

*Original article***Cat and dust mite allergen levels, specific IgG and IgG₄, and respiratory symptoms in adults**

Deborah Jarvis, MD,^a Jan-Paul Zock, PhD,^f Joachim Heinrich, PhD,^e Cecilie Svanes, MD,^h Giuseppe Verlato, MD,^c Mario Olivieri, MD,^d Simona Villani, PhD,^g Michela Ponzio, PhD,^g Benedicte Leynaert, PhD,^k Jordi Sunyer, MD,^{f,i,j} Anna Dahlman-Hoglund, PhD,^j Susan Chinn, DSc,^b Christina Luczynska, PhD,[†] Dan Norbäck, PhD,ⁱ and Peter Burney, MD^a London, United Kingdom, Verona and Pavia, Italy, Neuherberg, Germany, Barcelona, Spain, Norway, Uppsala and Göteborg, Sweden, and Paris, France

Background: Exposure to allergen may induce a modified T_H2 response characterized by high IgG₄ levels, absence of IgE sensitization, and a decreased risk of allergic respiratory symptoms.

Objective: To assess the association of IgG₄ level with allergic respiratory symptoms in a community-based sample of adults.

Methods: Information on exposure to cats, respiratory symptoms, and mattress allergen levels was obtained from 2780 adults. Levels of cat and house dust mite (HDM) specific IgE, IgG, and IgG₄ were measured. The association of exposure to allergen with IgG₄ and of IgG₄ with symptoms was assessed. **Results:** Geometric mean (GM) cat specific IgG and IgG₄ was higher in subjects who had a cat that was allowed in the bedroom than in subjects without a cat (adjusted ratio of GM IgG₄, 1.41; 95% CI, 1.25-1.57). Levels of HDM specific IgG and

IgG₄ were similar in subjects with undetectable and high (>20.22 µg/g) mattress Der 1 levels (adjusted ratio of GM IgG₄, 1.02; 95% CI, 0.89-1.17). There was no evidence that high cat or HDM specific IgG₄ levels were associated with less IgE sensitization or with fewer symptoms.

Conclusion: In this community-based sample of adults, high IgG₄ levels to cat or HDM were not associated with a lower risk of allergic respiratory symptoms.

Clinical implications: In adults, high cat allergen exposure does not protect against respiratory symptoms. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: ECRHS, IgG, cat, house dust mite

From ^athe Respiratory Epidemiology and Public Health Group, National Heart and Lung Institute, London; ^bthe Department of Public Health Sciences, King's College London; ^cthe Unit of Epidemiology and Medical Statistics and ^dthe Unit of Occupational Medicine, Department of Medicine and Public Health, University of Verona; ^ethe Institute of Epidemiology, GSF—National Research Center for Environment and Health, Neuherberg; ^fthe Centre for Research in Environmental Epidemiology, Municipal Institute of Medical Research, Barcelona; ^gthe Section of Medical Statistics and Epidemiology, Department of Health Sciences, University of Pavia; ^hthe Department of Medicine, Department of Thoracic Medicine, Haukeland Hospital, Bergen, Norway; ⁱthe Department of Medical Science, Occupational and Environmental Medicine, Uppsala University; ^jthe Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital, Sahlgrenska Academy at Göteborg University; ^kInstitut National de la Santé et de la Recherche Médicale U700—Epidémiologie, Faculté de Médecine Xavier Bichat, Paris; and [†]the Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona.

[†]Deceased.

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Reprint requests: Deborah Jarvis, MD, Respiratory Epidemiology and Public Health Group, National Heart and Lung Institute, Emmanuel Kaye Building, Manresa Road, London SW3 6LR. E-mail: djarvis@imperial.ac.uk. 0091-6749/\$32.00

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Exposure to allergen is associated with an immunologic response that includes an increase in serum allergen specific IgE, IgG, and IgG₄.¹ An IgG response to allergen is seen in subjects who are and are not IgE-sensitized,¹⁻³ but IgG₄ responses are more common in subjects with IgE.^{1,2} Prolonged immunization may lead to an IgG₄-dominant response,⁴ and IgG₄ responses have been observed during allergen immunotherapy.⁵ IgG₄ may act as a blocking antibody interfering with IgE-mediated effector cell triggering,⁶ but conversely, in the presence of antigen, may promote histamine release from basophils.⁷ Protection from clinical effects has been reported with high levels of bee venom IgG₄ in beekeepers⁴ and for anti-worm antibodies in subjects with helminth infections.^{8,9}

In children, high exposure to cat allergen may cause an increase in IgG₄, and this response in the absence of an IgE response is associated with little clinical disease.^{10,11} Platts-Mills et al¹⁰ argued that this reflected a modified T_H2 response and noted that although there was “tolerance” to cat allergen at high exposures, no such phenomenon was seen for house dust mite (HDM), a weak allergen that does not induce a “mature germinal center” in lymph nodes.¹²

In this report, we describe the association of cat and HDM specific IgG and IgG₄ with recognized risk factors for allergy, including exposure to allergen and their association with IgE sensitization. We also examine the association of respiratory symptoms with cat and HDM specific IgG and IgG₄. Our primary aim was to determine whether there was any evidence for an IgG-mediated

Abbreviations used

BMI:	Body mass index
ECRHS:	European Community Respiratory Health Survey
GM:	Geometric mean
HDM:	House dust mite
OR:	Odds ratio

tolerance to exposure to allergen in a population-based sample of adults.

METHODS

The methods for the European Community Respiratory Health Survey (ECRHS) I have been described elsewhere^{13,14} and are also given in greater detail in this article's Online Repository at www.jacionline.org. Between 1998 and 2002, participants in ECRHS I in 22 centers (5 in Spain; 3 in Italy and Sweden; 2 in Belgium, the United Kingdom, France, Germany; 1 in Estonia, Iceland, and Switzerland) were recontacted and invited to visit a local clinic to complete a detailed questionnaire and have blood samples taken.¹⁵ Of these, as many as 200 in each center were visited at home and had mattress dust samples taken. They were selected using criteria (see this article's Table E1 in the Online Repository at www.jacionline.org) that gave priority to subjects who were part of the random sample in ECRHS I, had not moved home during the previous 10 years, and provided serum samples. The analysis presented here is restricted to subjects who were selected at random in ECRHS I.

Respiratory symptoms

Information on several respiratory symptoms was collected, but 2 were identified a priori for this analysis: (1) wheeze (wheeze with breathlessness in the previous 12 months) and (2) asthma (positive response to, "Have you ever had asthma?" and an attack in the last 5 years). For analyses regarding IgG₄ against cat, reported symptoms (cough or chest tightness or wheezing or breathlessness on exposure to animals such as cats, dogs, or horses) was also included as an outcome.

Assessment of exposure to allergen

Information on current exposure to cat (no cat, cat but not allowed in bedroom, cat allowed in bedroom) and cat ownership in childhood was collected. Mattress dust samples were taken following a standardized protocol, and Fel d 1, Der p 1, and Der f 1 were measured in a single laboratory by using standardized ELISA methods.¹⁶⁻¹⁸ The lower limit of detection for the allergen assays was 0.1 µg/g dust, with no upper limit.

Fel d 1 was not detectable in 549 of 2498 (22.0%) mattress dust samples and ranged from undetectable to 123,000 µg/g (median, 0.38 µg/g; interquartile range, 0.12-2.70 µg/g). The level was strongly associated with the presence of a cat (median Fel d 1 in homes with no cat, 0.2 µg/g; in homes where cat lived but was not allowed in bedroom, 10.1 µg/g; in homes where cat allowed in bedroom, 197.1 µg/g). Both Der p 1 and Der f 1 levels were below the limit of detection in 815 of 2572 (31.7%) mattress dust samples.

Serum measures

Serum IgE, IgG, and IgG₄ to cat (epithelium plus dander) and to HDM were measured by using the AutoCAP system (Pharmacia, Uppsala, Sweden). The limits of detection of the assays were 2 to 200 mg_A/L for IgG and 150 to 30,000 µg_A/L (0.15-30 mg_A/L) for IgG₄. IgE was considered to be present if greater than 0.35 kU_A/L was detected.

Two hundred twenty of 2780 (7.9%) measures of cat specific IgG and 16 of 2572 (0.6%) of HDM specific IgG were below the detection limit. Three hundred eighty-six of 2780 (13.9%) values of cat specific IgG₄ and 297 of 2572 (11.5%) of HDM specific IgG₄ were below the detection limit. No subjects had cat specific IgG or IgG₄ levels above the detection limit, but 27 subjects (1.1%) had IgG to HDM above the detection limit. Values of both IgG and IgG₄ followed a censored log-normal distribution.

Statistical analysis

The analysis was restricted to subjects with information on allergen specific IgE, IgG, and IgG₄ and a measure of allergen exposure (cat ownership or mattress dust sample).

The associations of level of cat specific IgG and IgG₄ with exposure to cat (cat ownership in childhood and current cat keeping) were determined by using censored regression models (with the log value of the detection limits of the assay as the censored upper and lower limits; see this article's Online Repository at www.jacionline.org) adjusting for age group, sex, smoking status, number of siblings, body mass index (BMI), socioeconomic status,¹⁹ family history of allergic disease (reporting either mother or father with history of asthma, hayfever, or eczema), selection criteria fulfilled for home visits (selection group), and study center.

The association of IgG and IgG₄ with mattress Fel d 1 level and total group 1 allergen HDM level (Der p 1 plus Der f 1) was assessed in a similar way, with mattress allergen concentration considered as a continuous variable. To ease presentation and to enable comparison with previously published work, Fel d 1 was also considered in 6 categories as by Platts-Mills et al.¹⁰ Group 1 HDM allergen level was also considered in 6 groups.

Associations were expressed as ratio of geometric means (GMs) with 95% CIs. Effect modification of the association of allergen exposure with IgG level by IgE sensitization, and sex was assessed by interaction terms.

For comparison, the association of IgE with the same risk factors was assessed using logistic regression.

All associations reported were examined for heterogeneity between centers using standard methods for metaanalysis,²⁰ and heterogeneity is reported where observed at $P < .05$.

All analyses were conducted using STATA 9.0 (Stata Corp, College Station, Tex).²¹

Ethical permission for the study was obtained from appropriate local ethical committees.

RESULTS

There were 2780 participants (1294 men and 1486 women) aged between 27 and 56 years (median, 44; interquartile range, 38-49) with serum cat specific IgE, IgG, and IgG₄ measures and information on current cat ownership (2498 with mattress Fel d 1 level). There were 2572 subjects with IgE, IgG, and IgG₄ to HDM and mattress Der 1 allergen measured. The number of subjects from each center and country are shown in this article's Table E2 in the Online Repository at www.jacionline.org.

The level of cat specific IgG and IgG₄ was higher in subjects IgE sensitized to cat (6.1 mg_A/L and 671 µg_A/L, respectively) than in subjects who were not (5.2 mg_A/L and 478 µg_A/L) with an adjusted ratio of GM of 1.12 and 95% CI, 1.02 to 1.23 for IgG (IgG₄ adjusted ratio of GM, 1.36; 95% CI, 1.20-1.55). Mite specific IgG and IgG₄ were also higher in subjects who were IgE-sensitized

TABLE I. Associations of cat specific IgE, IgG, and IgG₄ with risk factors (n = 2780 for unadjusted analyses, 2704 after adjustment)

	IgE		IgG		IgG ₄	
	Prevalence (%)	Adjusted† OR (95%CI)	GM IgG* (mg _A /L)	Adjusted† ratio of GM (95%CI)	GM IgG ₄ † (μg _A /L)	Adjusted† ratio of GM (95%CI)
Sex						
Men	9.0	1.00	5.0	1.00	523	1.00
Women	8.2	0.84 (0.63-1.15)	5.5	1.11 (1.05-1.18)	464	0.85 (0.78-0.93)
Age group						
<35 y	9.4	1.00	5.1	1.00	473	1.00
35-45 y	9.0	0.87 (0.56-1.35)	5.1	1.01 (0.93-1.09)	503	1.02 (0.90-1.15)
>45 y	8.0	0.72 (0.45-1.14)	5.5	1.08 (0.99-1.18)	488	0.96 (0.85-1.09)
Smoking status						
Lifetime nonsmoker	10.0	1.00	5.5	1.00	503	1.00
Ex-smoker	8.5	0.79 (0.58-1.11)	5.6	1.00 (0.95-1.07)	498	0.94 (0.86-1.03)
Current	6.6	0.70 (0.49-1.00)	4.7	0.87 (0.81-0.93)	464	0.94 (0.86-1.03)
No. of siblings						
0	10.3	1.00	5.0	1.00	550	1.00
1	8.4	0.80 (0.49-1.31)	5.5	1.06 (0.96-1.16)	513	0.95 (0.83-1.08)
2	10.5	1.11 (0.68-1.82)	5.4	1.04 (0.94-1.13)	493	0.97 (0.85-1.11)
3 or more	6.8	0.76 (0.46-1.24)	5.2	1.01 (0.91-1.11)	455	0.92 (0.81-1.06)
Cat as a child						
No	9.4	1.00	5.2	1.00	483	1.00
Yes	7.7	0.79 (0.59-1.05)	5.4	1.00 (0.95-1.05)	502	1.04 (0.96-1.12)
Don't know or missing	5.5	0.65 (0.20-2.27)	4.9	0.96 (0.80-1.16)	445	0.98 (0.74-1.28)
Current cat ownership						
None	8.3	1.00	5.2	1.00	464	1.00
Cat but not in bedroom	10.6	1.26 (0.73-2.19)	5.2	1.01 (0.91-1.14)	550	1.18 (1.00-1.39)
Cat in bedroom	9.6	1.12 (0.75-1.66)	6.2	1.18 (1.10-1.28)	658	1.41 (1.25-1.57)
In separate model adjusted as above but excluding current cat ownership						
Fel d 1 level (ug/g)§						
<0.69	8.4	1.00	5.2	1.00	464	1.00
0.70-1.69	8.5	0.97 (0.56-1.66)	4.7	0.98 (0.89-1.08)	441	0.87 (0.76-1.01)
1.70-4.39	9.1	1.02 (0.56-1.87)	5.1	1.01 (0.90-1.13)	518	1.03 (0.76-1.01)
4.40-22.90	8.4	1.08 (0.59-1.97)	5.1	1.05 (0.94-1.18)	454	0.92 (0.78-1.08)
23.00-106.00	9.6	1.29 (0.67-2.49)	5.4	1.07 (0.94-1.22)	572	1.17 (0.97-1.41)
>106.00	9.3	1.05 (0.65-1.69)	6.3	1.23 (1.12-1.35)	692	1.44 (1.26-1.65)
		<i>P</i> for trend = .6		<i>P</i> for trend < .001		<i>P</i> for trend < .001

*Calculated on log scale with values below detection limit set to log of 1 mg/L.

†Calculated on log scale with values below detection limit set to log of 100 μg/L.

‡Adjusted for all factors in table plus parental history of allergy, BMI, socioeconomic status, center, and selection group.

§Levels of Fel d 1 presented as per paper by Platts-Mills et al¹⁰ for ease of comparison (number of subject in each group 1550, 235, 154, 166, 125, and 268, respectively).

to HDM (35.5 mg_A/L and 487 μg_A/L, respectively) compared with subjects who were not IgE-sensitized (37.3 mg_A/L and 376 μg_A/L), with an adjusted ratio of GM of 1.05 and 95% CI, 0.96 to 1.14 for IgG (IgG₄ adjusted ratio of GM, 1.39; 95% CI, 1.27-1.52).

Association of IgE, IgG, and IgG₄ with sex, age, smoking, family size, and family history of atopic disease

Cat. The associations of cat specific IgE, IgG, and IgG₄ with sex, age, smoking, and family size are shown in Table I. Cat specific IgG was higher in nonsmokers and in women, although the effect of sex varied between centers (*P* for heterogeneity = .008). In contrast, cat specific IgG₄ was significantly lower in women.

Associations were similar stratifying by sex. However, stratification by IgE sensitization to cat showed that the

effect of having many siblings on IgG₄ level was largely seen in subjects who were IgE-sensitized (*P* for interaction of IgE with number of siblings for IgG, *P* = .054; for IgG₄, *P* = .027; Table II).

HDM. The associations of HDM specific IgE, IgG, and IgG₄ with sex, age, smoking, and family size are shown in Table III. As for cat specific IgG, the association of HDM specific IgG with sex varied between centers (*P* for heterogeneity = .002). HDM specific IgG₄ levels were similar in men and women, but levels were lower in current smokers than nonsmokers, an association that was significantly more marked in men than women (*P* for interaction of smoking with sex for HDM specific IgG₄, *P* < .003).

All other associations were similar comparing men with women and subjects who were and were not IgE sensitized to HDM.

TABLE II. Association of cat specific IgG₄ with reported current cat keeping and family size in subjects who are and are not IgE-sensitized

	IgG ₄			
	IgE ⁻ (n = 2541)		IgE ⁺ (n = 239)	
	GM (μg _A /L)	Adjusted* ratio of GM (95% CI)	GM (μg _A /L)	Adjusted* ratio of GM (95% CI)
No. of siblings				
0	507	1.00	1096	1.00
1	497	1.02 (0.88-1.17)	735	0.57 (0.37-0.87)
2	473	1.03 (0.89-1.18)	665	0.62 (0.41-0.96)
3 or more	450	0.99 (0.86-1.15)	492	0.49 (0.31-0.73)
		<i>P</i> for trend = .796		<i>P</i> for trend = .005
Cat keeping				
None	454	1.00	572	1.00
Cat but not in bedroom	518	1.12 (0.95-1.32)	915	1.75 (1.09-2.82)
Cat in bedroom	614	1.33 (1.18-1.49)	1399	1.95 (1.36-2.82)

*Adjusted for age, sex, smoking, BMI, socioeconomic status, family history, center, selection group, and other factors in table.

TABLE III. Associations of HDM specific IgE, IgG, and IgG₄ to HDM with risk factors (n = 2572)

	IgE		IgG		IgG ₄	
	Prevalence (%)	Adjusted OR (95% CI)	GM IgG* (mg _A /L)	Adjusted ratio of GM (95%CI)	GM IgG ₄ † (μg _A /L)	Adjusted ratio of GM (95% CI)
Sex						
Men	18.5	1.00	34.1	1.00	395	1.00
Women	13.4	0.58 (0.46-0.76)	40.4	1.22 (1.14-1.39)	379	0.97 (0.90-1.03)
Age group						
<35 y	19.3	1.00	33.4	1.00	365	1.00
35-45 y	17.8	0.93 (0.65-1.30)	37.3	1.04 (0.94-1.16)	391	1.03 (0.93-1.14)
>45 y	13.3	0.65 (0.45-0.94)	38.4	1.07 (0.96-1.20)	391	0.97 (0.87-1.08)
Smoking status						
Lifetime nonsmoker	16.0	1.00	40.4	1.00	403	1.00
Ex-smoker	12.9	0.75 (0.58-1.04)	40.4	0.98 (0.91-1.06)	403	0.93 (0.86-1.01)
Current	18.4	1.18 (0.90-1.54)	29.9	0.78 (0.72-0.84)	340	0.82 (0.76-0.89)
No. of siblings						
0	16.3	1.00	38.1	1.00	419	1.00
1	17.5	0.99 (0.67-1.50)	39.2	1.06 (0.94-1.20)	391	0.93 (0.83-1.04)
2	15.9	0.91 (0.63-1.45)	37.3	1.02 (0.90-1.15)	391	0.96 (0.85-1.08)
3 or more	14.0	0.90 (0.60-1.37)	35.5	0.97 (0.80-1.09)	376	0.93 (0.83-1.05)
Der 1 level§						
Not detected	9.3	1.00	42.1	1.00	407	1.00
0.1 to <0.56	19.4	1.00 (0.65-1.54)	37.3	1.04 (0.92-1.17)	415	1.19 (1.06-1.35)
0.56 to <2.06	18.9	0.99 (0.64-1.51)	35.8	1.00 (0.89-1.14)	383	1.08 (0.95-1.23)
2.06 to <6.70	15.3	0.73 (0.46-1.15)	33.4	0.98 (0.87-1.12)	368	1.04 (0.92-1.18)
6.70 to <20.22	19.6	1.07 (0.68-1.66)	34.5	1.05 (0.92-1.19)	372	1.08 (0.94-1.23)
20.22‡	20.8	1.08 (0.69-1.71)	34.4	1.06 (0.92-1.21)	361	1.02 (0.89-1.17)
		<i>P</i> for trend = .76		<i>P</i> for trend = .45		<i>P</i> for trend = .68

*Calculated on log scale with values below detection limit set to log of 1 mg/L.

†Calculated on log scale with values below detection limit set to log of 100 μg/L.

‡Adjusted for all factors in table plus parental history of allergy, BMI, socioeconomic status, center, and selection group.

§Number in each category of exposure to Der 1, 815, 350, 353, 352, 351, 351.

Association of IgE, IgG, and IgG₄ with exposure to allergen

Reported cat keeping. IgE sensitization to cat showed no statistically significant ($P > .05$) association with childhood or current cat ownership (Table I). Cat specific IgG and IgG₄ levels were higher in current cat owners, particularly if the cat was allowed in the bedroom. The magnitude

of this effect was significantly greater in subjects who were IgE sensitized to cat (P for interaction of IgE with cat keeping for IgG, $P = .096$; for IgG₄, $P = .005$; Table II). Neither IgG nor IgG₄ was associated with reported childhood exposure to cats. Overall (in subjects with and without cats) levels of cat specific IgG₄ were not associated with community prevalence of cat ownership (data not shown).

TABLE IV. Association of cat specific IgG₄ with cat specific IgE and with respiratory symptoms in subjects with and without specific IgE to cat‡

	Cat specific IgE		Wheeze with shortness of breath in the last 12 months			
	Percent with IgE	Adjusted* OR (95% CI)	Cat specific IgE ⁻ (n = 2534)		Cat specific IgE ⁺ (n = 239)	
			Percent with wheeze	Adjusted* OR (95% CI)	Percent with wheeze	Adjusted* OR (95% CI)
Cat specific IgG ₄ quartile (μg _A /L)						
ND to 307	6.5	1.00	6.6	1.00	26.7	1.00
308-549	5.7	0.88 (0.56-1.40)	7.5	1.03 (0.66-1.61)	25.0	1.18 (0.36-3.88)
550-869	8.7	1.31 (0.86-2.00)	8.9	1.22 (0.79-1.90)	23.3	0.99 (0.34-2.88)
871-25,057	13.5	2.09 (1.39-3.12)	7.0	0.94 (0.58-1.51)	21.3	0.78 (0.27-2.18)
Per-unit increase in IgG ₄ (1000 ug/L)		1.22 (1.09-1.37)		0.83 (0.62-1.11)		0.85 (0.59-1.19)

ND, Not detected.

*From logistic regression adjusted for age, sex, smoking, BMI, number of siblings, socioeconomic status, family history, and center (†centers in Spain, Italy, and Germany combined at country level because of low prevalence of outcomes in some centers) and selection group.

‡Results are presented unstratified by IgE status in this article's Tables E3 and E4 in the Online Repository at www.jacionline.org.

TABLE V. Association of HDM specific IgG₄ with house dust mite specific IgE and with respiratory symptoms in subjects with and without IgE‡

	HDM specific IgE		Wheeze with shortness of breath in the last 12 months			
	Percent with IgE	Adjusted* OR (95% CI)	HDM specific IgE ⁻ (n = 2157)		HDM specific IgE ⁺ (n = 406)	
			Percent with wheeze	Adjusted* OR (95% CI)	Percent with wheeze	Adjusted* OR (95% CI)
IgG ₄ quartile (μg _A /L)						
ND to 253	10.2	1.00	6.7	1.00	9.9	1.00
254-397	16.1	1.67 (1.17-2.39)	6.4	0.88 (0.54-1.46)	26.2	3.08 (1.12-8.48)
397-615	13.8	1.61 (1.12-2.32)	7.5	1.07 (0.74-1.54)	9.4	0.96 (0.31-3.99)
616-30,050	22.5	3.26 (2.31-4.64)	8.6	1.12 (0.69-1.85)	19.9	2.80 (1.04-7.26)
Per-unit increase in IgG ₄ (1000 ug/L)		1.95 (1.61-2.37)		1.01 (0.71-1.44)		1.03 (0.83-1.28)

ND, Not detected.

*From logistic regression adjusted for age, sex, smoking, BMI, number of siblings, socioeconomic status, family history, center (†centers in Spain, Italy, and Germany combined at country level because of low prevalence of outcomes in some centers) and selection group.

‡Results are presented unstratified by IgE status in this article's Tables E3 and E4 in the Online Repository at www.jacionline.org.

These associations were similar in all centers (test for heterogeneity, $P > .05$)

Mattress Fel d 1. IgE sensitization to cat was not associated with mattress Fel d 1 level (Table I). In subjects who were IgE sensitized to cat, there was a linear increase in both IgG (data not shown) and IgG₄ levels with increasing mattress Fel d 1 level (see this article's Fig E1 in the Online Repository at www.jacionline.org). In subjects who were not IgE sensitized, a less pronounced increase in IgG (data not shown) and IgG₄ was observed (interaction of Fel d 1 exposure with sensitization for cat IgG, $P = .041$; for cat IgG₄, $P = .01$; see this article's Fig E1 in the Online Repository at www.jacionline.org).

These associations were similar in all centers (test for heterogeneity, $P > .05$).

Mattress Der 1. IgE sensitization to HDM was not associated with mattress Der 1 level (Table III). With Der 1 allergen considered in 6 categories (as in Table II), there was no evidence of an increase in HDM specific IgG and IgG₄ with increasing exposure to group 1 allergen and no

evidence that the association varied by IgE sensitization status (interaction of exposure with sensitization for HDM IgG, $P = .8$; for HDM IgG₄, $P = .1$; see this article's Fig E2 in the Online Repository at www.jacionline.org).

These associations were similar in all centers (test for heterogeneity, $P > .05$).

Association of IgE sensitization and symptoms with IgG and IgG₄

Cat. The prevalence of IgE sensitization to cat was higher in subjects with the highest cat specific IgG₄ levels (Table IV) a difference that persisted even after adjustment for exposure to Fel d 1 (data not shown).

The prevalence of wheeze, asthma, and symptoms on exposure to cats, dogs, or horses was higher in subjects who were IgE sensitized to cat than in subjects who were not. There was no evidence that higher levels of cat specific IgG₄ were associated with less wheeze (see this article's Table E3 in the Online Repository at www.jacionline.org), asthma (see this article's Table E4 in the Online Repository at www.jacionline.org), or symptoms on exposure (data

TABLE IV. Continued

Cough or wheeze or chest tightness or shortness of breath on exposure to cats, dogs, or horses				Asthma			
Cat specific IgE ⁻ (n = 2534)		Cat specific IgE ⁺ (n = 239)		Cat specific IgE ⁻ (n = 2534)		Cat specific IgE ⁺ (n = 239)	
Percent with symptoms	Adjusted* OR (95% CI)	Percent with symptoms	Adjusted† OR (95% CI)	Percent with symptoms	Adjusted* OR (95% CI)	Percent with symptoms	Adjusted† OR (95% CI)
3.1	1.00	26.7	1.00	3.2	1.00	6.7	1.00
3.2	1.03 (0.53-2.01)	41.0	2.03 (0.67-6.10)	3.2	1.21 (0.63-2.31)	10.0	0.67 (0.06-7.31)
4.0	1.34 (0.73-2.59)	30.0	1.08 (0.39-3.00)	3.5	1.18 (0.62-2.25)	15.0	3.05 (0.45-20.0)
4.4	1.28 (0.72-2.62)	41.9	1.72 (0.65-4.56)	3.3	1.28 (0.66-2.50)	7.5	1.44 (0.18-11.1)
	1.00 (0.79-1.27)		0.91 (0.73-1.14)		1.04 (0.79-1.36)		1.09 (0.72-1.65)

TABLE V. Continued

Asthma			
HDM specific IgE ⁻ (n = 2156)		HDM specific IgE ⁺ (n = 402)	
Percent with symptoms	Adjusted* OR (95% CI)	Percent with symptoms	Adjusted† OR (95% CI)
2.6	1.00	4.2	1.00
2.4	1.02 (0.44-2.32)	9.8	2.43 (0.54-10.9)
1.5	0.60 (0.25-1.44)	8.3	2.75 (0.59-12.8)
4.3	1.24 (0.58-3.67)	14.7	7.22 (1.72-30.3)
	1.30 (0.87-1.94)		1.19 (0.86-1.47)

not shown), even when the analysis was stratified by IgE sensitization (Table IV) or when adjustment for Fel d 1 exposure was made (data not shown).

HDM. The prevalence of IgE sensitization to HDM was higher in subjects with the highest mite specific IgG₄ levels, a difference that persisted even after adjustment for Der 1 levels (Table V).

The prevalence of wheeze and asthma was much higher in subjects who were IgE-sensitized to HDM. Higher levels of HDM specific IgG₄ were associated with more wheeze and asthma, independently of IgE sensitization (see this article's Tables E3 and E4 in the Online Repository at www.jacionline.org). In subjects with IgE to HDM, the prevalence of asthma was significantly higher in subjects with the highest IgG₄ levels, an association that persisted after adjustment for Der 1 level (odds ratio [OR] for asthma in IgE-sensitized subjects with IgG₄ in top quartile, 7.54; 95% CI, 1.8-31.5).

DISCUSSION

We have shown that in a community-based sample of adults, serum IgG and IgG₄ to cat and to HDM can be detected in most subjects and, for cat, are higher in subjects exposed to cat allergen. We have found no evidence that

exposure to high levels of cat allergen in the home is associated with a lower prevalence of IgE sensitization to cat, or that high levels of cat specific IgG or IgG₄ are associated with a decreased risk of IgE sensitization or respiratory symptoms.

Participants in this study were initially selected at random from a community-based sampling frame. At each subsequent component of the study, response rates varied, and consistent with earlier published work from the ECRHS,²² responders were more likely to be female, older, and nonsmokers. However, the association observed between allergen exposures and IgE, IgG, and symptoms in participants that have taken part should still reflect that observed in the population. The multicenter design of the study has been accounted for by adjustment for center, and variation in association between centers has been examined using meta-analytical techniques. Although there was variation in the association of IgG with sex between centers, there was no evidence that other reported associations varied greatly between the centers.

We have shown evidence for a strong IgG₄ response to exposure to mattress Fel d 1 that is greater in subjects IgE-sensitized to cat than in subjects who are not, with little evidence for a similar response to mattress HDM allergen. Evidence for stronger IgG₄ responses in atopics on exposure has been described in small clinical studies²³ and

occupational studies.²³ In adults who work in environments with high allergen exposure, high IgG₄ levels have long been considered to reflect the strength of exposure and an increased risk of clinical disease. One study of laboratory animal workers showed rat urinary allergen specific IgG₄ levels that were higher in subjects who were highly exposed, IgE sensitized, and had the most symptoms,²⁴ and a study of workers in the fur industry had similar results when IgG₄ to both mink and silver fox urine was measured.¹⁰

We found no evidence that high current exposure to cat allergen is associated with a reduced risk of IgE sensitization, although this has been reported in children²⁵ and in adults²⁶ at Fel d 1 levels in excess of 4.4 µg/g and 44 µg/g, respectively. Even though three quarters of our subjects had exposures below 4.4 µg/g, our sample included more than 250 subjects exposed to levels greater than 106 µg/g. Whether cat allergen exposure was measured divided into textiles (data not shown), measured divided into exposure groups used in other studies, or considered as a linear variable, we found no evidence of lower IgE sensitization with greater exposure. Even when we defined IgE sensitization by a higher cutoff (0.70 kU_A/L), our conclusions were unaltered.

We found no evidence that high IgG₄ was associated with less clinical disease; on the contrary, we noted more asthma in subjects who had high IgG₄ to HDM, independent of IgE sensitization. We used health outcomes that may be considered to reflect allergic respiratory disease, and the patterns of association were similar for all symptoms. However, even in this large study, the power to detect differences by exposure group, stratifying for sensitization status, is limited.

A modified T_H2 response to environmental allergen may best be observed in children rather than adults. However, wheeze was not associated with cat specific IgG levels in children (sample size, 224) in New Zealand²⁶ or in Germany (sample size, 750),³ and in children living in rural communities in Europe (sample size, 812) cat specific IgG₄ levels were only marginally raised in subjects exposed to cats, even though exposure to cat showed a strong negative association with wheeze and atopic asthma.²⁷

We have described other epidemiologic features of IgG sensitization to cat and HDM. We have confirmed earlier observations that smoking is associated with lower IgG responses to allergen,²⁸ although such an association may arise from a healthy smoker bias. We have described differences in IgG₄ levels with sex. Although these varied between centers, they are consistent with another study in France in which lower levels of IgG₄ have been observed in women (M. P. Oryszczyn, personal communication, April 2006). As has been suggested by other work, there are some differences in the strength of some of these associations when cat and HDM are considered separately. To our knowledge, the strong negative association of family size with IgG₄ responses to cat in subjects who are IgE-sensitized has not been previously documented, but the clinical relevance of this observation is uncertain.

We conclude that IgG and IgG₄ to cat and HDM can be detected in most European adults. For cat, IgG₄ levels reflected exposure to allergen but were not associated with a lower prevalence of IgE sensitization to cat or symptoms. Higher IgG₄ levels to HDM were associated with asthma.

REFERENCES

- Jennmalm MC, Bjorksten B. Development of immunoglobulin G subclass antibodies to ovalbumin, birch and cat during the first eight years of life in atopic and non-atopic children. *Pediatr Allergy Immunol* 1999;10:112-21.
- Kemeny DM, Urbanek R, Ewan PW, McHugh S, Richards D, Patel S, et al. The subclass of IgG antibody in allergic disease, II: the IgG subclass of antibodies produced following natural exposure to dust mite and grass pollen in dust mite and grass pollen in atopic and non-atopic individuals. *Clin Exp Allergy* 1989;19:545-9.
- Lau S, Illi S, Platts-Mills T, Riposo D, Nickel R, Gruber C, et al. Longitudinal study on the relationship between cat allergen and endotoxin exposure, sensitization, cat specific IgG and development of asthma in childhood: report of the German Multicentre Allergy Study (MAS 90). *Allergy* 2005;60:766-73.
- Aalberse RC, van der GR, van LJ. Serologic aspects of IgG4 antibodies, I: prolonged immunization results in an IgG4-restricted response. *J Immunol* 1983;130:722-6.
- Gehlar K, Schlaak M, Becker W, Bufer A. Monitoring allergen immunotherapy of pollen-allergic patients: the ratio of allergen specific IgG4 and IgG1 correlates with clinical outcome. *Clin Exp Allergy* 1999;29:497-506.
- Witteman AM, Stapel SO, Sjamsoedin DH, Jansen HM, Aalberse RC, der Zee JS. Fel d 1-specific IgG antibodies induced by natural exposure have blocking activity in skin tests. *Int Arch Allergy Immunol* 1996;109:369-75.
- Aalberse RC, Van Milligen F, Tan K, Stapel SO. Allergen-specific IgG4 in atopic disease. *Allergy* 1993;48:559-69.
- Hussain R, Grogil M, Ottesen E. IgG antibody subclasses in human filariasis. *J Immunol* 1987;139:2794-8.
- Hussain R, Poindexter R, Ottesen E. Control of allergic reactivity in human filariasis. *J Immunol* 1992;148:2731-7.
- Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitization, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001;357:752-6.
- Hesselmar B, Aberg B, Eriksson B, Bjorksten B, Aberg N. High dose exposure to cat is associated with clinical tolerance: a modified TH2 immune response. *Clin Exp Allergy* 2003;33:1681-5.
- Aalberse R, Platts-Mills T. How do we avoid developing allergy: modifications of the TH2 response from a B-cell perspective. *J Allergy Clin Immunol* 2004;113:983-6.
- European Community Respiratory Health Survey. Protocol for the European Community Respiratory Health Survey. London: United Medical and Dental Schools of Guy's and St Thomas's Hospitals, Department of Public Health Medicine; 1993.
- Burney P, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954-60.
- European Community Respiratory Health Survey II Steering Committee. The European Community Respiratory Health Survey II. *Eur Respir J* 2002;20:1071-9.
- Luczynska CM, Li Y, Chapman MD, Platts-Mills TAE. Airborne concentrations and particle size distribution of allergen derived from domestic cats (*Felis domesticus*): measurements using a cascade impactor, liquid impinger and a two site monoclonal antibody for Fel d 1. *Am Rev Respir Dis* 1990;141:361-7.
- Luczynska CM, Arruda LK, Platts-Mills TA, Miller JD, Lopez M, Chapman MD. A two-site monoclonal antibody ELISA for the quantification of the major Dermatophagoides spp. allergens, Der p I and Der f I. *J Immunol Methods* 1989;118:227-35.
- Zock JP, Heinrich J, Jarvis D, Verlat G, Norback D, Plana E, et al. Distribution and determinants of house dust mite allergen in Europe: The European Community Respiratory Health Survey II. *J Allergy Clin Immunol* 2006;118:682-90.

19. International Labour Office G. International Standard Classification of Occupations (ISCO-88). Geneva: International Labour Office; 1990.
20. Der Simonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
21. STATA statistical software, release 9. College Station (TX): Statacorp LP; 2005.
22. Chinn S, Jarvis D, Burney P, Luczynska C, Ackermann-Liebrich U, Anto JM, et al. Increase in diagnosed asthma but not in symptoms in the European Community Respiratory Health Survey. *Thorax* 2004;59:646-51.
23. Portengen L, de Meer G, Doekes G, Heederik D. Immunoglobulin G4 antibodies to rat urinary allergens, sensitization and symptomatic allergy in laboratory animal workers. *Clin Exp Allergy* 2004;34:1243-50.
24. Uitti J, Nordman L, Halmepuro L, Savolainen J. IgG4 response to fur animal allergens among fur workers. *Int Arch Occup Environ Health* 2005;78:71-4.
25. Custovic A, Hallam C, Simpson B, Craven M, Simpson A, Woodcock A. Decreased prevalence of sensitization to cats with high exposure to cat allergen. *J Allergy Clin Immunol* 2001;108:537-9.
26. Erwin EA, Wickens K, Custis NJ, Siebers R, Woodfolk J, Barry D, et al. Cat and dust mite sensitivity and tolerance in relation to wheezing among children raised with high exposure to both allergens. *J Allergy Clin Immunol* 2005;115:74-9.
27. Waser M, von Mutius E, Riedler J, Nowak D, Maisch S, Carr D, et al. Exposure to pets and the association with hay fever, asthma, and atopic sensitization in rural children. *Allergy* 2005;60:177-84.
28. McSharry C, Anderson K, McKay I, Colloff M, Feyerabend C, Wilson R. The IgE and IgG antibody responses to aerosols of *Nephrops norvegicus* (prawn) antigens: the association with clinical hypersensitivity and with cigarette smoking. *Clin Exp Immunol* 1994;97:499-504.

FURTHER INFORMATION ON METHODS FOR ECRHS I AND II

As part of ECRHS I, a random sample of subjects (1500 men and 1500 women) were identified from a community-based sampling frame and sent a postal questionnaire asking about respiratory symptoms. From those who responded, a random sample of 300 men and 300 women was identified, and they were invited to a testing center for further study. To enhance the number of subjects with asthma who were seen at this stage, subjects reporting symptoms suggestive of asthma in the postal questionnaire (but who had not been selected as part of the random sample) were also invited to the test center.

Any person who had undergone the more intensive study at the testing centers in ECRHS I was included in ECRHS II (most of whom who had been initially selected at random but some of whom came from the symptomatic sample). For the indoor protocol, resources were available to visit 200 homes per participating center. Centers were asked to recruit 200 participants who had not moved home, had provided a blood sample at ECRHS I, and were from the random sample (criteria 1). If 200 people meeting these criteria were not available for study (either because so few people met these criteria in the center or because some refused to take part), centers were advised to select those from the symptomatic sample who had blood taken and had not moved home (criteria 2). If 200 subjects could still not be recruited, they should move to criteria 3 (not moved home, questionnaire only, random sample). Thus, centers worked through the selection criteria as shown in Table E1 until 200 persons had been seen.

FURTHER INFORMATION ON USE OF CENSORED REGRESSION

A measure is said to be censored when some of the data are known only to be below the minimum or above the maximum value. This is commonly encountered in laboratory tests that have limits of detection. The assumption is that had it been possible to obtain a value for all the censored measures, the entire range of values would follow a normal distribution or a normal distribution if appropriately transformed. Our data suggest that IgG and IgG₄ as measured here follow a censored log-normal distribution. Interpretation of results are as one would expect for the usual multiple regression.

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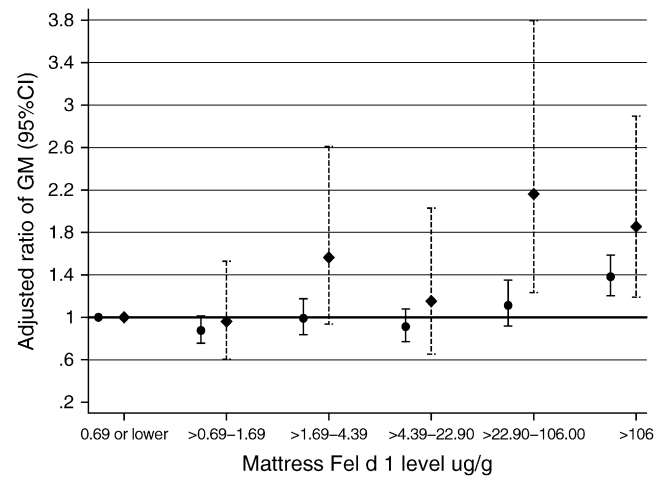


FIG E1. Adjusted ratio of GM (95% CI) of cat specific IgG₄ with increasing mattress Fel d 1 level in subjects with (dashed line) and without (solid line) serum cat specific IgE.

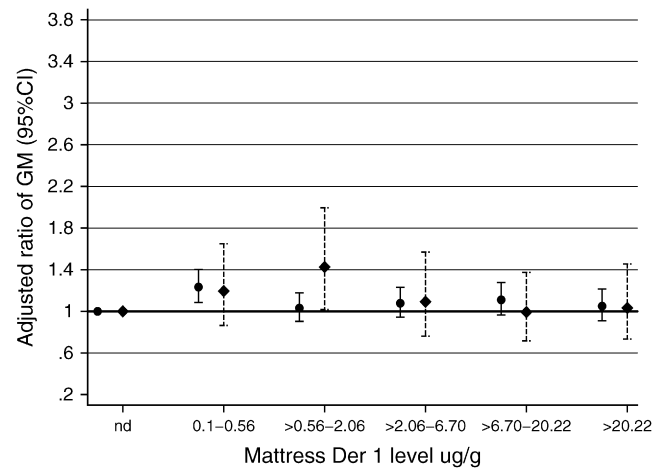


FIG E2. Adjusted ratio of GM (95% CI) of HDM specific IgG₄ with increasing mattress Der 1 level in subjects with (*dashed line*) and without (*solid line*) serum HDM IgE. *nd*, Not detected.

TABLE E1. Criteria for selection of 200 subjects for indoor protocol

1. Did not move into new home, random sample, provided blood
2. Did not move into new home, symptomatic sample, provided blood
3. Did not move into new home, random sample, questionnaire only
4. Did not move into new home, symptomatic sample, questionnaire only
5. Been in current home for 5 years or longer, random sample, provided blood
6. Been in current home for 5 years or longer, symptomatic sample, provided blood
7. Been in current home for 5 years or longer, random sample, questionnaire only
8. Been in current home for 5 years or longer, symptomatic sample, questionnaire only
9. Anyone remaining from the random sample
10. Anyone remaining from the symptomatic sample

TABLE E2. Number of subjects in each center

Country	Center	No. of subjects with information on cat ownership	No. of subjects with mite allergen measure
Belgium	South Antwerp	156	130
	Antwerp City	83	77
Germany	Hamburg	158	151
	Erfurt	188	186
Spain	Barcelona	116	108
	Galdakao	155	145
	Albacete	122	114
	Oviedo	122	120
	Huelva	100	89
France	Grenoble	158	151
	Paris	156	150
Italy	Pavia	58	44
	Turin	73	43
	Verona	94	79
UK	Ipswich	81	80
	Norwich	131	130
Iceland	Reykjavik	175	158
Sweden	Göteborg	131	125
	Umeå	134	127
	Uppsala	132	118
Switzerland	Basel	88	84
Estonia	Tartu	169	163
Total		2780	2752

TABLE E3. Association of IgE, IgG, and IgG₄ with symptoms of wheeze

	Prevalence of wheeze (%)	Adjusted* OR for wheeze	Adjusted OR† (95% CI) for wheeze	Adjusted† OR for wheeze with both IgE and IgG included	Adjusted† OR for wheeze with both IgE and IgG ₄ included
Cat					
IgE to cat					
No	7.5	1.00	1.00	1.00	1.00
Yes	24.3	3.62	4.09 (2.83-5.09)	4.01 (2.77-5.79)	4.19 (2.89-6.06)
IgG to cat (mg _A /L)					
<3.4	8.3	1.00	1.00	1.00	—
3.41-5.44	9.0	0.99	1.00 (0.67-1.50)	0.99 (0.66-1.48)	—
5.45-8.76	7.4	0.75	0.76 (0.50-1.16)	0.75 (0.49-1.16)	—
>8.76	10.9	1.10	1.19 (0.80-1.76)	1.08 (0.72-1.62)	—
IgG ₄ to cat (μg _A /L)					
ND* to 307	7.9	1.00	1.00	—	1.00
308-549	8.4	1.00	0.97 (0.65-1.46)	—	0.99 (0.65-1.49)
550-869	10.2	1.24	1.22 (0.83-1.81)	—	1.20 (0.81-1.79)
871-25,057	9.0	1.04	1.02 (0.67-1.54)	—	0.87 (0.57-1.34)
HDM					
IgE to HDM					
No	7.2	1.00	1.00	1.00	1.00
Yes	17.5	2.89	2.79 (2.01-3.88)	2.82 (2.03-3.91)	2.81 (2.02-3.90)
IgG to HDM (mg _A /L)					
<21.9	8.9	1.00	1.00	1.00	—
22.1-39.9	9.4	0.98	1.01 (0.69-1.49)	1.03 (0.69-1.52)	—
40.2-68.3	9.4	1.01	1.10 (0.68-1.49)	0.99 (0.67-1.48)	—
>68.3	7.8	0.83	0.84 (0.55-1.28)	0.81 (0.50-1.23)	—
IgG ₄ to HDM (μg _A /L)					
ND* to 253	7.1	1.00	1.00	—	1.00
254-397	9.5	1.39	1.33 (0.88-2.01)	—	1.23 (0.81-1.87)
396-615	7.8	1.12	1.14 (0.75-1.75)	—	1.07 (0.70-1.64)
616-30,050	11.1	1.69	1.62 (1.07-2.44)	—	1.37 (0.91-2.08)

Values in boldface are statistically significant at the 5% level.

ND, Not detected.

*From logistic regression adjusted for age, sex, smoking, BMI, number of siblings, socioeconomic status, family history, center (†centers in Spain, Italy, and Germany combined at country level because of low prevalence of outcomes in some centers), and selection group.

TABLE E4. Association of IgE, IgG, and IgG₄ with asthma

	Prevalence of asthma	Adjusted* OR for asthma	Adjusted OR† (95% CI) for asthma	Adjusted† OR for asthma with both IgE and IgG included	Adjusted† OR for asthma with both IgE and IgG ₄ included
Cat					
IgE to cat					
No	3.3	1.00	1.00	1.00	1.00
Yes	9.6	3.08	2.90 (1.70-4.95)	2.94 (1.72-5.02)	2.89 (1.68-4.98)
IgG to cat					
<3.4	3.3	1.00	1.00	1.00	—
3.41-5.44	4.2	1.31	1.15 (0.62-2.11)	1.14 (0.62-2.10)	—
5.45-8.76	4.3	1.29	1.28 (0.70-2.32)	1.32 (0.73-2.40)	—
>8.76	3.6	1.10	1.14 (0.61-2.12)	1.09 (0.58-2.07)	—
IgG ₄ to cat (μg _A /L)					
ND* to 307	3.4	1.00	1.00	—	1.00
308-549	3.6	1.11	1.21 (0.65-2.24)	—	1.21 (0.65-2.25)
550-869	4.5	1.33	1.48 (0.83-2.65)	—	1.44 (0.80-2.59)
871-25,057	3.9	1.16	1.37 (0.74-2.52)	—	1.19 (0.64-2.21)
HDM					
IgE to HDM					
No	2.6	1.00	1.00	1.00	1.00
Yes	10.3	4.23	4.90 (3.12-7.17)	4.73 (3.01-7.46)	4.43 (2.19-7.04)
IgG to HDM					
<21.9	3.4	1.00	1.00	1.00	—
22.1-39.9	2.9	0.85	0.81 (0.42-1.60)	0.84 (0.43-1.60)	—
40.2-68.3	3.7	1.21	1.17 (0.62-2.14)	1.11 (0.60-2.07)	—
>68.3	5.3	1.86	1.88 (1.03-3.27)	1.71 (0.95-3.09)	—
IgG ₄ to HDM (μg _A /L)					
ND* to 253	2.7	1.00	1.00	—	1.00
254-397	3.6	1.41	1.44 (0.88-2.01)	—	1.27 (0.65-2.45)
396-615	2.5	0.89	0.93 (0.75-1.75)	—	0.80 (0.39-1.62)
616-30,050	6.6	2.58	2.62 (1.43-4.81)	—	1.93 (1.04-3.58)

ND, Not detected.

*From logistic regression adjusted for age, sex, smoking, BMI, number of siblings, socioeconomic status, family history, center (†centers in Spain, Italy, and Germany combined at country level because of low prevalence of outcomes in some centers), and selection group.