried out (Table 3). At randomization, asthma in the child was not an exclusion criteria, and therefore this was entered into the model in addition to other confounders. Prophylactic measures showed an independent effect in preventing sensitization to HDM (OR: 0.14, CI: 0.03–0.79, $P = 0.03$; Table 4). Asthma in the child at randomization and country of origin were also highly significant but none of the other potential risk factors reached statistical significance.

In the prophylactic group, 30 (23.62%) children reported current (in the last 12 months) wheezing at randomization and 28 (22.05%) at 12 months follow-up. However, in the control group more children were wheezing at 12 months follow-up (29, 25.22%) than at randomization (23, 20%). Of 30 wheezy children in the prophylactic group at randomization, 14 (46.66%) had stopped wheezing at 12 months, whereas in the control group only 5 of 23 (21.74%) had stopped wheezing (OR: 0.32, CI: 0.09–1.08; $P = 0.09$).

Discussion

The effect of reducing exposure to HDM allergen in subjects with asthma or other atopic diseases (secondary prevention) has been studied previously. Although some studies did not show a protective effect of HDM allergen avoidance on allergic symptoms or bronchial responsiveness, the bulk of evidence favours a beneficial effect in asthma [18, 19], eczema [20] and allergic rhinitis [21]. Primary prevention, to prevent the development of sensitization and allergic disease, has also been described, when these methods were applied to at-risk infants [12, 13]. This is the first study that specifically looks at the possibility of preventing sensitization to dust mite in high risk, school age children by allergen avoidance.

At randomization, children were required to be sensitized to aeroallergens (other than HDM), to ensure selection of an atopic population with a high risk of HDM sensitization during the follow-up period. This would increase the likelihood of showing a difference between the two groups and reduce type 2 error. Moreover, we have previously shown that school age children are more sensitive to the level of exposure to HDM if they are sensitized to non-dust mite aero-allergens[10]. Both groups were balanced at randomization (Tables 1 and 2).

Although the attrition rate was low, as 88% of randomized children were seen and skin prick tested at 1 year, there was a greater loss to follow-up in the control group. This makes final analysis difficult and somewhat presumptive. It is also argued that a 3- or 2-mm cut-off is arbitrary and SPT reaction of any size indicates sensitization (although it may not be of clinical significance). To investigate whether the intervention has

Table 1. Demographic and other characteristics of prophylactic and control group children. There were no statistically significant differences between the groups

	Control group % (*n*/total *n*)	Prophylactic group % (*n*/total *n*)
Male sex	59.1 (68/115)	60.6 (77/127)
Family history of asthma		
Maternal	10.9 (12/110)	7.1 (9/126)
Paternal	7.4 (8/108)	5.6 (7/127)
Sibling	14.5 (16/110)	14/5 (17/117)
Other risk factors		
Low birth weight	9.6 (11/114)	5.5 (7/127)
Never breast fed	18.3 (21/115)	15.7 (20/127)
Open fireplace	21.7 (25/115)	17.3 (22/127)
Carpet child bedroom	80.0 (92/115)	85.8 (109/127)
Visible mould in the house	30.7 (35/114)	26.8 (34/127)
> four people in the house	38.3 (44/115)	27.6 (35/127)
Floor child's bedroom is on		
Ground or first	32.17 (37/115)	36.2 (46/127)
Second or third	33.91 (39/115)	32.28 (41/127)
Fourth or higher	33.91 (39/115)	31.50 (40/127)
Smoking in the house	38.3 (44/115)	39.7 (50/126)
Pets (cat and/or dog)	29.8 (34/114)	37.6 (50/126)
University education, mother	41.6 (47/113)	34.7 (43/124)
University education, father	45.9 (50/109)	34.1 (42/123)
Age at randomization		
Mean (95% confidence intervals)	6.61 (6.36–6.82)	6.72 (6.56–6.88)

Table 2. Baseline atopic features of children in the prophylactic and control groups

	Control group $n = 115$ % (*n*)	Prophylactic group $n = 127$ % (*n*)
Atopic diseases		
Ever asthma	23.5 (27)	19.7 (25)
Ever hayfever	17.4 (20)	21.3 (27)
Ever eczema	32.2 (37)	33.1 (42)
Ever (asthma, eczema or hayfever)		
One disease	33.0 (38)	33.1 (42)
Two diseases	14.8 (17)	15.7 (20)
All three diseases	3.5 (4)	3.1 (4)
Positive skin prick test		
Cat	46.1 (53)	48.0 (61)
Grass pollen	52.2 (60)	52.0 (66)
Additional allergen I	30.4 (35)	34.6 (44)
Additional allergen II	11.3 (7)	16.7 (12)
One or more		
One allergen	72.2 (83)	66.9 (85)
Two allergen	21.7 (25)	24.4 (31)
$\geq$ Three allergens	6.1 (7)	8.7 (11)
Mean weal sizes	Mean (95% CI)	Mean (95% CI)
Cat	1.50 (1.18–1.82)	1.74 (1.36–2.11)
Grass pollen	1.74 (1.42–2.05)	1.79 (1.47–2.11)
Additional allergen I	0.93 (0.65–1.20)	1.07 (0.81–1.34)
Additional allergen II	0.46 (0.10–0.82)	0.49 (0.22–0.77)

Additional allergens I: UK (tree pollen), Lithuania (birch pollen) and Greece (parietaria). Additional allergens II: UK (dog) and Greece (olive); control $n = 62$, prophylactic $n = 72$.

Table 3. Development of sensitization to house dust mite (*Derp* and/or *Derf*) in the control and prophylactic groups in each country and in the whole cohort

	UK		Greece		Lithuania		Total cohort			
	Cont	Pro	Cont	Pro	Cont	Pro	Cont	Pro	Significance OR (95% CI)	*P*
Children seen at 1 year: *n*	15	16	43	50	38	51	96	117		
Sensitized to dust mite: *n* (%)	3 (20.0)	1 (6.25)	0	0	6 (15.79)	2 (3.92)	9 (9.38)	3 (2.56)	0.25 (0.07, 0.97)	0.04

Cont = control group; Pro = prophylactic group; OR = odds ratio; 95% CI = 95% confidence interval.

down-regulated the development of HDM sensitization, mean weal size was compared between the groups. This confirms that the mean weal size was smaller in the prophylactic group and a statistically significant difference was observed when weal of any size was evaluated.

During the recruitment phase, it was observed that sensitization to HDM, in those with a history of allergy in the family, was relatively low in the Greek (2.2%) and Lithuanian (3.3%) children, compared with the UK (28.8%). However, in the high-risk population included in the study, 8% of children in Lithuania developed sensitization to HDM and 13% in UK, but none in Greece, effectively reducing our study sample from 242 to 130 (Table 2). This had contributed to the marginal statistical significance observed, despite a 3.5 times lower incidence of HDM sensitization rates in the prophylactic group. The logistic regression model was therefore adjusted for the country, which confirmed a highly significant independent effect of the country, in addition to a consistent effect of the prophylactic measures. From the data collected, we are unable to comment on why high-risk children in Greece did not develop sensitization to dust mite, but this is an interesting finding and should be investigated further.

A number of methods to reduce exposure to HDM have been investigated. These include removal of carpet, encasing mattress and bedding in HDM-impermeable coverings, reduction in humidity with mechanical ventilation, special vacuum cleaning systems, air cleaning devices, various acaricidal chemicals and so on. Not all methods for mite allergen reduction work [22–24]. Encasing the mattress seems to be the most effective way of reducing exposure to HDM and improving

Table 4. Adjusted odds ratio and 95% confidence interval to show the effect of prophylactic measures and other risk factors on the development of house dust mite sensitization at 12 months (logistic regression analysis)

Variable	Adjusted OR (95% CI)	*P*
Prophylactic group	0.14 (0.03–0.81)	0.03
Paternal asthma	6.15 (0.74–51.31)	0.09
Child ever had asthma	18.58 (2.88–119.71)	0.002
Child ever hospitalized	1.53 (0.33–7.13)	0.59
Visible mould in the house	2.25 (0.51–10.05)	0.29
Four people in the house	3.54 (0.78–16.18)	0.10
Pets (cat and/or dog)	0.70 (0.14–3.41)	0.66
Country	0.11 (0.02–0.52)	0.006

OR = odds ratio; 95% CI = 95% confidence interval. A number of other factors were included into the model but were non-significant and did not improve the fit of the model. These included maternal and sibling asthma, low birth weight, never breast fed, open fireplace, carpet in the child's bedroom, smoking in the house, parental education.

symptoms of asthma [14, 19], and it is probably one of the simplest to implement. Dust impermeable covers have been shown to reduce exposure not only to dust mite, but also to other indoor allergens [25]. Unfortunately, at 12 months follow-up, skin prick tests were done only to house dust mite. It is therefore difficult to comment on any preventive effect the covers may have had on sensitization to other allergens.

We did not measure dust mite allergen levels in the homes and therefore can not say if indoor allergen levels were reduced by preventing measures. However, our primary intervention was dust mite-impermeable mattress covers, which is to a large extent independent of allergen levels. Preventive measures have to be simple and inexpensive if they are to be recommended for widespread use. We therefore focused on the use of mattress covers. Compliance with the use of mattress covers was high, but supplementary measures, such as increased ventilation (regular opening of windows), removal of carpet, etc. were not different between the groups. Our data therefore suggest that encasing mattresses in appropriate covers can prevent the development of sensitization in atopic children at high risk.

A diagnosis of asthma at randomization was closely associated with the development of sensitization to HDM (Table 3). This is likely to be due to genetic factors. Although all children at randomization were atopic (positive SPT to an aeroallergen), those with asthma probably had a higher genetic predisposition and therefore were more likely to develop subsequent sensitization to HDM. Conversely, allergy to HDM is said to be the most important risk factor for the development of asthma in large parts of the world [26]. In such regions, prevention of HDM allergy may therefore protect against asthma. The follow-up in this study so far is too short to prove or disprove this hypothesis.

Cross-sectional and prospective studies [27, 28] have supported the hypothesis that exposure to HDM causes asthma. However, a recent prospective study [11] failed to show any relationship between exposure to HDM and the development of asthma, although, association between HDM exposure and sensitization was confirmed. Our study shows that reduction in exposure to HDM allergen can reduce the development of sensitization in at-risk children. Whether the development of asthma can also be prevented needs longer follow-up.

Only 2% of the population of school children were eligible for prophylactic measures, reducing the generalizability of the study. This figure, however, would probably be much higher for children attending an asthma or allergy clinic. The information needed (family history of atopy and SPT to aeroallergens) to select children for the intervention is routinely obtained at these clinics. Is it worth recommending mattress covers and simple HDM avoidance measures for children found to be at risk? The intervention is simple and relatively inexpensive but the number needed to prevent sensitization in one child is fairly high ($n = 15$). Further follow-up will clarify the situation. If the benefit continues and the ratio falls to, for example, 1 to 5, it might be something worth recommending.

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