

Current mite, cat, and dog allergen exposure, pet ownership, and sensitization to inhalant allergens in adults

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Background: Simultaneous exposure to more than one allergen might modify the effect of individual allergens.

Objective: The purpose of this study was to investigate the effect of current exposures to mite, cat, and dog allergen and pet ownership on sensitization in adults.

Methods: Questionnaires, skin tests, and home visits (Der p 1, Fel d 1, and Can f 1, ELISA; mattresses, living room floors) were performed in 2502 adults. Allergen exposure was treated as a continuous variable and divided into quartiles. To investigate the interaction between allergens, quartiles for 3 allergens were added, creating arbitrary combined exposure categories. **Results:** In the univariate analysis, mite sensitization was associated with Der p 1 in mattresses (odds ratio [OR], 1.10; 95% CI, 1.01 to 1.19; $P = .03$) and with Can f 1 in living room floors (OR, 1.08; 95% CI, 1.00 to 1.17; $P = .05$). In a multivariate regression analysis, Der p 1 in mattresses remained an independent associate of mite sensitization (OR, 1.12; 95% CI, 1.02 to 1.23; $P = .03$) and pollen sensitization (OR, 1.23; 95% CI, 1.11 to 1.36; $P = .0001$). The proportion of subjects sensitized to mite increased significantly with the increasing combined exposure categories ($P < .0001$). The highest prevalence of sensitization to cat and dog was in the medium combined exposure categories. Cat ownership was associated with a reduced prevalence of sensitization to cats ($P = .002$) and a reduced prevalence of sensitization to dog ($P = .003$) but had no effect on sensitization to mite and pollen.

Conclusions: Sensitization to dust mites increased with the increasing combined exposure. Cat ownership was associated with a lower prevalence of sensitization to cat and dog but not to mite and grass pollen. (*J Allergy Clin Immunol* 2003;111:402-7.)

Key words: Sensitization, asthma, cat, dog, dust mite, allergens, exposure

For house dust mite allergens there is a dose-response relation between exposure and sensitization.^{1,2} For allergens other than mites, the relation between exposure and

sensitization is less well defined. Several studies in inner-city areas reported that children are more likely to become sensitized to cockroach with increasing cockroach allergen exposure.^{2,3} Similarly, high exposure to mouse allergen appears to be associated with an increased prevalence of sensitization to mouse.^{4,5} Some studies have reported an increased prevalence of sensitization to cat with increasing exposure.^{6,7} On the other hand, recent cross-sectional studies suggested that cat ownership could decrease the risk of asthma and/or sensitization to cat.⁹⁻¹¹

The majority of studies have attempted to elucidate the role of allergen exposure in early life on subsequent development of sensitization.^{7,8} There are very few studies in adults investigating the relation between current allergen exposure with sensitization. Although such cross-sectional studies are difficult to interpret, this is an important issue because it is possible that it is cumulative exposure, or high exposure later on (rather than only exposure in early life) that might be important. Furthermore, if the exposure in adult life proves relevant, this would raise the question of whether changes in current exposure can change the phenotype.

Most of the studies in adults have investigated the role of individual allergens in elicitation of IgE-mediated responses. However, in real life, individuals are exposed to a mixture of several allergens, and their relative contributions and possible synergistic actions have not yet been investigated in population-based studies. Simultaneous exposure to high levels of more than one allergen might modify the effect of individual allergens.

In this publication, we report on the relation between current exposures to mite, cat, and dog allergens and pet ownership with sensitization in adults. The subjects are the parents of children recruited in a cohort study on atopy and asthma.¹²⁻¹⁴

METHODS

A detailed description of screening and recruitment is given elsewhere.¹²⁻¹⁴ Briefly, pregnant women and their partners attending Booking antenatal clinic completed a questionnaire giving demographic data, history of atopic disorders, pet ownership, and smoking habits. Skin testing was carried out by using the extracts of 4 inhalant allergens (*Dermatophagoides pteronyssinus*, cat, dog,

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TABLE I. Demographics and prevalence of sensitization, smoking, and animal ownership

	All subjects		Female subjects		Male subjects	
	Frequency	%	Frequency	%	Frequency	%
Smoking status						
Current smoker	527/2280	23.1	200/1140	17.5	327/1140	28.7
Sensitization to allergens						
House dust mite	831/2291	36.3	397/1143	34.7	434/1148	37.8
Cat	420/2299	18.3	215/1151	18.7	205/1148	17.9
Dog	185/2299	8.0	88/1137	7.7	97/1162	8.3
Grass pollen	897/2293	39.1	422/1148	36.8	475/1145	41.5
Atopic	1233/2284	54.0	579/1140	50.8	654/1144	57.2
Sensitized to 1 allergen	529/2284	23.2	233/1140	20.4	296/1144	25.9
Sensitized to 2 allergens	414/2284	18.1	200/1140	17.5	214/1144	18.7
Sensitized to 3 allergens	192/2284	8.4	100/1140	8.8	92/1144	8.0
Sensitized to 4 allergens	98/2284	4.3	46/1140	4.0	52/1144	4.5
Pet ownership						
Cat owner	444/2214	20.1	228/1109	20.6	216/1105	19.6
Dog owner	378/2214	17.1	190/1109	17.1	188/1105	17.0
Pet owner	778/2214	35.1	391/1109	35.3	387/1105	35.0

mixed grasses; Bayer, Elkhart, Ind). A weal diameter of ≥ 4 mm greater than the negative control was regarded as a positive response.

Measurement of allergen exposure

A total of 2502 subjects (1251 couples) agreed to a home visit that was carried out within 2 weeks of the recruitment. Samples of fine dust were collected from a 1-m² area of the mattress and living room floor (LF).

Der p 1, Fel d 1, and Can f 1 were assayed with immunometric ELISA, as previously described.¹⁵⁻¹⁷ The standard used to establish the control curve for Der p 1 (UVA 93/02) contained 2500 ng Der p 1/mL (relative to WHO/IUIS *D pteronyssinus* standard NIBSC 82/518, estimated to contain 12.5 μ g Der p 1/ampule). The Fel d 1 standard (UVA 94/01) contained 9.7 IU/mL Fel d 1 (international unit = 4 μ g protein). Can f 1 assay was quantified by using dog allergen standard (UVA 94/02; 10,000 IU Can f 1/mL) substandardized against WHO/IUIS International Reference Preparation of dog hair and dander (NIBSC 84/685), which contains 100,000 IU/mL Can f 1 (1 IU = 1 ng Can f 1 protein).

Statistical methods

The data were modeled for the sexes both individually and together to check for consistency. The risk of being sensitized to specific allergens was modeled by means of logistic regression, and the significance of potential risk factors was assessed by means of the log-likelihood ratio test at the 5% significance level. Der p 1, Fel d 1, and Can f 1 were log-transformed before analysis and initially treated as continuous variables. Adjustment for possible confounding variables (socioeconomic status, age, sex, and smoking) was made where appropriate.

Allergen levels were then categorized into quartiles by using the values from the mattress, and the proportion of subjects sensitized was calculated for each of the exposure categories. To investigate the possible interactions between 3 inhalant allergens, the quartile exposure data for mite, cat, and dog were assigned the values of 0, 1, 2, and 3. These values for 3 allergens were added, creating 10 arbitrary combined exposure categories ranging from 0 (lowest quartile for all 3 allergens) to 9 (highest quartile for all 3 allergens). To have a sufficient number of subjects in each combined exposure category, categories 8 and 9 were analyzed together. Statistical analysis was carried out by logistic regression, initially by univariate analysis, in which other quartiles (and combined exposure cate-

gories) were compared with the lowest exposure group. Variables were then tested in a multivariate analysis in which the synergistic effects were explored by deriving an appropriate combined exposure category, sociodemographic factors, age, sex, current smoking, and cat and dog ownership being considered possible confounders.

RESULTS

Initially, 3524 pregnant women and 2163 of their partners completed the questionnaire and were given skin tests, whereas 1306 declined the invitation.¹² A total of 2502 subjects agreed to a home visit. Demographic data and the prevalence of sensitization, smoking, and animal ownership in this group are shown in Table I in all subjects and by sex. The mean age of the study participants was 31.8 years, ranging from 18 to 58 years.

Allergen exposure and allergic sensitization

In the univariate analysis, mite sensitization was associated with Der p 1 in mattresses (OR, 1.10; 95% CI, 1.01 to 1.19; $P = .03$) and Can f 1 in living room floors (OR, 1.08; 95% CI, 1.00 to 1.17; $P = .05$), and a strong trend was observed for Fel d 1 in mattresses (OR, 1.07; 95% CI, 0.99 to 1.15; $P = .07$). In the multivariate regression analyses, Der p 1 levels in the mattresses remained an independent associate of mite sensitization (OR, 1.12; 95% CI, 1.02 to 1.23; $P = .03$) and pollen sensitization (OR, 1.23; 95% CI, 1.11 to 1.36; $P = .0001$). No significant association was found between sensitization to other allergens and allergen levels. There was a poor correlation between mite, cat, and dog allergen levels (all $r < 0.1$).

Combined effects of exposure to mite, cat, and dog allergens

Quartile analysis was undertaken on allergen levels from the mattresses. Cut points for quartiles (μ g/g) were as follows: 0.05, 1.06, and 5.50 for Der p 1; 0.05, 0.97, and 5.99 for Fel d 1; 0.05, 0.71, and 3.0 for Can f 1. The prevalence of skin test results positive to mite significant-

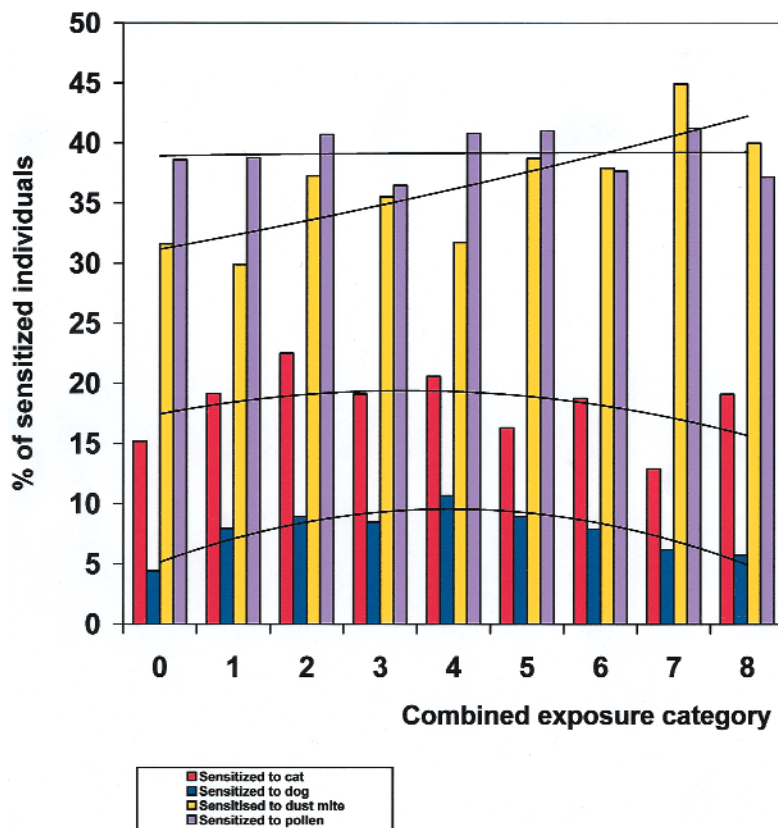


FIG 1. Significant increase in prevalence of sensitization to dust mites with increasing arbitrary combined exposure categories of dust mite, cat, and dog allergen exposure. The highest proportion of sensitization to cat and dog is seen with medium arbitrary combined exposure categories.

ly increased with increasing quartiles of Der p 1 exposure ($P = .007$). The risks of being sensitized to specific allergen(s) when the allergen levels are in the upper 3 quartiles compared with the lowest quartile are presented in Table II. In the univariate regression analysis, having current levels of Der p 1 in the highest quartile was a significant associate of an increased risk of sensitization to mites ($P < .01$; Table II). Furthermore, sensitization to dust mite was significantly associated with the 3 highest quartiles of Fel d 1 exposure. However, a different pattern was observed for sensitization to cat, which was a significant associate of 2 medium quartiles of Fel d 1, the risk being decreased in the highest quartile. No consistent pattern was observed for exposure to dog and sensitization.

We investigated the possible synergism between the 3 major inhalant allergens by creating 9 arbitrary combined exposure categories. There was a marked and highly significant increase in the proportion of subjects with skin test results positive to dust mite with the increasing arbitrary combined exposure categories ($P < .0001$; Fig 1). A different pattern was observed for sensitization to cat and dog, the highest proportion of sensitized subjects being seen in the medium combined exposure categories (Fig 1).

The relation between combined exposure to allergens and sensitization was further investigated by using logistic regression. The results of the univariate analysis are

presented in Table III. As seen in the Table, the risk of sensitization to dust mites increased with increasing combined exposure category. However, the proportion of subjects sensitized to dog was significantly increased with medium combined exposure (category 4), whereas a similar trend that failed to reach statistical significance was observed for sensitization to cat ($P = .07$).

Pet ownership

There was no difference in the proportion of either cat or dog ownership between atopic and nonatopic individuals. The association between pet ownership and specific sensitization is presented in Table IV. There was no association between either cat or dog ownership and sensitization to dust mite or grasses. However, reported cat ownership was associated with a reduced prevalence of sensitization to cat ($P = .002$) and a reduced prevalence of sensitization to dog ($P = .003$). A strong trend was observed for dog ownership to be associated with a reduced prevalence of sensitization to dog ($P = .07$), but no association was observed between dog ownership and sensitization to cat.

In the multivariate logistic regression analysis, cat ownership remained the only independent associate of a reduced prevalence of both sensitization to cat (OR, 0.66; 95% CI, 0.49 to 0.89; $P = .007$) and sensitization to dog

TABLE II. Risk of being sensitized to mite, cat, dog, and pollen allergen when Der p 1, Can f 1, and Fel d 1 allergen levels are in upper 3 quartiles compared with lowest quartile (odds ratios and 95% CIs)

	Sensitized to mite	Sensitized to cat	Sensitized to dog	Sensitized to grass
Der p 1				
Quartile 2	1.23 (0.96–1.56)	1.23 (0.92–1.64)	1.32 (0.97–2.01)	1.02 (0.81–1.30)
Quartile 3	1.13 (0.88–1.44)	0.94 (0.70–1.28)	0.99 (0.64–1.55)	0.81 (0.64–1.02)
Quartile 4	1.39 (1.09–1.77)*	0.98 (0.72–1.33)	1.17 (0.76–1.80)	0.99 (0.79–1.26)
Fel d 1				
Quartile 2	1.69 (1.34–2.15)*	1.41 (1.05–1.89)*	1.4 (0.93–2.11)	1.35 (1.07–1.70)*
Quartile 3	1.47 (1.15–1.87)*	1.51 (1.12–2.01)*	1.22 (0.80–1.88)	1.15 (0.91–1.45)
Quartile 4	1.46 (1.15–1.96)*	0.97 (0.71–1.33)	1.15 (0.75–1.77)	1.14 (0.91–1.45)
Can f 1				
Quartile 2	0.83 (0.65–1.05)	0.76 (0.56–1.02)	0.88 (0.58–1.33)	1.02 (0.81–1.29)
Quartile 3	0.90 (0.71–1.15)	0.66 (0.49–0.90)*	0.88 (0.57–1.33)	0.86 (0.68–1.08)
Quartile 4	1.19 (0.94–1.50)	0.87 (0.65–1.16)	0.86 (0.56–1.30)	1.07 (0.85–1.35)

*Significant associations (univariate analysis).

TABLE III. Odds ratios and 95% CIs for different outcomes in relation to combined exposure to dust mite, cat, and dog allergens (compared with category 0, lowest quartile for all 3 allergens)

Additive exposure	Sensitized to mite	Sensitized to cat	Sensitized to dog	Sensitized to grass
0 (n = 158)	1	1	1	1
1 (n = 214)	0.92 (0.59–1.44)	1.32 (0.76–2.30)	1.85 (0.75–4.59)	1.01 (0.66–1.54)
2 (n = 280)	1.28 (0.85–1.94)	1.62 (0.97–2.72)	2.11 (0.89–4.99)	1.09 (0.73–1.63)
3 (n = 320)	1.19 (0.79–1.79)	1.32 (0.79–2.21)	1.99 (0.85–4.67)	0.91 (0.62–1.35)
4 (n = 272)	1.00 (0.66–1.53)	1.45 (0.86–2.44)	2.57† (1.10–6.00)	1.10 (0.73–1.64)
5 (n = 394)	1.36 (0.92–2.02)	1.09 (0.65–1.81)	2.11 (0.92–4.85)	1.11 (0.76–1.62)
6 (n = 278)	1.32 (0.87–1.99)	1.29 (0.76–2.19)	1.85 (0.77–4.43)	0.96 (0.64–1.44)
7 (n = 178)	1.76* (1.13–2.75)	0.83 (0.45–1.54)	1.42 (0.54–3.75)	1.12 (0.72–1.73)
8 (n = 158)	1.44 (0.9–2.29)	1.32 (0.73–2.38)	1.31 (0.48–3.60)	0.94 (0.60–1.49)

* $P = .01$; † $P = .03$ (univariate analysis).

TABLE IV. Odds ratios and 95% CIs for allergen sensitization in relation to cat, dog, and pet ownership (univariate analysis)

	Sensitized to mite	Sensitized to cat	Sensitized to dog	Sensitized to grass
Cat owner	0.98 (0.81–1.19)	0.65 (0.50–0.85)*	0.54 (0.35–0.81)*	0.98 (0.81–1.18)
Dog owner	1.15 (0.94–1.40)	0.94 (0.73–1.23)	0.68 (0.45–1.03)	1.11 (0.91–1.34)
Pet owner	1.09 (0.93–1.27)	0.77 (0.63–0.95)*	0.61 (0.45–0.84)*	1.08 (0.93–1.26)

*Significant associations (all $P < .01$).

(OR, 0.60; 95% CI, 0.38 to 0.94; $P = .02$), whereas the lower rate of sensitization to dust mite was associated with the 2 lowest additive exposure categories (category 0: OR, 0.63; 95% CI 0.39 to 1.00; $P = .05$; category 1: OR, 0.57; 95% CI, 0.36 to 0.90; $P = .016$).

DISCUSSION

This study of adult participants investigated the relation and interactions between current exposures to dust mite, cat, and dog allergens with sensitization to inhalant allergens in a large sample of more than 2000 adults who completed a questionnaire and underwent skin prick testing and home visits for measurement of exposure to Der p 1, Fel d 1, and Can f 1. Our results indicate that there might be an effect of combined exposure to mite, cat, and dog allergens on sensitization. Furthermore, the dose-response relation between exposure and sensitization

appears to be different for cat and dog compared with dust mite allergen, the maximum prevalence of specific sensitization to pets occurring with moderate combined exposure. Reported cat ownership was associated with a reduced prevalence of sensitization to both cats and dogs, but there was no association between either cat or dog ownership and sensitization to dust mite or grasses.

In the current study we cannot exclude the possibility of selection bias (eg, atopic women might be more likely to agree to have skin tests; allergic patients might be more likely to allow home visits). However, we believe that this did not have a major influence on the results because we addressed the relation between allergen levels in homes and sensitization rather than the incidence of sensitization. One of the explanations for a protective effect of cat ownership might be the possibility that individuals affected with allergy avoid having animals in the house, as suggested by the recent study from the Netherlands.¹⁸ This,

however, seems unlikely because in the current study the proportion of cat ownership was identical among nonatopic and atopic individuals. That does not discount the possibility that among atopic individuals only those allergic to cats avoid having cats in home. However, we have shown that cat ownership was also protective against sensitization to dogs, whereas dog ownership did not exert a similar effect and was not less common among dog-sensitized (and cat-sensitized) participants.

It might be that having animals in the home leads to a higher level of endotoxin or an increase in microbial exposure that might protect against the development of allergy (as suggested within the context of the "hygiene hypothesis").¹⁹ However, in the current study, dog ownership did not appear to confer protection. Alternatively, the effect could be purely one of quantity of allergen exposure, continued high exposure leading to the induction of tolerance and a protection against the development of clinical signs of allergic disease caused by a modified protective T_H2 response.^{20,21}

One of the fundamental questions is whether the protective effect of cat ownership/high-dose *Fel d 1* exposure is specific to cat allergen but not other sensitization or is instead nonspecific—ie, protection is conferred to other allergens and allergic disease. For example, it has been reported that the prevalence of sensitization to birch and asthma in Sweden was lower in subjects who were exposed to cat in early life.¹¹ Dog exposure in early life was reported to prevent the development of frequent wheeze but did not seem to influence allergic sensitization.²² In the current study, cat ownership was associated with a lower prevalence of sensitization to cat and dog but not mite or pollen. One of the fascinating possibilities is that high-dose cat exposure might affect sensitization to some allergens (eg, cat, dog, or birch) but cannot override the effect of dust mites. Furthermore, this protective effect might be modified by the concurrent exposure to dust mite allergens. This could explain the observed differences between Scandinavia and Arizona (nonspecific protective effects of pet ownership with very low mite exposure) and the United Kingdom and the Netherlands (allergen-specific or no protective effect of cat ownership; moderate or high mite exposure). However, it also raises the question of what is special about house dust mite.

We used the measurement of current exposure as a surrogate for the cumulative exposure.

In the current study, the risk of sensitization to dust mite increased with increasing quartile of *Der p 1* exposure, whereas sensitization to cat was a significant associate of 2 medium quartiles of *Fel d 1* exposure, the risk being decreased in the highest quartile. We have recently analyzed the data on sensitization to cats in relation to deciles of cat allergen exposure in this cohort of patients and reported a decreased risk of sensitization to cat but not other allergens with high and low exposure to *Fel d 1*.²³ Clearly, sensitization to cat allergen might change with time, reflecting the effect of cumulative exposure acting differently on individuals with differing genetic risks. For example, within the same study, we have

observed that cat ownership might confer a huge risk for the development of sensitization to cat at 12 months of age in children at high risk of atopy (OR, 25)¹⁴; it might be of no importance in the same age group in children at low risk (both parents nonatopic),¹⁴ or it might be protective in the parents of these children.²³ It is worth noting that rates of sensitization to cat and dog are lower than rates of sensitization to mite or pollen at any exposure level.

In real life, individuals inhale a mixture of several allergens/irritants/pollutants, but the possible synergism between different allergens has not previously been investigated. Most allergens are low-molecular-weight (5 to 50 kD) water-soluble proteins or glycoproteins that rapidly penetrate mucosal membranes. Apart from these general properties, allergens are a diverse group of proteins without any known structural features that could be associated with their ability to stimulate IgE antibody production. Some inhalant allergens induce humoral and cellular responses in up to 30% of the general population after remarkably low-dose natural exposure (typically, only 1.5 μ g of dust mite allergen per year).²⁴ It has recently been suggested that nonimmunologic properties of certain allergens (eg, enzymatic activity) might contribute to their allergenicity. There are some indications that the proteolytic activity of *Der p 1* can enhance access to the antigen-presenting dendritic cells by cleaving the tight junction proteins, thus facilitating its own penetration through the mucosal membrane, though it is not clear whether these *in vitro* studies apply *in vivo*.^{25,26} The allergenicity of *Der p 1* might be due partly to its ability to introduce a bias toward T_H2 -like immune response by affecting mast cells, B cells, and T cells and creating a proallergic microenvironment within the target tissues.²⁷ If true, this could facilitate the effect of other allergenic proteins. Our data could indirectly support this view, as we have observed effects of allergen exposure that cannot be explained only by the exposure's affecting specific sensitization (eg, the risk of sensitization to pollen increased with increasing exposure to mite allergen). Furthermore, there appears to be an additive effect of combined exposure to several allergens on the pattern of sensitization.

We have observed differences in the effect of combined exposure to all 3 allergens on sensitization to dust mites compared with sensitization to cats and dogs. Although we demonstrated a marked and highly significant increase in the proportion of subjects with skin test results positive to dust mites with the increasing arbitrary combined exposure categories, a different pattern was observed for sensitization to cat and dog. The highest proportion of subjects sensitized to domestic pets was in the medium combined exposure categories.

In conclusion, the results of the current study suggest that concurrent exposure to several allergens might affect the pattern of sensitization. The dose-response relation between exposure and sensitization appears to be different for domestic pets compared with dust mite allergen. The maximum prevalence of specific sensitization to pets

occurred with moderate combined exposure, whereas the proportion of subjects with skin test results positive to dust mite increased with the increasing arbitrary combined exposure categories. Cat ownership was associated with a reduced prevalence of sensitization to both cat and dog, but there was no association between either cat or dog ownership and sensitization to dust mite or grasses.

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