

Randomized Trial to Prevent Sensitization to Mite Allergens in Toddlers and Preschoolers by Allergen Reduction and Education

One-Year Results

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Objective: To evaluate the effectiveness of prevention measures against dust mite sensitization.

Design: European (England, Germany, Greece, Lithuania) multicenter prospective single-blind randomized control trial with a follow-up of 12 months.

Participants: Toddlers and preschoolers, with at least 1 parent with atopic symptoms and sensitization, who initially were not sensitized to mite allergens.

Interventions: A combination of education and a simple preventive measure (mattress encasement) to reduce mite allergen exposure.

Setting: Community-based study.

Main Outcome Measures: Sensitization to mite allergens (skin-prick test or specific immunoglobulin E).

Results: Of 636 children (mean age, 3.1 years) included in the study, 566 (89%) participated in the first-year follow-up. The incidence of sensitization to mite allergens was 10 (3%) of 330 in the intervention vs 20 (6.5%) of 306 in the control arm, including loss of follow-up (intention-to-treat principle). Allergic symptoms were more common in sensitized than in nonsensitized children and so was the prevalence of physician-diagnosed asthma, eczema, and food allergy.

Conclusions: This simple, harmless, and inexpensive measure can be used in toddlers and preschoolers of parents with atopic disorders to reduce sensitization to mite allergens. With regard to clinical manifestations of atopy, follow-up studies are needed to determine the effectiveness of the intervention.

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THE PREVALENCE of allergic disorders in childhood is about 20% to 30% in Europe. In the last several decades, the prevalence of hay fever,¹ allergic asthma, and atopic eczema has increased.²⁻⁴ Atopic disorders share common characteristics, such as hereditary transmission, dependence on allergen exposure, childhood onset, and likelihood of progression to chronic disease. The incidence and prevalence of sensitization against inhalant allergens increase during the first decade of life.^{5,6}

For editorial comment see page 967

The best single predictor for asthma, which has the greatest effect on childhood morbidity in developed countries, is allergic sensitization to mite allergens.^{7,8} Sensitization to mite allergens commonly starts to be measurable by serum antibodies or by the skin-prick test (SPT) early in child-

hood. In a German study of 7-year-old children, of whom 3.5% had asthma and 7.5% had a diagnosis of recurrent bronchitis,⁹ a relative risk (RR) of 4.3 was determined for sensitization against mite allergens.⁶ Also, the incidence of asthmalike symptoms is related to mite sensitization.¹⁰

Besides being asthmatic, more than half of the children with atopic eczema are sensitized to mite allergens, which often exacerbates the clinical disease.^{11,12} The incidence of allergic sensitization depends on mite allergen exposure in childhood.^{6,13,14} A previous study showed that a vigorous reduction of the allergen load could have a preventive effect on sensitization.⁵ Additionally, children with a family history of atopy are most prone to sensitization.¹⁵

Following this evidence of potential risk factors, we designed an environmental intervention trial and investigated the effectiveness of simple avoidance measures, such as allergen-impermeable encasement of mattresses, for which mite allergen reductions are reported,¹⁶⁻²¹ along

with health education measures to prevent sensitization to house dust mites. The study as a whole included newborns, toddlers/preschoolers, and school-aged children of parents who had a history of atopic manifestation and thus a high atopic risk. This article reports the results in the toddlers and preschoolers after 12 months of observation.

SUBJECTS AND METHODS

The effects of reduction of mite allergen exposure on the prevention of sensitization to house dust mites and the development of allergic disease in toddlers and preschoolers (1.5-5 years of age) at high atopic risk were studied in 4 European countries (Germany, Greece, Lithuania, and England) in a randomized controlled environmental trial. The study followed the intention-to-treat principle. The study children were recruited in each country by using the National Health System Service for approach (eg, the general routine check-up of children in England, Germany, and Lithuania) or by using daycare centers (Greece).

Screening questionnaires were used to identify children at higher atopic risk by asking their parents if they themselves ever had asthma, hay fever, and eczema. The questions had been validated in large cohort studies (the German MAS and the ISAAC studies).^{22,23} Parents who had a positive questionnaire outcome were invited to undergo screening for sensitization either by SPT screening or specific IgE determination. An SPT or IgE determination was also performed in the child.

Before the parent(s) were informed about their child's test results, they received a self-administered questionnaire on demographic variables, birth characteristics of the child, the child's history of atopic and respiratory disorders, and household conditions. The question regarding parental educational attainment took different European systems into consideration and focused on years and type of education (school, university, manual training, etc). We asked about maternal smoking during the pregnancy and smoking in the household. Questions on household conditions asked about pets, carpets, and signs of molds, for example.

INCLUSION CRITERIA

We included children who (1) were local residents (migrants were excluded for ease of follow-up); (2) had a positive parental screening questionnaire result and positive parental SPT or parental IgE results; (3) were not sensitized to mite allergens at the beginning of the study (ie, had negative results on SPT or specific IgE against mite allergens); (4) and had atopic manifestations, such as bronchial asthma, hay fever, or atopic eczema.

INFORMATION AND RANDOM ALLOCATION

Parents of these children were informed about the study and asked to give their written informed consent. The study was approved by the local ethics committees of the participating institutions.

The allocation of children to the intervention and control arms was based on the day of the visit, according to a block randomization of a 2-week period. Since all parents received an educational program, the parents of participants were not made aware of the group to which they belonged, nor were the examiners in the follow-up. However, parents might have identified that only 1 group received a mattress cover. Thus, we defined the study as single-blinded.

ALLERGY ASSESSMENT

Skin-prick testing was carried out by trained staff members under the supervision of a physician, using the same equipment

and technique in all countries. The allergens *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, grass pollens, and cat dander (concentration: 10-histamine equivalent in SPT) (ALK Scherax, Hamburg, Germany) and the negative (sodium chloride, 9 g/L) and positive (histamine hydrochloride, 10 mg/mL) controls were applied to the forearm with the aid of an SPT needle. The wheal reactions were marked with a pen, and the circle was transferred to paper using a transparent strip. The largest and perpendicular diameters of each wheal reaction were measured by means of a transparent ruler, and the arithmetic mean was calculated. A positive test result required a wheal diameter of at least 3 mm larger than the negative control or, alternatively, a wheal diameter of at least 2 mm larger than the negative control and an allergen wheal to histamine ratio equal to or larger than 0.5. Sensitization to a mite allergen required a positive test for *D pteronyssinus* or *D farinae*. Alternatively, specific IgE concentrations against the same allergens were determined by the MagicLite (ML) test (Chiron Diagnostics, Fernwald, Germany). The test results were regarded as positive if values were equal to or greater than 1.43 ML units. Both approaches were compared and were found to provide identical classifications.²⁴

To assure equality of testing procedures between the different countries, at least 1 member of the staff participated in a centralized training, as did the supervising physician. During the course of the study, the conduction of SPT was controlled by site visits and monitoring in the different centers.

MEASURES OF PREVENTION, HEALTH EDUCATION, AND COUNSELING

All parents were given background information on allergies and the higher than average risk of their child to develop an allergy. A booklet on environmental influences on children's health and detailed preventive recommendations was handed out to the parents of the prevention/intervention group, with additional oral explanations if necessary. A similar booklet, without information on mattress covers, was distributed to parents of the control group. Both groups were told that some "measures" were being employed.

INTERVENTION ARM

Environmental measures primarily focused on reduction of mite allergens. The child's mattress was covered with a special dust mite-impermeable encasement (ACb; Dr Beckmann, GmbH, Seefeld, Germany) unless it had a vinyl mattress (as in England). Other mattresses in the child's room were also covered. All of this material was provided by the study. Parents were advised to discourage the child from sleeping in or playing on uncovered beds. Advice was also given to remove the carpet from the child's room and to select curtains that could be washed in hot water. Weekly washing of soft toys and bedding (as well as of pillows and blankets) in hot water was recommended to eliminate mites (alternatively, soft toys could be deep frozen for 3 days per week). Parents were advised to ventilate the child's room whenever possible. They were told to use a damp cloth when dusting and to vacuum once per week in the absence of the child. Storage of toys, books, and clothes in cupboards was recommended so they would not collect dust. Smoking was discouraged in the house, as well as pet holding. If pet holding occurred despite the recommendation, parents were advised not to allow the pet to visit the child's bedroom. In most centers, a health care visitor made a home visit at 6 months to ensure that the dust mite-impermeable encasement was in place and to repeat the instructions. In Germany, however, the use of the encasement was ascertained by questionnaire. In addition, information about the child's symptoms was obtained in all centers.

CONTROL ARM

The brief standard recommendations of the relevant health authorities in each country were reiterated. These were slightly different among the participating centers. Recommendations common to all countries were avoidance of exposure to pets in bedrooms, good ventilation of rooms, and avoidance of cigarette smoking. As in the intervention group, information about the child's atopic symptoms was obtained at the 6-month follow-up.

FOLLOW-UP INVESTIGATIONS

After 12 months, the parents and their child were invited to participate in a follow-up examination, including SPT or IgE determination and a questionnaire on symptoms (for the wording of atopic symptoms, see Table 4). The SPT (England and Greece) or IgE determination (Germany and Lithuania) was blinded.

STATISTICAL ANALYSIS

The data were entered at each facility and then sent to the data center to be checked for consistency. EPI-INFO (Centers for Disease Control and Prevention, Atlanta, Ga) was used for data entry, as this tool was available in all centers, and SAS (SAS Institute, Cary, NC) was used for data analyses.²⁵

Following the intention-to-treat principle,^{26,27} we included all randomized children in the arms in which they were randomly assigned, regardless of their compliance and regardless of subsequent loss of follow-up. To compensate for the loss of follow-up, we applied 2 approaches: we assumed that (1) all participants lost to follow-up acquired an allergic sensitization to mite allergens (SPT or IgE); and (2) all participants lost to follow-up did not develop an allergic sensitization (SPT or IgE).

The LOGIST procedure of the SAS was used to estimate the crude and adjusted RRs. We controlled for potential confounding of environmental factors despite randomization. We included information from the initial questionnaire on individual characteristics (sex, low birth weight), smoking of the parents (during pregnancy and in the household), and housing conditions (pets, molds, carpets) as sources of antigens. The education of the parents was grouped as low level (finished school before age 18 years), medium level (finished school at age 18 years or later with and without theoretical education), or high level (college/university degree). The education of the parents was grouped as medium level (finished school at age 18 years or later with and without theoretical education) or high level (university). Confounders were excluded if they were only weakly associated with sensitization ($RR \geq 1.1$ or $RR \leq 0.9$) in the crude analysis or if they did not change the association between intervention and sensitization by more than 10%.²⁸ Additionally, we statistically controlled for the effect of the centers in all models. To verify that the randomization was effective, we also compared the prevalence of symptoms and of household conditions in the intervention and control arms.

RESULTS

Between May 1997 and May 1998, we recruited 636 toddlers and preschoolers (**Figure 1**). On average, 7.7 families had to be screened per 1 child included (636/4871). Three hundred thirty children were randomly allocated to the intervention group and 306 to the control group.

Regarding parents' characteristics or child's asthma, with the exception of education, there were no impor-

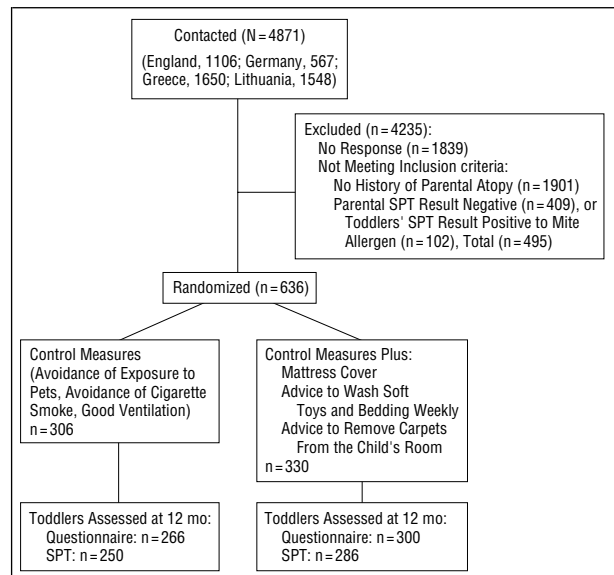


Figure 1. Profile of the trial of primary prevention of asthma in high-risk toddlers and preschoolers. SPT indicates skin-prick test.

tant initial differences between the centers and the 2 arms (**Table 1**). Compared with the other centers, more parents from the Isle of Wight (England) finished school before age 18 years ($P < .001$). However, there was no statistical difference between the intervention and control arms. After 12 months, for 90.9% of the children in the intervention and 86.9% of those in the control arm, questionnaires were returned (Table 1). Participation was lower in the Lithuanian sample. Fewer children participated in the SPT/IgE determination but the proportion did not show statistically significant differences between the control and intervention arms.

When assuming that all participants lost to follow-up had no allergic sensitization, 20 children (6.5%) in the control and 10 (3.0%) in the intervention group developed sensitization to mite allergens after 1 year (**Table 2**, $P = .04$ for the crude association). When assuming that all participants lost to follow-up developed a sensitization, the incidence of allergic sensitization to mite allergens was 24.8% for the control and 16.4% for the intervention group ($P = .008$ for the crude association). The difference showed up in all centers, with the exception of the Isle of Wight center. The samples from the individual centers are too small to gain statistical significance.

After adjusting for necessary confounding variables, we found that the control group was at significantly higher risk than the intervention group for sensitization at 12 months (**Table 3**). The presence of pets was the only confounder that had to be controlled for.

A comparison of atopic manifestations in children with and without sensitization to mites can emphasize the clinical significance of the SPT/specific IgE determination. The prevalence of clinical manifestations is available for the 566 children who participated in the 12-month follow-up. Children with sensitization had a higher prevalence of symptoms of asthma and eczema (**Table 4**) and a higher prevalence of reported physicians' diagnoses of food allergy and asthma (**Figure 2**).

Our hypothesis was that allergen avoidance measures reduce allergic sensitization. In this environmental prospective randomized controlled trial, it was found that after 1 year of introduction of dust mite avoidance measures, the incidence of sensitization to mite allergens (primary outcome variable) was 3% in the intervention group vs 6.5% in the control group. The RR of the preventive measures was 0.36 (95% confidence interval, 0.16-0.83).

To increase the efficacy, participation, and compliance of the study, we included only toddlers and preschoolers at high risk of atopy. It was required that 1 parent have a history of asthma, atopic eczema, or hay fever, and that at least 1 parent was sensitized (positive SPT or specific IgE results) to one of the common allergens tested. We were interested in new cases of sensitization to mite allergens and excluded all children whose SPTs were positive for *D pteronyssinus* or *D farinae* in the initial screening. When we planned the study, we purposely chose

countries in which the incidence of house dust mite sensitization would vary. However, we were surprised that the Greek sample had such a low incidence (total of 2 cases in the control arm, Table 2).

To our knowledge, only 2 other prospective randomized trials on the prevention of sensitization have been published. A clinical trial on house dust mites and food allergen avoidance in newborns, conducted in Isle of Wight, showed a reduction in the incidence of both positive SPTs for house dust mites and eczema at ages 1, 2, and 4 years in the intervention group.^{5,13,29} We followed the selection criteria of high-risk children in this study and included parents with a history of atopy (asthma, eczema, hay fever). A recently published trial on the prevention of asthma in newborns from Canada focused on asthma as the selection criterion.³⁰ This study did not report a reduction in sensitization; however, it reported a reduction in the incidence of asthma in newborns. A third ongoing trial in newborns, which has not yet published clinical outcomes, showed a reduction of the mite allergen concentration on encased mattresses of about 95%.³¹

Table 1. Characteristics of the Participating Groups and Proportion of Participation in the Initial Examination*

Characteristics	Isle of Wight, England		Freiburg, Germany		Athens, Greece		Kaunas, Lithuania		Total	
	Intervention (n = 58)	Control (n = 51)	Intervention (n = 53)	Control (n = 38)	Intervention (n = 151)	Control (n = 152)	Intervention (n = 68)	Control (n = 65)	Intervention (n = 330)	Control (n = 306)
Mean age of the child, y	2.4	2.2	2.62	2.85	3.3	3.2	3.6	3.5	3.1	3.1
Boys, %	53.5	58.8	39.6	63.2	57.6	47.4	58.8	61.5	54.2	54.3
Mean age of mother at the time of child's birth, y	29.8	28.4	29.3	29.2	30.2	30.0	25.8	26.0	29.1	28.7
Mean age of father at the time of child's birth, y	34.0	31.9	32.5	32.5	33.8	33.5	27.6	27.4	32.3	31.9
Education, %, y										
Mother										
Low	67.2	64.7	32.1	13.6	11.9	13.8	16.2	24.6	25.7	24.5
Medium	27.6	25.5	54.7	57.9	39.7	51.3	44.1	38.5	40.9	45.1
High	3.5	7.8	13.2	29.0	48.3	34.9	39.7	36.9	33.0	33.1
Father										
Low	67.2	56.9	52.8	50.0	15.2	24.3	22.1	29.2	31.8	34.0
Medium	15.5	29.4	18.9	10.5	33.1	32.2	38.2	30.8	28.8	28.8
High	13.8	9.8	28.3	39.5	51.0	43.4	36.8	38.5	37.9	36.3
Child, ever asthma, %	20.7	19.6	0.0	0.0	17.9	15.8	2.9	7.7	12.4	12.8
Child, ever wheezing, %	46.6	43.1	28.3	31.6	37.1	50.7	38.2	33.9	37.6	43.5
Children participating in the questionnaire, %	100	96.1	100	97.4	94.0	89.5	69.1	67.7	90.9	86.9
Children participating in the SPT or IgE determination, %	94.8	96.1	100	92.1	87.4	82.2	67.7	63.1	86.7	81.7

*SPT indicates skin-prick test values in parentheses in column headings indicate the initial number of children.

Table 2. Crude Incidences in the Different Countries in the 12-Month Observation Period

Crude Incidences	Isle of Wight, England			South-Baden, Germany		
	Intervention (n = 58)	Control (n = 51)	P Value	Intervention (n = 53)	Control (n = 38)	P Value
Incidence of allergic sensitization to mite allergen in the 12-month observation, assuming all participants lost to follow-up have no allergic sensitization, %	8.6	7.8	.88	3.8	10.5	.20
Incidence of allergic sensitization to mite allergen in the 12-month observation, assuming all participants lost to follow-up developed an allergic sensitization, %	13.8	11.8	.75	3.8	18.4	.02

*Values in parentheses in column headings indicate the initial number of children.

Overall, regarding mite allergen avoidance, Custovic et al³² listed 28 studies of patients who either had asthma, allergic rhinitis, or atopic eczema. A variety of measures were applied, including insecticides, regular vacuum cleaning, air filtration, ionizers, and plastic and semipermeable mattress covers. With encasement of mattresses, a significant reduction of the allergen load was reported for different age groups of patients.¹⁶⁻²¹ We did not assess allergen load, but rather investigated the clinical outcomes related to allergen-impermeable mattress covers and other mite allergen avoidance measures.

The benefits of mite allergen avoidance for the prevention of sensitization have only been assessed in newborns. This is the first report, to our knowledge, that avoidance seems to be effective in toddlers and preschoolers. We had to recruit 4871 families to select 636 children at higher risk of atopy (7.7 parents per selected child). In a Canadian randomized trial in newborns, 6.8 women who were registered to give birth were screened to select each newborn recruited for the intervention program.³⁰ One thousand one hundred sixteen families were screened to include 120 children at risk of atopy whose parents agreed to follow the stringent allergen-avoidance methods applied in the Isle of Wight intervention study (10.7 families per selected child).^{5,13}

Some variables showed differences in the distribution between control and intervention arms within 1 country and others between centers (eg, education, Table 1). However, in total, all confounders except 1 could be removed from the explanatory model. This reassured us that random allocation was effective. Additionally, preceding symptoms of the child and parental variables were not unequally distributed in the intervention and control arms (Table 1). The only other predictor, which was confounding and showed a significant association with the incidence of sensitization, was the presence of a pet in the home, ascertained in the initial survey (Table 3). There was no important initial difference in holding the pet; 29.4% of the households in the control arm and 31.8% in the intervention arm had a pet. This proportion was higher in children in England (54.9% vs 65.5%) but not significantly different, and lower in children in Greece (19.4% vs 21.9%). Additionally, there was a difference in the incidence of sensitization between these 2 countries. Thus, joint confounding of country and pets in the household, which could not be removed by randomization, might explain why pet holding had to remain in the model. It is known that cat allergens remain suspended in the air for

extended periods even after removal of the cat from the home, taking 12 to 16 weeks to fall below the levels triggering asthma.³³ Data from areas with low sensitization to mite allergens show that sensitization to domestic animals has the strongest association with asthma.³⁴

All parents received advice and a booklet about the prevention of asthma. However, we cannot exclude that parents of a child who did not receive a mattress cover may have known their child was in the control group. For this reason, we did not investigate symptoms but focused on SPT or IgE results that could not be influenced by parental information. Nevertheless, the association between sensitization and clinical manifestations emphasizes the clinical significance of sensitization and its prevention. Symptoms of asthma and eczema were 2 to 3 times more common in sensitized than in nonsensitized children, and the prevalence of asthma and food allergy was higher, according to doctors' diagnoses (Table 4, Figure 2).

We have demonstrated that a multifaceted intervention program focused on encasement of mattresses

Table 3. Crude Incidence (%) and Crude and Adjusted Relative Risk (RR) for Sensitization to Mite Allergens in the First Year of Observation*

	Crude Incidence	Crude RR (95% CI)	Adjusted RR (95% CI)†‡
Intervention arm, n = 330	3.0	0.45 (0.21-0.97)	0.36 (0.16-0.83)
Individual characteristics			
Boys (n = 345)	5.5	1.48 (0.69-3.17)	...
Low birth weight (<2500 g) (n = 38)	10.5	2.59 (0.85-7.83)	...
Smoking habits			
Maternal smoking during pregnancy (n = 89)	4.5	0.94 (0.32-2.76)	...
Smoking in the household (n = 262)	4.2	0.82 (0.38-1.75)	...
Housing conditions			
Ever had a pet since the start of the study (n = 195)	8.7	3.26 (1.52-6.96)	2.84 (1.11-5.57)
Carpet in the living room (n = 596)	4.7	0.89 (0.20-3.87)	...
Carpet in child's bedroom (n = 564)	4.3	0.48 (0.19-1.22)	...
Mold reported (n = 166)	4.8	1.03 (0.45-2.35)	...

*CI indicates confidence interval; ellipses, not applicable.

†Adjusted for "ever had a pet," intention-to-treat, and country.

‡All dropouts (16%) are considered negative (no incidence of allergic sensitization).

Athens, Greece			Kaunas, Lithuania			Total		
Intervention (n = 151)	Control (n = 152)	P Value	Intervention (n = 68)	Control (n = 65)	P Value	Intervention (n = 330)	Control (n = 306)	P Value
0	1.3	.17	4.4	15.4	.03	3.0	6.5	.04
12.6	19.1	.12	36.8	52.3	.07	16.4	24.8	.008

Table 4. Association Between Symptoms and New Sensitization to Mite Allergen at the 12-Month Follow-up

	No Sensitization (n = 536)	Sensitization to Mite Allergens (n = 30)	P Value†
Has your child had wheezing or whistling in the chest in the last 12 months?	23.5	50.0	<.001
How many attacks of wheezing has your child had in the last 12 months?			
1-2	13.4	23.3	.006
3-12	8.6	23.3	
>12	1.1	0	
In the last 12 months, how often on average has your child's sleep been disturbed due to wheezing?			
<1 night per week	6.5	6.7	.12
≥1 night per week	3.2	10.0	
In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only 1 or 2 words at a time between breaths?	2.6	6.7	.19
In the last 12 months, has your child's chest sounded wheezy during or after exercise?	7.3	13.3	.22
In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?	24.3	40.0	.05
Has your child had an itchy rash at any time in the last 12 months?	28.9	60.0	<.001
Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?	21.8	50.0	<.001
Has this rash cleared completely at any time during the last 12 months?	22.6	36.7	.004
In the last 12 months, how often, on average, has your child been kept awake at night by this itchy rash?			
<1 night per week	4.5	16.7	<.001
≥1 night per week	2.2	16.7	

*Data are given as percentage of positive responses.

†Obtained by χ^2 analysis.

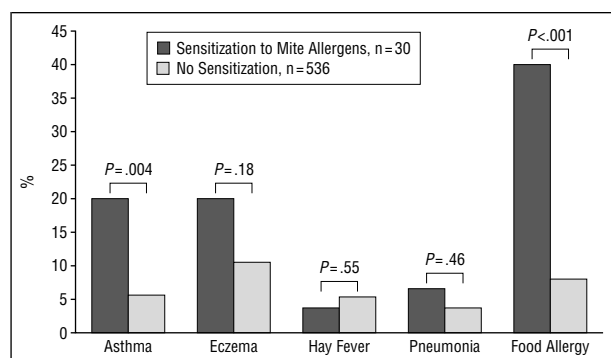


Figure 2. Association between reported physicians' diagnoses and new sensitization to mite allergen.

reduced the incidence of sensitization to mite allergens in high-risk children. The intention of the study was to test effectiveness. For this purpose, we focused on toddlers/preschoolers who were at higher risk, which limits generalizability to all children aged 1.5 to 5 years. However, we assume that our finding offers evidence that reducing exposure to house dust mite allergen also reduces the risk of developing sensitization in toddlers and preschoolers. All applied measures offer a simple and effective approach to the reduction of mite allergen exposure in children at high atopic risk. It is important to determine if prolonged avoidance of mite allergens can produce a sustained primary preventive effect on sensitization and a secondary preventive effect in sensitized children by lowering the occurrence of symptoms.

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What This Study Adds

Very few trials have attempted to establish asthma-prevention methods in children. Sensitization to dust mite allergens is a major risk factor for the development of asthma. We conducted a randomized trial to determine whether the use of allergen-impermeable mattress covers and parental education reduces the risk of allergic sensitization to mite allergens in children between 1.5 and 5 years of age. The incidence of sensitization was statistically significantly lower in the intervention arm (3%) than in the control arm (6.5%). This finding suggests that a simple program of prevention measures in childhood may reduce the risk for later development of asthma.

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