

Placebo-controlled Trial of House Dust Mite-impermeable Mattress Covers

Effect on Symptoms in Early Childhood

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We investigated the effect of house dust mite (HDM)-allergen avoidance on the development of respiratory symptoms, atopic dermatitis, and atopic sensitization by performing a double blind, placebo-controlled trial. In total, 1,282 allergic pregnant women were selected (416 received HDM allergen-impermeable mattress covers for the parents' and child's mattress in the third trimester of pregnancy [active], 394 received placebo covers, 472 received no intervention). Data on allergen exposure, clinical symptoms, and immunoglobulin E were collected prospectively. The prevalence of night cough without a cold in the second year of life was lower in the group with active covers compared with the group with placebo covers (adjusted odds ratio 0.65; 95% confidence interval 0.4–1.0). No effect of the intervention was seen on other respiratory symptoms, atopic dermatitis, and total and specific immunoglobulin E. It can be concluded that application of HDM-impermeable mattress covers on the child's and parents' beds reduced night cough, but not other respiratory symptoms, atopic dermatitis, and atopic sensitization in the first 2 years of life. Follow-up will determine the long-term effect of the intervention on the development of atopic disease.

Keywords: mite control; wheezing; asthma; atopy; allergens

Several studies have shown that exposure to house dust mite (HDM) allergens is associated with mite sensitization in early childhood (1, 2) and that sensitization to HDM allergen is a strong risk factor for the development of atopic disease (3, 4). Whether there is a causal relation between exposure to HDM allergen and the development of atopic disease is controversial (5). In a prospective study, exposure to HDM allergen at 1 year of age was related to sensitization to HDM and asthmatic symptoms at the age of 11 (1). Furthermore, a cross-sectional study in infants found a positive association between levels of

HDM allergen in the home and respiratory symptoms at age 1 year (6), although other studies could not confirm these findings (7, 8). In two combined food- and indoor-allergen avoidance studies, allergen avoidance decreased the prevalence of atopic disease at the age of 1 year and sensitization to food- and inhalant allergens at age 2 years (9–11). Because various avoidance measures were taken, the specific effect of avoidance of HDM allergens could not be separated from avoidance of food allergens. In a Japanese study in infants with atopic dermatitis and food allergy but no sensitization to HDM, reduction of HDM allergen exposure significantly reduced the subsequent development of sensitization to HDM and wheezing after 1 year of follow-up (12). In a recently published primary prevention study from Manchester, UK, stringent environmental manipulations aiming at reducing HDM allergen exposure were not associated with a reduction in the prevalence of wheezing, night cough (apart from colds), and eczema in the first year of life (13). However, in the same study, a significantly lower prevalence of attacks of severe wheeze with shortness of breath, prescription of medication for wheezy attacks, and wheeze after playing was observed in the active group compared with the control group (13).

We performed a randomized, placebo-controlled study to investigate the effect of a simple HDM allergen avoidance strategy (application of HDM allergen-impermeable mattress covers), starting in the third trimester of pregnancy, on the development of respiratory symptoms, atopic eczema, and mite sensitization in children born to mothers with allergy. We now report data from the first 2 years of life.

METHODS

Approximately 10,000 pregnant women completed a validated screening questionnaire on allergic disease (14). Of 2,825 allergic women, 1,327 (47%) agreed to participate in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study and gave informed consent. Women were randomly allocated into an intervention study (IS, $n = 855$) or a natural history study (NHS, $n = 472$). In 810 of the 855 families participating in the IS, the intervention was actually applied. The remaining 45 families could not be reached or decided to withdraw from the study when application of the intervention was planned. Children were born between May 1996 and December 1997. The study was approved by the local medical ethics committees.

The 810 remaining participants of the IS were almost equally distributed between an active group (IS active, $n = 416$) and a placebo group (IS placebo, $n = 394$). Mattress covers for the beds of the infant and parents, and pillow covers for the parents were applied by the investigator in the third trimester of pregnancy. The IS-active group received polyester-cotton mattress covers (ACb; Allergy Control Products, Saratoga Springs, NY), and the IS-placebo group received cotton placebo covers. The investigators and parents were blinded to group

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assignment. In the NHS ($n = 472$), no intervention took place, and these children were considered as a second control group.

Parents completed questionnaires during pregnancy and when the children were 3 months, 1 year, and 2 years old (IS and NHS). Uniform criteria for the definition of atopic disease in early childhood are lacking (10). Therefore, we chose a symptom-based approach, using questionnaires about respiratory symptoms in the previous year at age 1 and 2 years (adapted from the International Study of Asthma and Allergies in Childhood protocol [15]). Data were collected on wheezing, recurrent wheezing (at least four episodes per year), night cough without a cold, runny nose without a cold, use of asthma medication, and sleep disturbance due to wheezing. In addition, data were collected on birth characteristics and indoor environmental, socioeconomic, lifestyle, and demographic factors. Allergic disease in the father and siblings was assessed by questionnaires (14, 15). Atopic dermatitis at 1 year of age was determined by physical examination and questionnaire, using the U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis (IS only) (16).

Total immunoglobulin (Ig) E at 1 year of age was measured as described previously by Stallman and coworkers (17). Specific IgE against HDM, cat, dog, and food allergens was determined with a radioallergen sorbent fluorescent immunoassay (IS only) (18).

Dust samples were taken by trained fieldworkers from the parents' and infant's mattresses in the third trimester of pregnancy and 3 months after birth. The sampling, storing, and extraction procedures are described in detail elsewhere (19). By adding the amount of dermatophagoides (Der) p per square meter to the amount of Der f per square meter, the total exposure to Group 1 HDM allergens was cal-

culated (Der per square meter). Data on HDM allergen exposure were only available for children participating in the IS.

Statistical analyses were performed by SPSS (version 10.0; SPSS Inc., Chicago, IL). We used Pearson's χ^2 tests to compare categorical data, independent samples t tests for parametric continuous data, and Mann-Whitney U tests for nonparametric continuous data. An association was considered statistically significant when the p value was less than or equal to 0.05. Multivariate regression analyses were used to estimate the independent effect of the intervention on various outcome variables. To investigate the effect of HDM allergen exposure (independent of group assignment) on the development of symptoms, the children were arbitrarily divided into four groups: (1) children without detectable HDM allergens on their mattress at 3 months of age (reference); (2) Der 1, less than 200 ng/m²; (3) Der 1, 200–500 ng/m²; and (4) Der 1, greater than 500 ng/m².

RESULTS

Response

The flow of the participants through each stage of the study until the age of 2 years is summarized in Figure 1 (20). In the children participating in the NHS, no dust samples before the birth of the child were taken, no blood samples at 1 of age year were collected, and no physical examinations at 1 year of age were performed. Loss to follow-up and missing data were more common in the IS than in the NHS. Within the IS, loss to follow-up and missing data were somewhat more common in

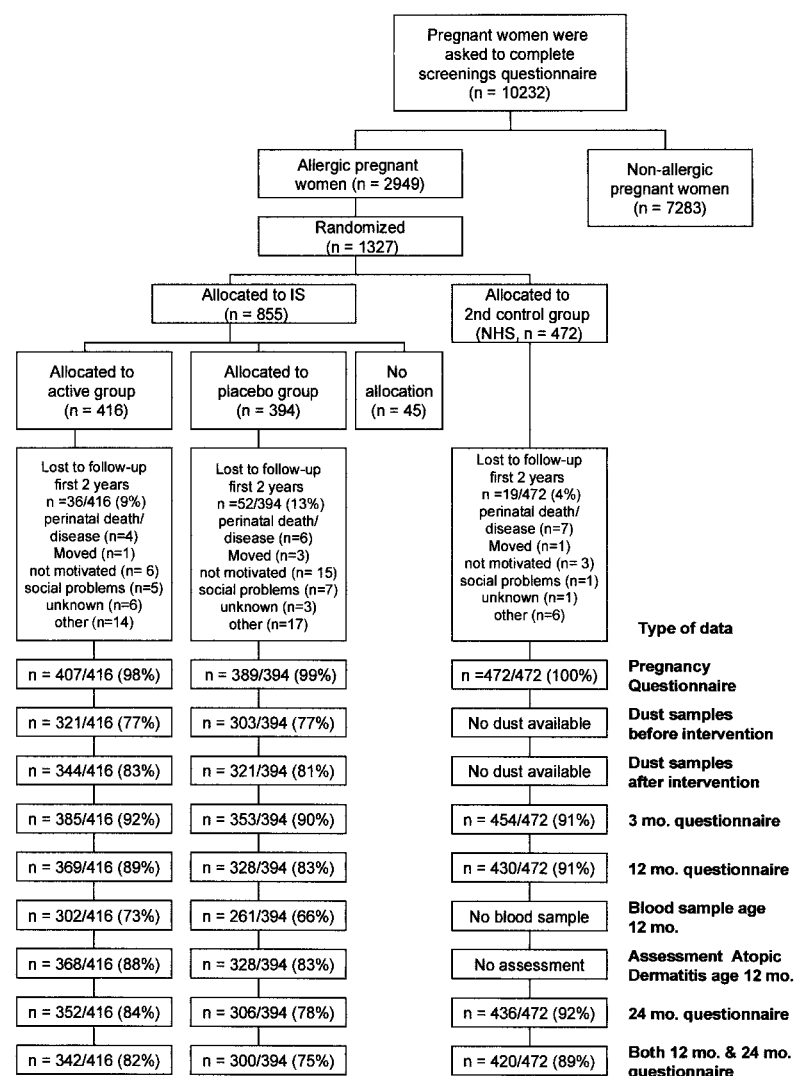


Figure 1. PIAMA flowchart.

the IS-placebo group compared with the IS-active group. To assess selective loss to follow-up, the children with incomplete data for the 1- or 2-year questionnaire (17% of the total study population, IS and NHS) were compared with children with complete data. Children with incomplete data were not different from the other children with respect to atopic disease in the father and siblings, parental age, sex, season of birth, duration of pregnancy, number of siblings, day care attendance, pet keeping, and indoor environmental factors. However, children with incomplete data were more likely to have a mother with asthma (33 versus 24%, $p = 0.01$), to have a mother who smoked during pregnancy (27 versus 16%, $p = 0.002$), to be exposed to environmental tobacco smoke at 1 year of age (37 versus 24%, $p = 0.03$), to be exclusively formula-fed at 3 months of age (61 versus 51%, $p = 0.009$), to have a nonworking mother (47 versus 33%, $p = 0.01$), to have a nonworking father (13 versus 4%, $p = 0.02$), and to have two parents with low level of education (14 versus 7%, $p = 0.04$). In addition, children with incomplete data had a lower birth weight (3.364 versus 3.508 kg, $p = 0.02$). Before birth, the geometric mean quantity of HDM allergen (Der p 1 + Der f 1) on the parents' mattresses of families with incomplete data was 427 ng/m² as compared with 295 ng/m² for families with complete data ($p = 0.02$). No statistically significant differences in HDM-allergen exposure between families with incomplete data and those with complete data were observed on the child's mattresses before birth (267 versus 206 ng/m²) and after birth (201 versus 188 ng/m²) and on the parents' mattress after birth (231 versus 198 ng/m²).

General Characteristics

In Table 1 the general characteristics of the study population are summarized. Children participating in the IS more often had a mother who was allergic to HDM allergen and were less

often born in the winter compared with children in the NHS. The IS-active group contained fewer boys compared with the IS-placebo group and the NHS group. Pet ownership and exclusive formula feeding at 3 months of age were more common in the IS-active group and NHS group as compared with the placebo group. All other characteristics were similar for the three groups.

Effect of the Intervention

Effect of the intervention on HDM allergen exposure. HDM allergens were detectable on 58% of the children's mattresses at 3 months after birth. In the period between the first (1–2 months before birth) and the second (3 months after birth) sampling time, HDM-allergen levels were reduced more by the allergen-impermeable covers (active group) than by the placebo covers (placebo group). This effect was more pronounced for the parental beds (which had all been in use before the study) than for the child's mattresses (many of which had not been used before the child was born). Detailed information about the effect of the intervention on HDM allergen levels will be published separately.

Effect of the intervention on the prevalence of clinical symptoms. IS-active versus IS-placebo. No statistically significant differences in the prevalence of wheezing at least once, night cough without a cold, or runny nose without a cold were observed between children in the active and the placebo groups (see online data supplement for details). Children in the IS-active group had a higher prevalence of recurrent wheeze in the first year of life than did those in the IS-placebo group (10.6 versus 6.3%, $p = 0.05$). The prevalence of atopic dermatitis in the first year of life was similar in both groups (13.3% in the IS-active group versus 14.9% in the IS-placebo group, $p = 0.6$). **IS-placebo versus NHS.** The prevalence of runny nose

TABLE 1. GENERAL CHARACTERISTICS OF THE STUDY POPULATION, STRATIFIED FOR GROUP ALLOCATION

	IS-Active (<i>n</i> = 416)	IS-Placebo (<i>n</i> = 394)	NHS (<i>n</i> = 472)
Mother allergy for HDM according to questionnaire, %	58	61	51
Mother ever asthma, %	26	28	23
Allergic father according to questionnaire, %	37	34	30
Father allergy for HDM according to questionnaire, %	15	13	16
Father ever asthma, %	7	8	6
Allergic sibling, %	32	29	31
Sibling ever asthma, %	7	8	7
Sex boy, %	46*	55	54
Smoking during pregnancy, %	16	17	20
Smoke exposure in the home at age 1, %	24	26	25
Born in winter, %	16	18	25†
Premature birth (< 37 weeks of gestation), %	4	7	5
Mean birth weight, kg (SD)	3.487 (0.561)	3.482 (0.567)	3.502 (0.564)
Mean weight at age 1 kg (SD)	9.7 (1.1)	9.8 (1.2)	9.8 (1.1)
Exclusive formula feeding at 3 months, %	55	48	54
At least 1 sibling, %	51	47	48
Day care at age 1, %	67	66	63
Exposure to pets, %	55	46‡	54
Living in apartment-flat, %	8	10	9
Damp- or mould spots in the home, %	10	11	13
Carpet floor bedroom child, %	47	45	54
Carpet floor bedroom parents, %	59	64	65
Median age mattress child, yrs (5th, 95th percentile)	1 (0–8)	1 (0–9)	1 (0–9)
Mean age mother of the child, yrs (SD)	30.5 (3.9)	29.9 (3.9)	29.8 (3.8)
Both parents low level of education, %	8	7	7
Mother with paid job, %	65	66	68
Father with paid job, %	96	96	96

Definition of abbreviations: HDM = house dust mite; IS = intervention study; NHS = natural history study.

* $p = 0.01$ for difference between IS-active and IS-placebo and $p = 0.02$ for difference between IS-active and NHS.

† $p = 0.02$ for difference between NHS and IS-active and $p = 0.03$ for difference between NHS and IS-placebo.

‡ $p = 0.02$ for difference between IS-placebo and IS-active and $p = 0.03$ for difference between IS-placebo NHS.

without a cold in the first year of life and in the first and second years of life was significantly higher in the IS-placebo group than in the NHS group (47.2 versus 35.2%, $p = 0.001$ and 22.7 versus 14.3%, $p = 0.004$, respectively). **Logistic regression analysis.** After adjustment for potential confounders (Table 2), the children in the IS-active group were found to be less likely to develop night cough without a cold in the second year of life compared with children in the IS-placebo group (adjusted odds ratio, 0.65; 95% confidence interval 0.4–1.0). However, children participating in the NHS were also less likely to develop night cough without a cold in the second year of life compared with the IS-placebo group (adjusted odds ratio, 0.69; 95% confidence interval, 0.4–1.0). No significant differences between the IS-active group, IS-placebo group, and NHS group were observed for wheezing, recurrent wheezing, runny nose without a cold, any respiratory symptoms, and atopic dermatitis (Table 2).

Effect of the intervention on symptom severity. In the first year of life, asthma medication was prescribed in 6.6% of the children in the IS-active group, in 8.3% of the children in the IS-placebo group, and in 7.3% of the children in the NHS ($p = 0.59$ for trend, χ^2). Of the children who were wheezing in the first year of life, sleep disturbance at least one night per week was reported in 23.0% of the cases in the IS-active group, in 22.8% of the cases in the IS-placebo group, and in 18.0% of the cases in the NHS ($p = 0.40$ for trend, χ^2). In addition, in the second year of life, no statistically significant differences were seen between the three groups in the prescription of asthma medication and prevalence of sleep disturbance due to wheezing (data not shown).

Effect of the intervention on total and specific IgE. Serum levels of total IgE at 1 year of age were similar for the IS-active group and the IS-placebo group (Table 3). Specific IgE against HDM (RAST-class ≥ 1) was found in only four children (two in the IS-active group and two in the IS-placebo

group). Ten children had specific IgE against cat dander and eight children had specific IgE against dog dander. Fourteen percent of the children were IgE positive for at least 1 allergen (mainly cow's milk or hen's egg) if a cutoff value of RAST class 2 was chosen. No differences in specific IgE at 1 year of age were found between the IS-active group and the IS-placebo group.

Relation between HDM Allergen Exposure and the Development of Symptoms

Table 4 shows the associations between various levels of exposure to HDM allergen (Der 1) at 3 months of age and the development of respiratory symptoms and atopic dermatitis in the first 2 years of life, using children without detectable levels of HDM allergen on their mattress as the reference group (42% of the total IS cohort). Results given are for the total group (active and placebo); similar results were seen when we stratified for group allocation (data not shown). Atopic dermatitis in the first year of life was less prevalent in children who were exposed to HDM allergens on the mattress as compared with children who were not exposed to HDM allergens. Exposure to HDM allergen was associated with wheezing at least once in the first year of life, and a trend was seen for wheezing in the second year of life and persistent wheezing. All other associations between HDM allergen exposure and the development of respiratory symptoms were not statistically significant. No dose-response relation was observed between exposure to HDM allergen and the development of atopic dermatitis and wheezing because the odds ratios for exposure Groups II, III, and IV were similar.

DISCUSSION

In this large randomized and placebo-controlled birth cohort study we found that a simple HDM-allergen avoidance strategy can reduce exposure to HDM allergens in early childhood.

TABLE 2. ADJUSTED ODDS RATIO AND 95% CONFIDENCE INTERVAL FOR GROUP ALLOCATION IN RELATION TO THE DEVELOPMENT OF WHEEZING, NIGHT COUGH WITHOUT A COLD AND RUNNY NOSE WITHOUT A COLD IN THE FIRST 2 YEARS OF LIFE AND ATOPIC DERMATITIS IN THE FIRST YEAR OF LIFE, USING THE PLACEBO GROUP AS THE INDEX GROUP

	Study	First Year		Second Year		First and Second Year	
		AOR*	95% CI	AOR*	95% CI	AOR*	95% CI
Wheezing at least once	IS-placebo	1.00		1.00		1.00	
	IS-active	0.97	0.7–1.4	0.98	0.6–1.4	0.96	0.6–1.6
	NHS	1.20	0.8–1.7	0.80	0.5–1.2	1.04	0.6–1.7
Recurrent wheezing	IS-placebo	1.00		1.00		1.00	
	IS-active	1.57	0.8–3.0	0.96	0.5–1.7	1.83	0.6–5.3
	NHS	1.77	1.0–3.2	0.61	0.3–1.1	1.28	0.4–3.7
Night cough without a cold	IS-placebo	1.00		1.00		1.00	
	IS-active	0.87	0.6–1.3	0.65	0.4–1.0	0.65	0.3–1.2
	NHS	0.77	0.5–1.1	0.69	0.4–1.0	0.63	0.3–1.3
Runny nose without a cold	IS-placebo	1.00		1.00		1.00	
	IS-active	0.90	0.6–1.2	0.82	0.5–1.2	0.80	0.5–1.2
	NHS	0.61	0.4–0.8	0.80	0.5–1.1	0.52	0.3–0.8
Any respiratory symptom [†]	IS-placebo	1.00		1.00		1.00	
	IS-active	0.81	0.6–1.1	0.76	0.5–1.1	0.78	0.5–1.1
	NHS	0.78	0.6–1.1	0.74	0.5–1.0	0.74	0.5–1.0
Atopic dermatitis	IS-placebo	1.00	ND	ND	ND	ND	ND
	IS-active	1.05	0.6–1.7	ND	ND	ND	ND
	NHS	ND	ND	ND	ND	ND	ND

Definition of abbreviations: AOR = adjusted odds ratio; CI = confidence interval; IS = intervention study; ND = no data; NHS = natural history study.

* Adjusted for maternal asthma, atopic disease father and sibling, sex, maternal smoking during pregnancy, type of feeding at 3 months, birth weight, having siblings, day care, maternal age, parental education, and having pets.

[†] Any respiratory symptoms: wheeze, night cough without cold, or runny nose without a cold.

TABLE 3. TOTAL AND SPECIFIC IMMUNOGLOBULIN E AT 1 YEAR OF AGE

	IS-Active (n = 296)	IS-Placebo (n = 256)	p Value
Total IgE, geometric mean IU/ml (geometric SD)	6.83 (4.34)	6.57 (4.42)	0.78*
Specific IgE against HDM, % RAST-class $\geq$ 1	0.7	0.8	0.57†
Specific IgE against any allergen, % RAST-class $\geq$ 2	14.4	14.0	0.90†

Definition of abbreviations: HDM = house dust mite; IgE = immunoglobulin E; IS = intervention study.

* Difference between IS-active group and IS-placebo group calculated by means of *t* test.

† Difference between active group and placebo group calculated by means of χ^2 .

In the children who received HDM allergen-impermeable mattress covers (IS-active group), a slightly, but significantly lower prevalence of night cough without a cold in the second year of life was observed. No significant effect of the mattress covers was seen on the development of wheezing, runny nose without a cold, atopic dermatitis, specific IgE against HDM, and respiratory symptom severity in the first 2 years of life. Exposure to HDM allergens at 3 months of age (independent of group allocation) was associated with an increased risk to wheeze at least once in the first year of life. Surprisingly, we found a decreased prevalence of atopic dermatitis at 1 year of age in children who were exposed to HDM allergen at 3 months of age. No evidence for a dose-response relation between HDM-allergen exposure and wheezing, and atopic dermatitis was found.

Choice of Outcome Parameters

No clear definition of atopic disease in early childhood exists; therefore, most studies rely on the description of symptoms (21). The diagnosis of asthma is particularly difficult because

no objective parameters are available for this age group. Wheezing and recurrent wheezing are usually chosen as surrogate markers of asthma in epidemiologic studies, although it is clearly established that wheezing during the first years of life is strongly associated with viral infections and the majority of wheezy children will not develop asthma later in life (22). In addition, other respiratory symptoms in early childhood, such as night cough and runny nose without a cold, only partly reflect atopic disease. For this reason, this early evaluation of the effect of the intervention does not exclude possible benefits at a later stage, and the study will therefore be continued after 2 years of age.

Effect of the Intervention on Exposure and Symptoms

We chose a simple strategy to reduce HDM-allergen exposure by applying covers for the parents' and child's mattress. Studies, such as the Manchester Allergy and Asthma Study (MAAS), that rely on more strenuous reduction programs affecting factors such as ventilation, furniture, and floor covers might be more successful in reducing HDM allergen exposure,

TABLE 4. ADJUSTED ODDS RATIO AND 95% CONFIDENCE INTERVAL FOR ASSOCIATION BETWEEN EXPOSURE TO ALLERGEN AT 3 MONTHS AFTER BIRTH (ONLY INTERVENTION STUDY, INDEPENDENT OF GROUP ALLOCATION) AND THE DEVELOPMENT OF RESPIRATORY SYMPTOMS AND ATOPIC DERMATITIS IN FIRST 2 YEARS OF LIFE

		First Year		Second Year		First and Second Year	
	Exposure HDM*	AOR†	95% CI	AOR†	95% CI	AOR†	95% CI
Wheezing at least once	Group I	1.00		1.00		1.00	
	Group II	1.46	0.8–2.5	1.64	0.9–2.9	1.66	0.8–3.6
	Group III	1.75	1.0–3.1	1.69	0.9–3.1	1.98	0.9–4.6
	Group IV	1.53	0.9–2.6	1.30	0.7–2.4	1.65	0.7–3.7
Recurrent wheezing	Group I	1.00		1.00		1.00	
	Group II	0.78	0.3–1.9	1.54	0.7–3.5	1.32	0.3–5.3
	Group III	0.89	0.3–2.3	1.36	0.5–3.4	1.34	0.3–6.0
	Group IV	0.70	0.3–1.8	1.44	0.6–3.5	0.97	0.2–4.5
Night cough without a cold	Group I	1.00		1.00		1.00	
	Group II	1.42	0.8–2.5	1.14	0.6–2.1	1.15	0.5–2.8
	Group III	1.10	0.6–2.1	1.36	0.7–2.6	1.40	0.6–3.5
	Group IV	0.96	0.5–1.8	1.21	0.6–2.3	1.04	0.4–2.6
Runny nose without a cold	Group I	1.00		1.00		1.00	
	Group II	0.76	0.5–1.2	1.49	0.8–2.6	1.07	0.6–2.0
	Group III	1.22	0.7–2.0	1.67	0.9–3.0	1.81	0.9–3.5
	Group IV	0.68	0.4–1.1	1.49	0.8–2.7	0.86	0.4–1.8
Any respiratory symptom‡	Group I	1.00		1.00		1.00	
	Group II	1.05	0.6–1.7	1.49	0.9–2.5	1.43	0.7–2.8
	Group III	1.41	0.8–2.4	1.59	0.9–2.7	1.65	0.8–3.3
	Group IV	0.88	0.5–1.5	1.36	0.8–2.3	1.08	0.5–2.1
Atopic dermatitis	Group I	1.00					
	Group II	0.43	0.2–1.0				
	Group III	0.49	0.2–1.2				
	Group IV	0.39	0.2–0.9				

Definition of abbreviations: AOR = adjusted odds ratio; CI = confidence interval; HDM = house dust mite; IS = intervention study.

† Adjusted for maternal asthma, atopic disease father and sibling, sex, maternal smoking during pregnancy, type of feeding at 3 months, birth weight, having siblings, day care, maternal age, parental education, and having pets.

‡ Any respiratory symptom = 1 or more of the following symptoms: wheeze, night cough without cold, or runny nose without a cold.

but it is very difficult to conduct such studies in a double-blind, placebo-controlled fashion (23). Also, simple measures are more likely to be implemented widely if they can be shown to have a reasonable effectiveness.

One could argue that the difference in allergen exposure between the active group and the placebo group in the IS was too small to expect a clinical effect of the intervention. Overall, HDM allergen levels were low in both the IS-active and IS-placebo groups, and levels in the placebo group were 2- to 10-fold lower than those previously found in other studies in the Netherlands (19, 24). This can be explained because most infants were sleeping on new mattresses at the time of dust sampling: mite infestation could only have taken place for a limited time period. HDM allergen quantities were higher on the parents' mattresses, which were older, than on the infant's mattresses, and the effect of the intervention was greater. It is likely that, in time, the allergen load on the child's mattress will further increase in the placebo arm of the study. Another possible explanation for the low allergen levels is an increased public awareness of the potential adverse effect of allergen exposure, in particular among atopic families (24). In addition, participation in an intervention trial might have resulted in allergen avoidance and consequently low allergen levels in the IS-placebo group. This is supported by results of the MAAS, in which even lower HDM allergen levels were found in the control arm of the study compared with the placebo arm of the PIAMA study (23). Therefore, our results cannot be extrapolated to countries such as the U.K. and Australia, where allergen levels were shown to be much higher (1, 25).

As in the PIAMA study, in the MAAS no reduction of the prevalence of wheezing, night cough apart from colds, eczema, and sensitization to HDM allergen was observed in the active group as compared with the control group (13). In contrast to the PIAMA study, the prevalence of severe respiratory manifestations, such as recurrent wheeze with shortness of breath and medication prescription for wheezing, was found to be lower in the active group compared with the control group in the MAAS. Various possible explanations for this discrepancy can be postulated. The definitions for disease severity that were used in the PIAMA study were slightly different from the definitions used in the MAAS. Furthermore, as was mentioned earlier, the method of intervention and the study design differed between the studies. It should be mentioned that although a significant difference in respiratory symptom severity was found between the active group and the control group of the MAAS, the absolute numbers of affected children was small, resulting in wide confidence intervals. In addition, no attempt was made to control for potential confounders.

According to a review by Pearce and colleagues, the causal relationship between exposure to HDM allergens and the development of asthma can be questioned (26). The key study that links early allergen exposure to the development of asthma later in life in fact found a nonsignificant trend toward an association (1). In a recent publication from the German MAS study, no consistent association was found between HDM allergen exposure at 6 months of age and current wheeze, ever wheeze, and doctor-diagnosed asthma at 7 years of age (27). In the same study, a strong association was found between early allergen exposure and mite sensitization after the age of 5 years on the one hand, and an association between mite sensitization and wheezing after the age of 3 years, on the other hand. On the basis of these findings, the authors concluded that the strong association between sensitization to HDM and asthma reflects the susceptibility of an individual with asthma to become sensitized to perennial allergens that are most prevalent in the environment rather than an in-

creased risk of asthma when exposed to allergens. Despite overall low levels of HDM allergen exposure, the prevalence of respiratory symptoms and atopic dermatitis in our study was not lower than in other prospective birth cohort studies (11, 22, 28). This might also indicate that HDM allergen exposure is not an important factor for the development of respiratory and skin symptoms, at least in the first years of life.

Atopic Dermatitis and Respiratory Symptoms in Relation to Allergen Exposure

We found an inverse relation between exposure to HDM allergen at 3 months of age and the development of atopic dermatitis in the first year of life. This association remained highly statistically significant after adjusting for potential confounders and was independent of group allocation. To our knowledge, this kind of inverse association has not been published previously, and we can only speculate about the potential mechanism. A possible explanation might be that parents of children who develop skin symptoms in the first weeks will increase the frequency of cleaning, which results in lower HDM allergen levels in the dust samples. However, parents completed weekly symptom cards in the first years of life, and we could not find an association between reported skin symptoms in the first weeks of life and the amount of HDM allergen found on the child's mattress at 3 months of life (data not shown). We found a positive association between HDM allergen exposure and wheezing at least once in the first year of life and an association of borderline statistical significance for wheezing at least once in the second year of life and persistent wheezing in both the first and second year of life. Because no such association was found for recurrent wheezing, this relationship may not be due to allergic inflammation. An alternative explanation might be that proteolytic digestive enzymes present in animal feces increase the risk of nonallergic airway inflammation (8).

Validation Issues

In general, the prevalence of respiratory symptoms seemed to be somewhat lower in children participating in the NHS compared with children in the IS-placebo group. This is also the case for night cough without a cold in the second year of life, which is the only symptom that differs significantly between the IS-active group and the IS-placebo group, after adjustment for confounders. This observation might be the effect of enrollment into an intervention study resulting in overreporting of respiratory symptoms. Responses to questionnaires at ages 1 and 2 years were higher in the NHS compared with the IS, which probably reflects the less intense study procedures used in the NHS. Within the IS, responses to questionnaires were slightly higher in the IS-active group as compared with the IS-placebo group, and nonresponders had somewhat higher initial HDM allergen quantities on the parents' mattress at the beginning of the study. The differences in response between the two groups might be a result of parents' awareness of the group they were allocated because the appearance of the active cover and the placebo cover were slightly different. An alternative explanation is that the difference is a result of chance. Absolute follow-up differences were small, and overall follow-up rates were highly acceptable in both groups. So, although there are some indications of participation bias, we do not believe that this can explain the limited effect of the intervention so far. Because nonsmoking parents of high socioeconomic status were more likely to provide complete data, the generalizability of the study for the total population might be somewhat limited.

In conclusion, we were unable to demonstrate a protective effect of HDM-impermeable mattress covers on the preva-

lence and severity of respiratory symptoms, atopic dermatitis, and atopic sensitization in the first 2 years of life. Follow-up of the cohort will determine whether this intervention can reduce the prevalence of asthma and atopy later in childhood.

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