

Bronchial Responsiveness in Atopic Adults Increases with Exposure to Cat Allergen

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Rationale: The association of asthma with sensitization and allergen exposure is known to be complex. There have been few studies of bronchial responsiveness in relation to both risk factors in adults. **Objectives:** To determine the relation of bronchial responsiveness to allergen exposure and IgE sensitization in a community study taking into account the major determinants of bronchial responsiveness in adulthood.

Methods: Cross-sectional data were drawn from 1,884 participants in 20 centers in the European Community Respiratory Health Survey follow-up, which included measurement of house dust mite and cat allergen in mattress dust samples, and IgE sensitization to four allergens. Bronchial responsiveness to methacholine was expressed as a continuous variable, and analyzed by multiple regression.

Measurements and Main Results: The trend toward greater bronchial responsiveness with increasing exposure to cat allergen was greater in those sensitized to any of the four allergens than those not sensitized ($p = 0.001$); there was no significant interaction between cat sensitization and Fel d 1 exposure. No trend was found with house dust mite allergen exposure. The difference in bronchial responsiveness between those exposed to the highest levels compared with the lowest was approximately -2.02 doubling doses of PD₂₀ (95% confidence interval, -3.06 to -0.97), and nearly as great in those exposed to more moderate levels.

Conclusions: Cat allergen exposure at moderate levels may be harmful to all atopic adults. The clinical implication is that it is insufficient to test patients with asthma for cat sensitization; all atopic individuals may benefit from reduced cat exposure.

Keywords: asthma; bronchial responsiveness; sensitization; cat; mite

The associations of the prevalence and incidence of asthma with allergen sensitization and exposure are complex (1). Asthma is strongly related to sensitization to indoor allergens (1, 2).

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Asthma is strongly related to sensitization to indoor allergens. Patients have greater bronchial responsiveness when exposed to allergens to which they are sensitized.

What This Study Adds to the Field

In the general population, bronchial responsiveness is positively associated with increasing cat allergen exposure in all atopic adults. All atopic individuals may benefit from reduced cat exposure.

Sensitization does not develop in the absence of exposure (2), but may be influenced by its timing and intensity, and differ between allergens (3, 4). However, there is a lack of direct evidence between exposure and asthma incidence (5), and it has been suggested that allergy “has been overinterpreted as a risk factor for asthma” (6).

Prospective studies in children have suggested that early exposure to cat allergen increases the risk of sensitization (7–9), whereas a cross-sectional study of 12- to 13-year-old children reported that high exposure to cat allergen was associated with reduced prevalence of sensitization to cat (10). One cross-sectional study in adults reported decreased prevalence of sensitization to cat in those currently highly exposed (11), whereas no association was found in young adults in the European Community Respiratory Health Survey (ECRHS) (12). In contrast, studies have found the risk of sensitization to house dust mite to increase with exposure in children (7, 8, 13–15), and with current exposure in adults in one study (16). However, there was no association in the ECRHS (12).

It is generally assumed that current exposure is required to produce symptoms in sensitized individuals, so that secondary prevention measures aim to reduce exposure (17–19). There have been relatively few population studies of the relation of asthma prevalence or incidence to both sensitization and current exposure, and even fewer that have tested their interaction.

Bronchial responsiveness (BHR) to a nonspecific provocation agent, such as methacholine, is the objective measure of choice

in epidemiological studies on asthma, complementing the more subjective information provided by symptom data. Patients with asthma have greater BHR when exposed to the allergen to which they are sensitized (20–22), and BHR may be increased in atopic patients with asthma when exposed to allergens to which they are not sensitized (23). However, it is not known if these findings hold in a general population study.

The ECRHS was a multicenter study in which the prevalence of cat ownership varied widely between centers at the first survey (ECRHS I) (24). House dust mite and cat allergen exposures were measured in dust samples collected in a subsample of homes in the follow-up study (ECRHS II) (25). The cross-sectional relations of BHR to sensitization in ECRHS I (26) and other risk factors (27) have been published, and the association of change in BHR with smoking has also been reported (28). We analyzed BHR in relation to cat and house dust mite exposure and IgE sensitization to cat, house dust mite, timothy grass, and *Cladosporium*, together with previously determined risk factors for BHR (27). Some of the results of this study have been previously published in the form of an abstract (29).

METHODS

Subjects

The ECRHS II took place from 1998 to 2002 (25) (*see the online supplement*). Only cross-sectional data from participants selected in the random sample are included in this article. Data are taken from ECRHS II except where otherwise specified. The majority of centers, 20 in total, performed methacholine challenge and took part in an indoor protocol.

Allergen Concentrations

Details of the indoor substudy protocol and the distributions of Der f 1, Der p 1, and Fel d 1 allergen concentrations have been described elsewhere (30, 31). Details of the methods are given in the online supplement.

Total and Specific IgE

Serum total IgE and specific IgE to cat, house dust mite (*Dermatophagoides pteronyssinus*), *Cladosporium*, and timothy grass were measured using the Pharmacia CAP System (Pharmacia Diagnostics AB, Uppsala, Sweden) (*see the online supplement*).

Questionnaire Data

Details of the questions used to define smoking status, cat ownership, currently or in childhood, and childhood illnesses are given in the online supplement.

Body Mass Index and Lung Function Testing

Details are published elsewhere (28), and are available in the online supplement.

Bronchial Challenge

The details of the methacholine challenge are given elsewhere (26–28), and in the online supplement. The term “slope” is used for transformed log slope as used in the ECRHS (26–28), with a low slope indicative of high BHR, with values ranging from 1 to 20. For graphical presentation, results were converted to approximate change in the dose producing a 20% fall in FEV₁ (PD₂₀), in doubling dose units (32).

Statistical Analysis

Concentrations of Fel d 1 and Der 1 (Der p 1 plus Der f 1) had highly positively skewed distributions, with a large proportion below the detection limit of 0.1 $\mu\text{g} \cdot \text{g}^{-1}$. Data were therefore divided into undetectable ($< 0.1 \mu\text{g} \cdot \text{g}^{-1}$) and four quartile groups of detectable concentrations for each allergen (Fel d 1: 0.1–0.22, 0.23–0.64, 0.65–8.0, $> 8.0 \mu\text{g} \cdot \text{g}^{-1}$; Der 1: 0.1–0.75, 0.76–4.01, 4.02–16.3, $> 16.3 \mu\text{g} \cdot \text{g}^{-1}$).

In the main analysis, BHR slope was analyzed by multiple linear regression adjusted for age, sex, height, and center, in relation to the

following: each specific IgE; titers of IgE sensitization; Der 1 and Fel d 1 exposure; log-transformed total IgE; body mass index (BMI); smoking; serious respiratory infection in childhood; hospitalization for lung disease before the age of 2 years; cat ownership in childhood; family history of allergic disease; and season of testing. In addition, BHR was adjusted for FEV₁ expressed as a difference from internally derived predicted values for age, height and sex, and FEV₁/FVC (26, 27). Interactions considered are specified in the online supplement. Secondary analyses were performed to estimate the relation of BHR to Fel d 1 and Der 1 exposure separately for sensitized and nonsensitized individuals, and for cat owners and non-cat owners in relation to cat allergen exposure. The effect of current cat ownership, in addition to or as a substitute for Fel d 1 exposure, as well as Der p 1 and Der f 1 as separate exposures, was considered.

RESULTS

Participants

In the random sample, 3,119 homes were visited, providing dust samples that resulted in 2,890 measurements of Der 1 and 2,817 measurements of Fel d 1. A total of 2,084 random sample participants in the indoor protocol in 20 centers had data for BHR slope. Men were more likely to be current (31.1%) or ex-smokers (32.6%) than women (27.3 and 25.0%, respectively). Ages ranged from 27 to 56 years. Mean FEV₁ was 4.09 L in men and 3.03 L in women, FEV₁/FVC values were 80.0 and 81.1%, respectively. More men than women were sensitized to house dust mite, 18.5% compared with 13.4% ($p < 0.001$), and to timothy grass, 16.7 and 14.0%, respectively ($p = 0.058$), but there was little difference in sensitization to cat (9.0 and 8.3%, $p = 0.506$) or *Cladosporium* (1.3 and 0.8%, $p = 0.200$). More men than women (31.6% compared with 24.6%, $p < 0.001$) were sensitized to any of the four allergens.

Exposure to House Dust Mite and Cat Allergen

Cat allergen was ubiquitous, although levels were low in Spain (31), whereas Der 1 levels were low in Scandinavia and detected in only one home in Reykjavik (28). Exposure to cat allergen was higher in women than in men ($p = 0.001$), with 23.3% of men and 17.7% of women exposed to undetectable levels, and 17.4 and 22.3%, respectively, exposed to the group of highest values (Table 1). There was no significant difference between men and women in exposure to Der 1 ($p = 0.311$).

Exposure to Cats

Exposure to childhood cats and current cat ownership are shown in Table E1 of the online supplement. Women were more likely than men to own a cat currently and to allow it in the bedroom.

TABLE 1. DISTRIBUTIONS OF EXPOSURE TO DER 1 AND FEL D 1 BY SEX

	Men, n (%)	Women, n (%)
Der 1 exposure, $\mu\text{g} \cdot \text{g}^{-1}$		
Undetectable	410 (30.5)	518 (33.5)
0.1 to 0.76	228 (16.9)	262 (17.0)
0.77 to 4.01	226 (16.8)	265 (17.2)
4.02 to 16.3	240 (17.8)	249 (16.1)
> 16.3	242 (18.0)	250 (16.2)
Total	1,346 (100.0)	1,544 (100.0)
Fel d 1 exposure, $\mu\text{g} \cdot \text{g}^{-1}$		
Undetectable	306 (23.3)	265 (17.7)
0.1 to 0.22	245 (18.6)	278 (18.5)
0.23 to 0.64	270 (20.5)	324 (21.6)
0.65 to 8.0	265 (20.2)	298 (19.9)
> 8.0	228 (17.4)	334 (22.3)
Total	1,314 (100.0)	1,499 (100.0)

TABLE 2. THE RELATION OF BRONCHIAL RESPONSIVENESS SLOPE TO DER 1 ALLERGEN LEVELS IN MATTRESS DUST

House dust mite allergen, $\mu\text{g} \cdot \text{g}^{-1}$	Adjusted for All Potential Risk Factors*			
	Difference from Reference Group (95% CI)	p Value	Trend in Slope per Group (95% CI)	p Value for Trend
Undetectable	0 (reference group)		−0.03 (−0.12 to 0.07)	0.562
0.1 to 0.76	0.06 (−0.29 to 0.41)	0.733		
0.77 to 4.01	−0.05 (−0.42 to 0.31)	0.772		
4.02 to 16.3	−0.14 (−0.52 to 0.24)	0.468		
> 16.3	−0.04 (−0.45 to 0.37)	0.852		

Definition of abbreviation: CI = confidence interval.

* Adjusted for cat allergen exposure, center, sex, age, total IgE, sensitization, and degree of sensitization to each allergen with center interaction terms, and for interaction of sex with house dust mite sensitization, FEV₁ as standardized difference from predicted, FEV₁/FVC, smoking status, height, body mass index, season of testing, serious respiratory infection before age of 5 years, hospitalization for lung disease in first 2 years, family history of allergic disease, and ownership of cat in childhood.

Associations of BHR with Exposure to Allergens

In the multivariable analysis, BMI was treated as continuous, because nonlinearity was not detected. There were 1,884 participants with complete data. Interactions of center with sensitization to each of the four allergens and the interaction of sex with sensitization to house dust mite were retained, the latter suggesting a greater increase in BHR in sensitized women than in sensitized men ($p = 0.028$). The relations of BHR to house dust mite, adjusted for these interactions and all other main effects, are shown in Table 2. There was no significant relation overall between BHR and house dust mite exposure group ($p = 0.870$), or trend with increasing exposure ($p = 0.562$). When cat allergen exposure was considered as the five groups as defined above and shown in Table 3, cat allergen level was not significantly related to BHR ($p = 0.298$), but there was a statistically significant trend for greater BHR (lower slope) with increasing cat allergen exposure (p for trend = 0.033; Table 3). As shown in model 2 of Table 3, there was little change in the relation of BHR to cat allergen level when only factors significantly associated with BHR were included. The difference in BHR slope between the highest and lowest exposure groups corresponded to approximately −0.62 doubling doses of PD₂₀ (95% confidence interval [CI], −1.16 to −0.08), and the trend to −0.13 doubling doses per group (95% CI, −0.26 to −0.01). There was no significant variation in the trend between the 20 centers (p for heterogeneity = 0.328).

Secondary Analyses of Fel d 1 Exposure

In subjects without cats in the home, the association of BHR with cat allergen level was weak (Table 4). The overall trend was largely due to the strong association of BHR with cat allergen levels in those with a cat allowed in the home. However, the trend in this group was not statistically significant ($p = 0.072$), nor was the interaction of cat ownership and trend in exposure ($p = 0.173$). The trend in BHR with the exposure group was marginally statistically significant ($p = 0.040$) in the majority group whose members were not sensitized to cat. The trend was greater in the small group that was IgE-sensitized to cat ($n = 157$) compared with those not sensitized, but not significantly so ($p = 0.089$). However, the trend in BHR in those sensitized to any of the four allergens was as large as in those sensitized to cat, and highly significant ($p < 0.001$), and almost as great as in those sensitized to house dust mite, grass, or *Cladosporium*, but not to cat. There was a very large estimate of trend in the 44 individuals sensitized only to cat ($p = 0.009$). No trend was observed in those not sensitized to any of the four allergens.

The association of BHR with Fel d 1 exposure was significantly greater in those sensitized to at least one of the four allergens than in those not sensitized to any allergen (interaction $p = 0.001$). This interaction is shown in Figure 1 in approximate doubling dose units. In those not sensitized, the difference in BHR between those exposed to the highest and lowest groups of Fel d 1 corresponded to approximately −0.28 doubling doses of PD₂₀ (95% CI, −0.90 to 0.34); in those sensitized, the difference

TABLE 3. THE RELATION OF BRONCHIAL RESPONSIVENESS SLOPE TO CAT ALLERGEN LEVELS IN MATTRESS DUST

Cat Allergen ($\mu\text{g} \cdot \text{g}^{-1}$)	Model 1: Adjusted for All Potential Risk Factors*			Model 2: Adjusted for Variables Associated with BHR†			
	Difference from Reference Group (95% CI)	p Value	Trend in Slope per Group (95% CI)	Difference from Reference Group (95% CI)	p Value	Trend in Slope per Group (95% CI)	p Value
Undetectable	0 (reference group)		−0.08 (−0.16 to −0.01)	0.033	0 (reference group)	−0.08 (−0.16 to −0.01)	0.033
0.1 to 0.22	−0.15 (−0.46 to 0.17)	0.361			−0.14 (−0.45 to 0.17)	0.362	
0.23 to 0.64	−0.18 (−0.50 to 0.14)	0.274			−0.16 (−0.48 to 0.15)	0.309	
0.65 to 8.0	−0.23 (−0.56 to 0.10)	0.173			−0.19 (−0.52 to 0.13)	0.235	
> 8.0	−0.37 (−0.70 to −0.04)	0.029			−0.38 (−0.70 to −0.05)	0.024	

Definition of abbreviations: BHR = bronchial responsiveness; CI = confidence interval.

* Adjusted for Der 1 allergen exposure, center, sex, age, total IgE, sensitization, and degree of sensitization to each allergen with center interaction terms, and for interaction of sex with house dust mite sensitization, FEV₁ as standardized difference from predicted, FEV₁/FVC, smoking status, height, body mass index, season of testing, serious respiratory infection before age of 5 years, hospitalization for lung disease in first 2 years, family history of allergic disease, and cat ownership in childhood.

† Adjusted for center, sex, total IgE, sensitization, and degree of sensitization to each allergen with center interaction terms, and for interaction of sex with house dust mite sensitization, FEV₁ as standardized difference from predicted, FEV₁/FVC, smoking status, and body mass index.

TABLE 4. TREND IN BRONCHIAL RESPONSIVENESS SLOPE PER GROUP OF CAT ALLERGEN LEVEL IN SUBGROUPS*

Subgroup	n	Trend in BHR Slope per Group	95% CI	p Value
No cat inside home	1,569	−0.07	−0.16 to 0.02	0.130
Cat inside home	314	−0.32	−0.66 to 0.03	0.072
Not sensitized to cat	1,727	−0.08	−0.16 to −0.00	0.040
Sensitized to cat	157	−0.31	−0.56 to −0.05	0.017
Not sensitized to cat, house dust mite, timothy grass, or <i>Cladosporium</i>	1,373	−0.03	−0.11 to 0.06	0.516
Sensitized to any of cat, house dust mite, timothy grass, or <i>Cladosporium</i>	511	−0.30	−0.45 to −0.16	< 0.001
Sensitized, but not to cat	354	−0.29	−0.46 to −0.12	0.001
Sensitized only to cat	44	−0.60	−1.05 to −0.15	0.009
Total group	1,884	−0.08	−0.16 to −0.01	0.033

For definition of abbreviations, see Table 3.

* Adjusted as in model 2 of Table 2.

was approximately -2.02 doubling doses (95% CI, -3.06 to -0.97). Those sensitized and exposed to levels in the next highest exposure group (0.65 to $8 \mu\text{g} \cdot \text{g}^{-1}$) showed nearly as great an increase in BHR as those exposed to more than $8 \mu\text{g} \cdot \text{g}^{-1}$.

Other Secondary Analyses

The relation of BHR to Der 1 exposure was neither significant nor monotonic in those sensitized or not sensitized to any allergen. There was no additional effect of current cat ownership to Fel d 1 level on BHR, nor was cat ownership significantly related to BHR when Fel d 1 level was omitted from the analysis. Neither Der p 1 nor Der f 1 exposure was related to BHR when the two components of Der 1 were analyzed.

DISCUSSION

In this population-based study, higher levels of cat allergen in mattress dust were associated with increased BHR. We hypothesized *a priori* that the association of BHR with allergen exposure would be greater in those sensitized to the relevant allergen. We did not find a significantly greater trend in BHR with increasing Fel d 1 in those sensitized to cat than in those not sensitized, but the overall trend in BHR with increasing Fel d 1 led us to examine the relation in those sensitized to any allergen, and to

any allergen excluding cat; each group showed a strong relation of increasing BHR with greater exposure.

The random sample that provided data for this analysis has the following strengths: subjects were not selected according to atopic or asthmatic status, and the sample was large compared with previous studies of adult BHR in relation to adult cat exposure in the general population (33–35). It was large enough to adjust for all potentially confounding main effects, and for interactions of center with IgE sensitization, which was found necessary in a cross-sectional analysis of ECRHS I data (27). Community studies have to balance the amount of information collected with a feasible and affordable sample size, and no study may be large enough to detect or rule out all interactions of potential interest.

Our study has a number of strengths apart from sample size. It was a multicenter study, performed to a common protocol, with a range of prevalence of cat ownership from less than 10% in two centers in Spain to more than 35% in the U.K. centers (31). Der 1 concentrations also differed substantially, from being virtually undetectable in Iceland to almost all homes having detectable levels reported in three centers in Spain (30). Despite the considerable variation, no heterogeneity in the relation of BHR to allergen level across centers was detected.

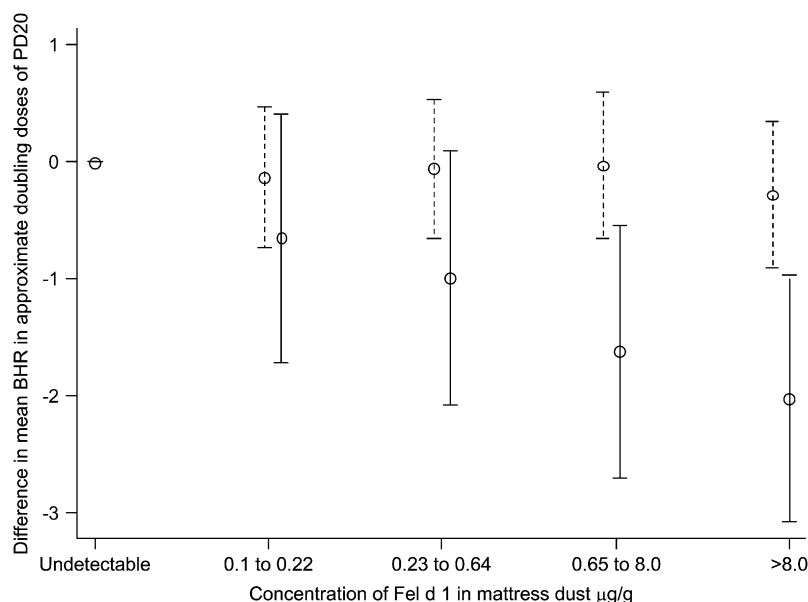


Figure 1. Mean differences in bronchial responsiveness (BHR), with 95% confidence intervals, from the lowest level of Fel d 1 exposure in those sensitized to any of four allergens (solid lines) and those not sensitized (dashed lines), in approximate doubling dose units of PD_{20} , adjusted for center, sex, total IgE, sensitization, and degree of sensitization to each allergen with center interaction terms, and for interaction of sex with house dust mite sensitization, FEV_1 as the standardized difference from predicted, FEV_1/FVC , smoking status, and body mass index.

Plaschke and colleagues found increased BHR in sensitized patients with asthma exposed to a cat at home compared with those not exposed (20). With exposure defined as more than $10 \mu\text{g} \cdot \text{g}^{-1}$ Fel d 1, Langley and colleagues found that the lowest mean PD_{20} (i.e., the greatest BHR) in patients both sensitized and exposed to cat, but a larger mean PD_{20} in those exposed and not sensitized than in those not exposed or sensitized, contributed to the weakly significant interaction between sensitization and exposure (22). In a later report by the same authors, PD_{20} did not differ significantly between non-cat-sensitized atopic patients with asthma who were exposed or not exposed to cat (23). They concluded that atopic subjects with asthma who are exposed to high levels of house dust mite or cat have evidence of increased BHR. To some extent, our findings support this earlier work. Our results show that individuals sensitized to house dust mite, timothy grass, or *Cladosporium*, but not cat, and who are exposed to high levels of cat allergen, have raised BHR (Table 4), but we did not see the equivalent result for exposure to house dust mite allergen. Some caution must be expressed over the results, as the subgroup analyses and tests of interaction were not all preplanned.

In a follow-up in adulthood of 224 participants in a childhood study in New South Wales, de Meer and coworkers reported nonsignificantly greater BHR at age 28 in those owning a cat at age 18 years or older compared with never cat owners (33). A study in Melbourne followed the main ECRHS protocol, but performed a separate indoor protocol (34, 35), and their data were not included in the current analysis. Their separate cross-sectional analysis suggested that "current asthma," defined as BHR with wheeze, was increased in the highest quartile group of bed Fel d 1 exposure (34). In their longitudinal analysis, a doubling of Fel d 1 exposure at follow-up was associated with a 73% greater odds of incident self-reported doctor-diagnosed asthma, but not with a significant increase in BHR (35).

The relation of IgE sensitization to mattress Fel d 1 concentration was not statistically significant in the ECRHS II (12), although sensitization was marginally related to allowing a cat indoors in ECRHS I (24). There is little consensus on the association of IgE sensitization to cat and the keeping of cats in childhood, with some studies reporting a positive association (7–9, 36, 37), and others suggesting that early exposure may be protective (24, 38, 39). Results in relation to exposure in adults are harder to interpret. Custovic and colleagues found decreased sensitization in adults exposed to high levels of Fel d 1 (11), and in those reporting current cat ownership (11, 16). Oryszczyn and coworkers found a positive skin-prick test to cat to be reduced in adults with early exposure to a cat or dog, but unrelated to current pet exposure (40). Adults with symptoms may avoid cat ownership, and selective avoidance may contribute to the inconsistent findings (16, 41). In addition, the definition of "high" exposure varies. A concentration of at least $8 \mu\text{g} \cdot \text{g}^{-1}$ has been suggested as a threshold for symptoms of asthma (34), and more than $10 \mu\text{g} \cdot \text{g}^{-1}$ has also been used (22), but most authors have divided their skewed distributions into quantile groups. Studies have varied according to whether carpet (7, 35, 42) or mattress concentration (8, 11, 16, 36), or both (9, 22, 23, 34), were measured.

The reported adverse association between cat allergen exposure and BHR was not confined to cat-sensitized subjects. Exposures other than cat allergen, but which are related to cat allergen concentration or cat ownership, may be implicated. One possible confounding exposure is environmental tobacco smoke. Munir and colleagues (43) found a positive correlation between Fel d 1 and small airborne particles, the latter dominated by tobacco smoke in the homes of smokers. No significant relation was found in ECRHS I between BHR and environmental tobacco smoke (44), and adjusting for the number of smokers in the

home in ECRHS II did not alter the association (Table 4) between BHR and Fel d 1 in those sensitized but not to cat. Building characteristics are also possible confounders, but adjusting for age of house, reported water damage in the last 12 months, or reported mold or mildew in the last 12 months did not alter the estimate. Several studies—for example, Heinrich and colleagues (45)—have found higher concentrations for endotoxin in cat owners' homes. In addition to its known immune-stimulating properties, in one study endotoxin was marginally significantly associated with asthmatic symptoms (46). Thus, cat allergen exposure or cat ownership may be a proxy for increased exposure to endotoxin that leads to increased BHR, and we cannot rule out this explanation in the current data.

No relation of BHR to mattress Der 1 level was detected, nor interaction with any sensitization, even after adjustment for the interaction of Fel d 1 with sensitization (not shown). BHR was strongly related to sensitization to house dust mite, and to degree of sensitization, in ECRHS I, with some between-center heterogeneity in the latter association (26), and studies have shown the prevalence of asthma to be related to sensitization to house dust mite. Sensitization to house dust mite has been shown to be related to exposure in several studies (1). Sporik and Platts-Mills gave reasons why a direct relation between exposure and asthma might not be observed (2), including seasonal variation, variation in the dominant allergen between areas, and possible nonlinearity between exposure and sensitization. However, house dust mite is present at all seasons in most environments, with no suggestion that high levels are protective. Sporik and colleagues reported a relation of incidence of asthma and early exposure to house dust mite in one U.K. study (14), and of prevalence of asthma with exposure in atopic children when three case-control studies were combined (47). Allergen exposure modification studies in adults with asthma have been targeted at reduction of mite allergen exposure (17, 18). Our results suggest that this may be less important for adults than reduction of cat allergen exposure, even for individuals not sensitized to cat. At least one study has found wheezing in children to be related to cat allergen but not to mite (48).

Despite the relation of BHR to allergen exposure found here, and the relation of exposure to community cat prevalence (31), it was not possible to demonstrate a relation of BHR in non-cat owners to community cat prevalence across the 20 centers (not shown). This is not surprising, because the range of allergen levels in the home is much greater than the range of geometric mean values across the centers (31), and there are many factors associated with BHR besides cat exposure.

We considered whether our results could be explained by insensitivity of specific IgE measurement for cat sensitization, but we believe this to be unlikely. First, the cutoff we used for presence of IgE to cat was low ($0.35 \text{ kU}_A \cdot \text{L}^{-1}$). Second, there was almost no trend in those not IgE-sensitized to any of the four allergens. Third, we estimate that a zero trend in those sensitized to one of three allergens but not to cat would require around half of these 354 participants to have false-negative test results for IgE to cat. Fourth, a review of skin-prick test data collected in the first survey for 316 of these 354 subjects showed that only 31 had a positive weal ($> 0 \text{ mm}$) for cat. The trend in BHR with Fel d 1 in the 285 subjects negative to both serum IgE at follow-up and skin-prick test about 9 years earlier was -0.17 (95% CI, -0.35 to 0.01 ; $p = 0.058$), which, although less than the estimate presented in Table 4 and not quite statistically significant, is compatible with a relation in those not sensitized to cat. An alternative explanation is that there are false negatives in each test. Whichever is true, advice should be against cat ownership in those showing sensitization to any allergen. Gehring and colleagues reported increased breathlessness and cough at

night in subjects exposed to Fel d 1 of more than $8 \mu\text{g} \cdot \text{g}^{-1}$, and who were not IgE-sensitized to any of 13 allergens (46). However, a relatively high cutoff of $0.7 \text{ kU} \cdot \text{L}^{-1}$ or greater was used to define sensitization.

Our results suggest that avoidance of exposure to cat allergen and cats may be beneficial in terms of BHR for a wider group of individuals than previously anticipated. Over a quarter of adults in the ECRHS were sensitized to at least one of the four allergens, and hence at risk. Cat allergen levels are ubiquitous in cat-owning communities (42), and our results show an effect at levels below that usually regarded as high enough to produce symptoms (34), and associated with a cat in the home (2). The estimated effect on BHR of cat allergen exposure in the highest compared with the lowest exposure group, in those sensitized to at least one of the four allergens, was almost as great as the difference between participants with and without asthma in the U.K. centers in ECRHS I (32).

The findings suggest that, within the population, there are people who may benefit from reduced cat exposure even though serum IgE tests suggest that they are not sensitized to cats. This group of individuals can be identified by their IgE sensitization to common allergens. A reduction in cat ownership in countries in which this exposure is high could benefit a large section of the population.

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On-line data supplement

Bronchial responsiveness in atopic adults increases with exposure to cat allergen

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Methods

Statement of potential overlap in publications

The data for each of the main variables used in the analyses for this paper have been included in previous publications, but not together. Bronchial responsiveness (BHR) at ECRHS II was used in the calculation of change in BHR, which was analyzed in relation to change in smoking (E01). IgE sensitization at ECRHS II was analyzed in relation to allergen levels (E02), and the distributions of the allergen levels have been published (E03,E04).

Subjects

ECRHS II took place in 29 centers at periods varying between centers from 1998 to 2002, when participants were aged 26 to 56 years (E05). The study had a self-administered postal questionnaire followed by a clinical stage, which included an administered questionnaire, blood sampling, and measurement of spirometric lung function. The majority of centers, 20 in total, performed methacholine challenge and took part in an indoor protocol.

Allergen concentrations

Details of the indoor sub-study protocol and the distributions of Der f 1 and Der p 1 allergen concentrations have been described elsewhere (E03), as has the distribution of Fel d 1 in the study (E04). The objective was to make measurements in 200 homes in each center, with priority to subjects who did not move home during the follow-up, provided a blood sample, and belonged to the random population sample. A sample of dust was taken from each participant's mattress. A short video showing the dust sampling procedure was shown to all fieldworkers during a locally arranged training meeting. The bed of the participant was stripped of regularly changed bed linen. Any

mattress covers or protectors that had been in place for at least three months were left on the mattress. A template of 80×125 cm was placed on the area of the bed where the participant usually slept. An ALK dust collection filter (ALK-Abello, Horsholm, Denmark) was attached to an Electrolux “Mondo” vacuum cleaner (1,300 W) and the area within the template (1 m²) was vacuumed for 2 minutes. Samples were frozen (−20°C) within three days for 24 hours to kill mites, and subsequently stored at room temperature until transported with a silica gel desiccant to one central laboratory. Samples were sieved (1 µm) to obtain fine dust for extraction. 5% w/v extracts in borate-buffered saline of sieved dust samples were assayed for Fel d 1, Der p 1, Der f 1 and Group 2 using monoclonal antibody ELISA assays (Indoor Biotechnologies, UK). The lower limit of detection was 0.1 µg allergen per gram of dust with no upper limit. The level of Der Group 1 allergens was calculated by summing Der p 1 and Der f 1 levels, ignoring levels below the detection limit.

Total and specific IgE

Serum total IgE and specific IgE to cat, house dust mite (*D. pteronyssinus*), *Cladosporium* and Timothy grass were measured using the Pharmacia CAP System (Pharmacia Diagnostics AB, Uppsala, Sweden). The measurement range for total IgE was 2 to 2000 kU/L, and 0.35 to 100 kU_A/L for specific IgE. Sensitization was defined as a specific IgE of 0.35 kU_A/L or greater.

Questionnaire data

The questions ‘Do you keep a cat?’, and if yes, ‘Is your cat (are your cats) allowed inside the house? Is your cat (are your cats) allowed in the bedroom?’ were asked. Individual ownership was categorized as none or outside only, cat allowed in house

but not bedroom, cat allowed in bedroom. ‘Was there a cat in your home’: during the first year of life; when aged 1 to 4 years; and when aged 5 to 15 years, were also asked. Participants were divided into never smokers, ex-smokers and current smokers based on answers to the questions ‘Have you ever smoked for as long as one year?’, and ‘Do you now smoke, as of one month ago?’. Due to the finding in ECRHS I data of increased BHR in participants who reported a serious respiratory infection before the age of five years or a family history of allergic disease, information on these items was extracted from the ECRHS I questionnaire (E05). In addition the question ‘Were you hospitalized before the age of two years for lung disease?’ was asked in ECRHS II. ‘Don’t know’ was an accepted answer to the early life questions.

Weight and BMI

Weight was recorded to the nearest kilogram. Participants were weighed in light clothing without shoes. BMI was calculated as weight in kilograms divided by the square of height in meters. In a minority of centers participants were asked their height and weight, or measured only if they were unsure. BMI was analyzed as a categorical variable divided into underweight (<20), normal weight (20 to <25), overweight (25 to <30) and obese (≥ 30) initially, but as a continuous variable if non-linearity was not detected.

Lung function and methacholine challenge

Clinic appointments were made so that participants who were taking medication were seen at least four hours after inhaled medication and at least eight hours after oral medication. Appointments were made at a time of day convenient to participants, as it was not possible to standardize testing by time of day in the young adult population.

The maximum forced expiratory volume in one second (FEV₁) of up to five technically acceptable blows was determined, and similarly for forced vital capacity (FVC).

The details of the bronchial challenge have been given elsewhere (E07). In ECRHS II BHR was measured in eligible subjects using dosing to a maximum of 2 mg. Methacholine was delivered via a Mefar dosimeter (Mefar, Bovezzo, Italy), FEV₁ was recorded two minutes after each inhalation and the test stopped when either a 20% fall in FEV₁ was achieved or the final dose had been given. For consistency with other publications only data from the doses 0.0078 to 1mg are used here.

The measure of dose response slope adopted for between center analyses in the ECRHS is used as the measure of BHR. The term 'slope' is used for transformed log slope as used in the ECRHS (E06-E09), with a low 'slope' indicative of high BHR, values ranging from 1 to 20. For presentation some results were converted to approximate change in the dose producing a 20% fall in FEV₁ (PD₂₀), in doubling dose units (E08).

Interactions tested in statistical analyses

Interactions of center with IgE-sensitization to each of the four allergens were included, as in the ECRHS I paper (E06), and as between center heterogeneity in the relation of BHR to sensitization had been detected (E09). Interactions of exposure with IgE sensitization were included as they were of *a priori* interest. The interaction of BMI with smoking was included as this was detected in the ECRHS I analysis (E06), and interactions of smoking with sex and age were tested. Interactions of

smoking with sensitization and with exposure were tested due to the relations between sensitization and smoking (E10). Interactions between sex and sensitization, BMI, respiratory infection in the first five years and hospitalization before the age of two were considered. Except for the center with IgE-sensitization terms interactions were retained only if statistically significant at the 5% level.

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Table E1. Cat exposure in random sample participants for whom there was information on cat and/or house dust mite allergen exposure levels.

Exposure	Men n (%) N=1357 ⁺			Women n (%) N=1545		
Cat in home:	No	Yes	Don't know	No	Yes	Don't know
In first year of life	972 (71.6)	302 (22.3)	83 (6.1)	1109 (71.8)	352 (22.8)	84 (5.4)
When aged 1 to 4 years	953 (70.2)	356 (26.2)	48 (3.5)	1062 (68.7)	443 (28.7)	40 (2.6)
When aged 5 to 15 years	851 (62.7)	498 (36.7)	8 (0.6)	926 (60.0)	609 (39.4)	9 (0.6)
At any age	789 (58.1)*	568 (41.9)	-	865 (55.9)*	682 (44.1)	-
	No or outside only	Allowed in house, but not in bedroom	Allowed in bedroom	No or outside only	Allowed in house, but not in bedroom	Allowed in bedroom
Current cat ownership	1132 (83.6)	60 (4.4)	162 (12.0)	1231 (79.7)	73 (4.7)	241 (15.6)

* Includes 'Don't know' answers. ⁺ N=1354 for current cat ownership.