

Pet-keeping in childhood and adult asthma and hay fever: European Community Respiratory Health Survey

Cecilie Svanes, MD, PhD,^{a,b} Joachim Heinrich, PhD,^c Deborah Jarvis, MFPHM,^d
Susan Chinn, MA,^d Ernst Omenaas, MD, PhD,^a Amund Gulsvik, MD, PhD,^a
Nino Künzli, MD, PhD,^e and Peter Burney, MD^d Bergen, Norway, Neuherberg, Germany,
London, United Kingdom, Basel, Switzerland, and Los Angeles, Calif

Background: Whether pet-keeping early in life protects against or promotes allergy remains unclear.

Objective: Our aim was to examine the effects of childhood pet-keeping on adult allergic disease in a large international population-based study, including information on sensitization, adult pet-keeping, and pet prevalence in the populations.

Methods: We used information from structured interviews (n = 18,530) and specific IgE to common aeroallergens in blood samples (n = 13,932) from participants in the European Community Respiratory Health Survey (ECRHS) to analyze the associations between keeping pets and adult asthma and hay fever.

Results: Keeping cats in childhood was associated with asthma only among atopic subjects, an association that varied between centers ($P = .002$) and was stronger where cats were less com-

mon (< 40% cats: odds ratio_{wheeze} [OR_{wheeze}] = 1.84, 95% CI = 1.31-2.57; 40%-60% cats: OR_{wheeze} = 1.33, 95% CI = 1.10-1.61; ≥60% cats: OR_{wheeze} = 0.98, 95% CI = 0.73-1.33). Dogs owned in childhood or adulthood were associated with asthma among nonatopic subjects (childhood: OR_{wheeze} = 1.28, 95% CI = 1.13-1.46; adulthood: OR_{wheeze} = 1.31, 95% CI = 1.14-1.51; both: OR_{wheeze} = 1.69, 95% CI = 1.40-2.04). In atopic subjects, those who had owned dogs in childhood had less hay fever (OR = 0.85; 95% CI = 0.73-0.98) and no increased risk of asthma (OR_{wheeze} = 1.01, 95% CI = 0.87-1.17). Respiratory symptoms were more common in subjects who had owned birds during childhood (OR_{wheeze} = 1.12; 95% CI = 1.02-1.23) independent of sensitization.

Conclusions: The effects of pet-keeping in childhood varied according to the type of pet, the allergic sensitization of the individual, and the wider environmental exposure to allergen.

Cats owned in childhood were associated with more asthma in sensitized adults who grew up in areas with a low community prevalence of cats. Dogs owned in childhood seemed to protect against adult allergic disease but promote nonallergic asthma. (J Allergy Clin Immunol 2003;112:289-300.)

Key words: Cats, dogs, birds, asthma, hay fever, sensitization, tolerance, hygiene hypothesis, ECRHS

Whether pet-keeping early in life protects against or promotes allergic disease remains unclear. Traditionally, pets have been considered a major promotor of allergic disease, and several studies show how pets increase the risk for asthma (Table I).^{1,2} However, an increasing bulk of evidence indicates protective effects of early exposure to pets³⁻¹³ (Table I) or animals in a farm environment.^{14, 15} The literature is complex and contradictory and subject to a bias toward publication of more "interesting" results. Little information exists on whether the effects of exposure to pets in early life on asthma and allergy persist into adulthood.²⁻⁵

To date, we know of 3 possible mechanisms through which contact with animals might influence immunologic priming early in life: allergen stimulation causing sensitization, allergen stimulation inducing tolerance, and microbial stimulation enhancing immune deviation toward a nonallergic T_H1 profile. The common assumption that exposure to allergens is the main determinant of allergy has lately been vigorously debated.¹⁶⁻¹⁸ Since the hygiene hypothesis was introduced in 1989,¹⁹ there has been increasing focus on how altered microbial stimulation during immunologic priming early in life could contribute to the recent increase in allergy in the Western world.²⁰⁻²² The concept of tolerance is applied in

From ^aSection of Respiratory Medicine, Institute of Medicine, University of Bergen, Bergen; ^bDepartment of Medicine, Haraldsplass Hospital, Bergen; ^cGSF-National Research Center for Environment and Health, Institute of Epidemiology, Neuherberg; ^dDepartment of Public Health Sciences, King's College London, London; ^eUniversity of Basel, Basel, and University of Southern California, Los Angeles.

The coordination of this work was supported by the European Commission. The following grants helped to fund the local studies: *Australia:* Allen and Hanbury's, Australia. *Belgium:* Belgian Science Policy Office, National Fund for Scientific Research. *France:* Ministère de la Santé, Glaxo France, Institut Pneumologique d'Aquitaine, Contrat de Plan Etat-Région Languedoc-Rousillon, CNMATS, CNMRT (90MR/10, 91AF/6), Ministre délégué de la santé, RNSP. *Germany:* GSF, and the Bundesminister für Forschung und Technologie, Bonn. *Greece:* The Greek Secretary General of Research and Technology, Fisons, Astra, and Boehringer-Ingelheim. *India:* Bombay Hospital Trust. *Italy:* Ministero dell'Università e della Ricerca Scientifica e Tecnologica, CNR, Regione Veneto grant RSF n. 381/05.93. *New Zealand:* Asthma Foundation of New Zealand, Lotteries Grant Board, Health Research Council of New Zealand. *Norway:* Norwegian Research Council project no. 101422/310. *Portugal:* Glaxo Farmacêutica Lda, Sandoz Portuguesa. *Spain:* Ministerio Sanidad y Consumo FIS grants #91/0016060/00E-05E and #93/0393, and grants from Hospital General de Albacete, Hospital General Juan Ramón Jiménez, Consejería de Sanidad Principado de Asturias. *Sweden:* The Swedish Medical Research Council, the Swedish Heart Lung Foundation, the Swedish Association against Asthma and Allergy. *Switzerland:* Swiss national Science Foundation grant 4026-28099 and PROSPER 32-48922.96 (NK). *United Kingdom:* National Asthma Campaign, British Lung Foundation, Department of Health, South Thames Regional Health Authority. *United States:* United States Department of Health, Education and Welfare Public Health Service grant no. 2 S07 RR05521-28.

Received for publication January 17, 2003; revised March 23, 2003; accepted for publication April 4, 2003.

Reprint requests: Cecilie Svanes, MD, PhD, Department of Medicine, Haraldsplass Hospital, 5009 Bergen, Norway.

© 2003 Mosby, Inc. All rights reserved.

0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.1596

TABLE I. Literature overview of childhood pet-keeping and (subsequent) atopic sensitization and disease

Population	Findings: atopic sensitization	Findings: atopic disease	Reference
Meta-analysis of 32 studies of children		Previous pets related to more wheeze in children >6 y (+) and less wheeze in children younger than 6 y (–)	Apelberg 2001 ¹
Cohort studies			
1314 children 1-3 y	Positive dose-response relationship between cat allergen and skin prick test cat (+) Comment: Low cat allergen* exposures		Wahn 1997 ⁴⁷
1218 children 0-4 y		Pets protective for eczema at 4 y (–)	Tariq 1998 ⁴⁸
2472 children 7-13 y	Cat first year protective for skin prick test cat (–)	Pet first year related to less allergic rhinitis and less asthma	Hesselmar 1999 ⁶
939 children 0-7 y		No association of indoor allergens with asthma and wheeze (0)	Lau 2000 ⁴⁹
2531 children 0-4 y		Dog and cat protective for atopic eczema at 0-6 mo, particularly when parental atopy (–) Pets protective for hay fever at 4 y (–) Dogs at birth related to more bronchial hyperresponsiveness at 0-2 y (+)	Nafstad 2000 ⁷
412 children 12-13 y	Lower sensitization rate in areas with low community cat prevalence (+)		Hesselmar 2001 ⁵⁰
1246 children 0-13 y	Dog or cat early in life not related to skin prick test (0)	Dog early in life protective for wheeze (–) No association with cat (0)	Remes 2001 ¹³
3339 children 7-8 y		Pets protective for prevalent asthma and wheeze (–), related to more incident wheeze (+)	Rönmark 2001 ⁵¹
498 children 0-5 y with parental allergy		Cat protective for wheeze when no maternal asthma (–), related to more wheeze when maternal asthma (+) No association of dogs and wheeze (0)	Celedon 2002 ¹¹
226 children 0-5 y with parental allergy		Dog protective for wheeze (–) Cat allergen protective for wheeze (–)	Litonjua 2002 ¹²

(continued on next page)

*Abbreviations used*ECRHS: European Community Respiratory Health Survey
OR: Odds ratio

immunotherapy. It has recently been suggested that high-dose cat exposure might induce tolerance toward cat sensitization.^{23,24} This implies that a change from high to moderate exposure to cat allergen could, paradoxically, increase cat sensitization in a community. Finally, early life exposure to animals might possibly influence the development of the airways and the lung parenchyma through nonallergic mechanisms involving endotoxin or other pro-inflammatory substances²⁵ or transmission of microbes causing manifest lower airways infections.^{26,27} The individual response to each of these mechanisms is likely to depend on host factors.^{18,28}

On the basis of today's knowledge, it is not possible to give confident advice concerning pet-keeping and allergy. In this article, we analyze data from the multicultural and population-based European Community Respiratory Health Survey (ECRHS) to study how keeping cats, dogs, and birds in childhood is related to adult asthma and hay fever. We have taken into account atopic sensitization, current adult pet-keeping, and more general exposure to cats measured as the population prevalence of cat

ownership. The associations of pets and atopic sensitization in the ECRHS are specifically dealt with previously. Svanes et al³ revealed that subjects who had kept a dog in childhood were less often sensitized toward common aeroallergens (cat, grass, house dust mite); for childhood cat exposure a protective effect was restricted to sensitization toward grass and cat in those with parental allergy. Roost et al⁵ showed more sensitization toward cat in adults who currently kept a cat, but less cat sensitization in predisposed subjects who had kept a cat in childhood.

METHODS**Data collection**

The methodology for the ECRHS has been fully described elsewhere.²⁹ Participating centers selected an area defined by pre-existing administrative boundaries with a population of at least 150,000. A random population sample of at least 1500 men and 1500 women aged 20 to 44 years was selected. In stage I, subjects were sent the ECRHS self-completed screening questionnaire. In stage II, a smaller random sample of subjects who had completed the screening questionnaire was invited to attend for a more detailed interviewer-led questionnaire, lung function testing, and blood tests. Specific IgE to common aeroallergens was measured in serum samples and was considered to be positive if >0.35 kU/L. Details of the IgE measurements are described elsewhere.³⁰ The informed consent of all participants was obtained, and the study was approved by all the involved ethics committees.

TABLE I. Continued

Population	Findings: atopic sensitization	Findings: atopic disease	Reference
835 children 6-7 y	Two or more dogs or cats first year of life protective for sensitization (skin prick test, specific IgE) at age 6-7 y (–)		Ownby 2002 ¹⁰
3431 children 6-9 y	Cat ever protective for skin prick test cat (–) Dog ever protective for skin prick test dog when parental allergy (–)	Cat ever protective for asthma when asthma in family (–) Dog ever protective for asthma	Perzanowski 2002 ⁹
Cross-sectional studies 2646 adults 20-44 y		Pet in childhood protective for asthma starting before age 15 y (–) Not associated with asthma starting after age 15 (0)	Sunyer 1997 ⁴
2999 adults 20-44 y	Current cat not associated with skin prick test cat (0)	Current cat or pet related to more wheeze and asthma (+) No association with childhood pet (0)	Noertjojo 1999 ²
13,509 adults 20-44 y	Cat in childhood protective for adult IgE cat when parental allergy (–) Comment: Current cat related to more IgE cat		Roost 1999 ⁵
314 children 12-14 y	No association between cat allergen* and skin prick test cat (0)		Sporik 1999 ¹⁶
13,932 adults 20-44 y	Dog in childhood protective for adult sensitization (IgE grass, house dust mite, cat) (–) Cat in childhood protective for sensitization when parental allergy (–)		Svanes 1999 ³
2108 children 10-11 y	Current cat protective for skin prick test cat when atopic heredity (–)		Braback 2001 ³⁶
2502 adults 18-58 y	Inverse U-shaped association between cat allergen* and IgE cat (–)		Custovic 2001 ²³
431 adolescents	Childhood cat protective for cat sensitization (–) No association of dog and dog sensitization (0)		Henriksen 2001 ³⁷
226 children 12-13 y	Inverse U-shaped association between cat allergen* and IgE cat (–) Comment: high exposure to cat allergen*		Platts-Mills 2001 ²⁴
2729 children 7-12 y	Current pet protective for sensitization (–), no association of past pet (0) Pet first 2 years protective for pollen sensitization (–)	No association between current pet exposure, and asthma, wheeze, and bronchial hyperresponsiveness (0), but a positive association past pet ownership and asthma (+)	Anyo 2002 ³⁴
5360 children 5-14 y	Dogs first year of life and currently protective for IgE pollen (–) Cats first year of life associated with high IgE cat (+)		Hoelscher 2002 ³⁹

(+), Positive association; (–), negative association, (0), no association.

*Additional measurement of cat allergen in settled house dust.

This analysis includes data collected from 1991 to 1993 for 18,530 subjects from 36 centers representing 16 countries, of which 13,932 subjects (75%) provided blood tests for measurement of specific IgE. Information on pet-keeping, symptoms, and potential confounding variables was obtained from the interviewer-led questionnaire. The wording of the questions on pet-keeping is given in the footnote to Table II. Atopy was defined as having specific IgE to cat, timothy grass, house dust mite, and/or *Cladosporium*.

Statistical analysis

Logistic regression models were used to assess the independent effects of pet-keeping in childhood and adulthood on adult symptoms of asthma and hay fever. Adjustments were made for other childhood factors, sex, age, smoking habits (never, ex-smoker, and current smoking), occupation (European Economic Community Status Groups-14),³¹ and study center. Potential heterogeneity between centers was studied by meta-analyses.³² Stratified analyses and analyses of interaction did not show differences in association between keeping pets in childhood and adult symptoms according to sex or smoking status. All analyses were carried out using the statistical software program Stata.³³

RESULTS

Pet-keeping was common in all centers (Table II), and 65% of the subjects had kept pets in childhood, whereas 41% currently kept pets. People often had more than 1 pet and tended to keep the same pet in childhood and adulthood (Table III). Asthma and allergy in parents and siblings did not seem to influence systematically the decision to keep pets. Smokers more often kept pets, and this was true among our study subjects and their parents. Subjects from large families more often had cats or dogs in childhood but less often had cats and dogs when adults. Women more often kept cats in childhood and adulthood. Childhood cats were more common in the earlier birth cohorts, whereas children in the later birth cohorts were more likely to keep birds.

Respiratory symptoms were more common in subjects who had kept dogs or birds in childhood and in subjects who currently kept a dog (Table IV). Keeping a dog dur-

TABLE II. Prevalence of pet-keeping in subjects aged 20 to 44 years by country

Country	Number	Childhood			Adulthood		
		Cats* (%)	Dogs* (%)	Birds* (%)	Cats† (%)	Dogs† (%)	Birds† (%)
Iceland	564	41	26	36	12	6	9
Norway	835	47	35	28	15	13	7
Sweden	1,856	50	45	36	19	15	8
Estonia	431	58	57	34	15	25	2
Ireland	454	38	77	44	11	32	6
Great Britain	1,579	49	59	47	29	25	10
Netherlands	1,247	38	60	56	23	24	22
Belgium	1,122	60	66	58	24	17	16
Germany	1,983	27	28	50	15	8	14
Switzerland	853	44	36	46	20	8	9
France	2,125	48	48	31	19	15	3
Spain	1,942	39	44	53	8	14	20
Italy	894	42	41	30	21	19	9
New Zealand	1,254	83	60	59	59	35	15
Australia	668	64	72	61	35	38	15
United States (Portland)	723	68	86	39	45	36	10
Totals	18,530	48	49	45	22	19	12

*“Yes” to the following question: “When you were a child, did anyone in your household keep any of the following pets [cats, dogs, birds, etc]?”

†“Yes” to the following questions: “Do you keep a cat?” “Do you keep a dog?” “Do you keep a bird?”

TABLE III. Factors related to childhood and adult pet-keeping (mutually adjusted and adjusted for center) in 17,546 men and women with complete information on all included variables

	Childhood			Adult		
	Cat	Dog	Bird	Cat	Dog	Bird
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Childhood cat	—	2.68 (2.51-2.87)	1.52 (1.42-1.62)	2.10 (1.93-2.28)	0.90 (0.82-0.98)	0.87 (0.78-0.97)
Childhood dog	2.68 (2.51-2.87)	—	1.88 (1.75-2.00)	0.92 (0.84-1.00)	1.85 (1.98-2.02)	1.09 (0.98-1.22)
Childhood bird	1.52 (1.42-1.62)	1.88 (1.75-2.00)	—	1.14 (1.06-1.24)	1.12 (1.03-1.21)	1.87 (1.69-2.07)
Additional adult pet	—	—	—	1.21 (1.11-1.32)	1.52 (1.40-1.66)	1.39 (1.25-1.54)
Mother asthma/ allergy	0.98 (0.90-1.06)	1.05 (0.97-1.14)	1.03 (0.95-1.11)	1.03 (0.94-1.13)	1.04 (0.94-1.14)	1.03 (0.92-1.17)
Father asthma/ allergy	0.97 (0.89-1.05)	0.97 (0.89-1.06)	1.04 (0.96-1.13)	0.87 (0.79-0.97)	0.93 (0.84-1.04)	0.97 (0.85-1.11)
Sister asthma/ allergy	1.03 (0.94-1.12)	0.99 (0.91-1.08)	1.14 (1.05-1.24)	1.03 (0.94-1.14)	0.93 (0.84-1.04)	1.03 (0.91-1.16)
Brother asthma/ allergy	0.96 (0.88-1.05)	0.88 (0.81-0.96)	1.01 (0.93-1.09)	1.03 (0.94-1.14)	1.01 (0.91-1.12)	0.83 (0.73-0.94)
Parental smoking	1.01 (0.94-1.09)	1.41 (1.31-1.52)	1.17 (1.09-1.26)	1.11 (1.02-1.22)	1.08 (0.98-1.19)	1.07 (0.96-1.20)
Current or ex-smoker	1.08 (1.01-1.15)	1.21 (1.13-1.29)	1.14 (1.07-1.22)	1.20 (1.11-1.31)	1.24 (1.14-1.35)	0.94 (0.85-1.04)
Siblings—per one sib	1.14 (1.11-1.17)	1.13 (1.10-1.16)	0.99 (0.96-1.02)	0.91 (0.88-0.94)	0.97 (0.93-1.00)	1.03 (0.99-1.07)
Sex, F/M	1.09 (1.02-1.16)	0.96 (0.90-1.03)	0.99 (0.93-1.06)	1.16 (1.07-1.25)	1.06 (0.98-1.15)	1.10 (1.00-1.22)
Age (y)						
20-24	1	1	1	1	1	1
25-29	1.07 (0.96-1.19)	1.02 (0.91-1.13)	0.93 (0.84-1.03)	0.88 (0.78-1.01)	0.77 (0.68-0.88)	0.77 (0.65-0.91)
30-34	1.15 (1.03-1.29)	0.97 (0.87-1.09)	0.88 (0.79-0.98)	0.90 (0.79-1.02)	0.75 (0.65-0.86)	0.84 (0.71-0.99)
35-39	1.19 (1.07-1.33)	1.00 (0.89-1.11)	0.77 (0.69-0.86)	0.92 (0.80-1.04)	0.88 (0.77-1.01)	1.03 (0.88-1.21)
40-44	1.41 (1.26-1.57)	1.00 (0.90-1.12)	0.76 (0.69-0.85)	1.10 (0.96-1.24)	1.02 (0.90-1.17)	1.17 (1.00-1.36)
Occupation* 1	1	1	1	1	1	1
Occupation 2	1.05 (0.97-1.14)	1.00 (0.93-1.09)	1.05 (0.97-1.13)	0.98 (0.89-1.08)	1.06 (0.96-1.16)	1.31 (1.17-1.47)
Occupation 3	0.86 (0.76-0.96)	0.94 (0.84-1.06)	1.07 (0.96-1.20)	0.91 (0.78-1.04)	0.97 (0.83-1.13)	1.11 (0.93-1.33)

OR, Odds ratio.

*Occupations: 1 includes all professional, skilled, and semiskilled workers; 2 is laborers and clerical, sales, and service workers; 3 is unclassified/unknown.

Boldfaced odds ratios refer to associations with $P < .05$.

ing childhood was related to less adult hay fever. These associations differed significantly according to atopic status (Table V). Data for wheeze are presented, but the results were similar for the other respiratory symptoms and asthma medication. Among atopic subjects, keeping a cat during childhood was related to more adult respiratory symptoms, whereas keeping a dog in childhood

seemed to protect against adult hay fever. Among those who were not atopic, dogs kept at any time of life were related to more adult respiratory symptoms. The association between birds kept during childhood and adult respiratory symptoms was independent of atopic status.

In atopic subjects, the association between keeping a cat during childhood and wheeze (and other respiratory

TABLE IV. Childhood and adult pet-keeping as related to adult asthma and hay fever

Variable	Wheeze*		Wheeze,† breathlessness*		Wheeze without cold*		Asthma medication*		Hay fever*	
	Percent	OR (95% CI)†	Percent	OR (95% CI)†	Percent	OR (95% CI)†	Percent	OR (95% CI)†	Percent	OR (95% CI)†
Childhood cat										
No	21	1	10	1	13	13	1	26	1	
Yes	25	1.08 (0.99-1.17)	13	1.08 (0.97-1.20)	14	0.97 (0.88-1.08)	3	1.08 (0.89-1.30)	28	1.01 (0.93-1.09)
Childhood dog										
No	20	1	10	1	12	13	1	26	1	
Yes	26	1.10 (1.01-1.20)	13	1.04 (0.93-1.16)	16	1.16 (1.04-1.28)	3	0.98 (0.82-1.19)	27	0.90 (0.83-0.98)
Childhood bird										
No	21	1	10	1	13	13	1	26	1	
Yes	25	1.14 (1.05-1.23)	13	1.21 (1.09-1.34)	15	1.11 (1.01-1.22)	3	1.04 (0.87-1.25)	27	1.00 (0.93-1.08)
Adult cat										
No	22	1	11	1	13	13	1	26	1	
Yes	25	0.97 (0.88-1.06)	13	0.97 (0.86-1.09)	15	0.98 (0.88-1.10)	4	0.80 (0.65-0.99)	29	0.98 (0.90-1.07)
Adult dog										
No	22	1	11	1	13	13	1	26	1	
Yes	28	1.12 (1.02-1.23)	14	1.13 (1.00-1.28)	17	1.17 (1.04-1.31)	5	1.25 (1.02-1.54)	29	1.04 (0.95-1.15)
Adult bird										
No	23	1	12	1	14	13	1	27	1	
Yes	23	0.99 (0.87-1.11)	11	0.92 (0.79-1.08)	13	0.97 (0.84-1.12)	3	0.92 (0.69-1.23)	26	1.09 (0.97-1.23)

Boldfaced odds ratios refer to associations with $P < .05$.

OR, Odds ratio.

*Respiratory symptoms during last 12 months, current asthma medication, current hay fever.

†Odds ratios with 95% CIs as estimated by logistic regression adjusting for parental allergy, siblings allergy, parental smoking, number of siblings, age, sex, current smoking, current occupation, and study center. Approximately 17,500 subjects with complete information were included in the analyses.

symptoms) varied greatly between centers ($P_{\text{heterogeneity}} = .002$) (Fig 1, A). The magnitude of the associations was inversely related to the prevalence of keeping cats during childhood in each center ($r = -0.488$) (Fig 1, B). In centers in which more than 60% reported having a cat during childhood, there was no increase in risk for wheeze related to cats kept during childhood (OR 0.98, 95% CI = 0.73-1.33). In centers with 40% to 60% childhood cats, the OR was 1.33 (95% CI = 1.10-1.61), and in centers with <40% childhood cats the OR was 1.84 (95% CI = 1.31-2.57). This interaction by prevalence of cats kept during childhood was significant (<40% versus $\geq 60\%$ childhood cats: $P_{\text{interaction}} = .008$), whereas there was no association with prevalence of cat ownership in the center at the time of the survey.

The increased asthma risk in nonatopic subjects who had kept a dog in childhood was consistent across centers ($P_{\text{heterogeneity}} = .3$) (Fig 2), whereas the lack of association between dogs kept during childhood and wheeze among atopic subjects showed some heterogeneity ($P_{\text{heterogeneity}} = .046$). Differences in the prevalence of keeping dogs during childhood could not explain this heterogeneity. The protective effect of dogs kept during childhood on hay fever among the atopic subjects was homogeneous across centers ($P_{\text{heterogeneity}} = .5$) (Fig 3),

as was the association of birds kept during childhood and adult asthma ($P_{\text{heterogeneity}} = .2$).

The association of cats kept during childhood and asthma among atopic adults was significant in those who kept a cat only in childhood but not currently as adults (Table VI). The strongest associations between respiratory symptoms and dog ownership among the nonatopic were among those who had kept dogs both in childhood and adulthood. The protective effect of keeping a dog on hay fever among atopic subjects was restricted to those who had kept a dog in childhood.

DISCUSSION

Keeping a cat during childhood was associated with asthma but only among atopic subjects. This association was, however, highly heterogeneous between centers, and the magnitude of the association was inversely related to the prevalence of cats kept during childhood. Thus, in subjects who grew up in an area with relatively low public exposure to cats, having their own cat was associated with an increased risk for adult asthma. In subjects from areas with a very high prevalence of cats, however, a cat at home was not associated with increased asthma risk. Dog keeping in childhood or adulthood was related to

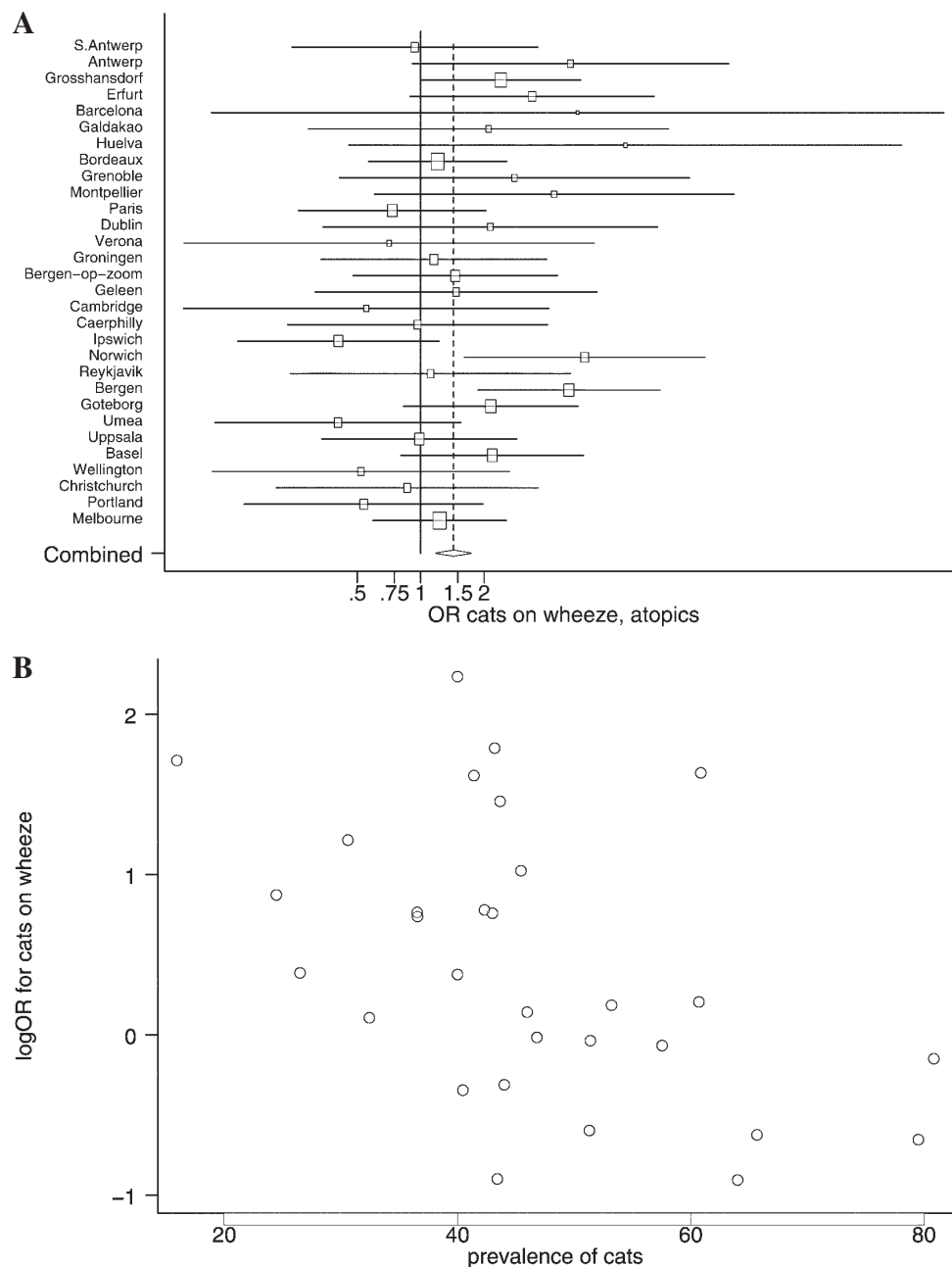


FIG 1. **A**, Odds ratios for the association of childhood cats and adult wheeze in sensitized subjects by center. Adjustment within center for other childhood pets, adult pets, parental and sibling allergy, own and parental smoking, number of siblings, age, sex, and occupation. For each center, horizontal lines indicate 95% CI. For combined odds ratio, diamond indicates 95% CI from model, with center as random effect. The size of each square is proportional to the sample size. **B**, Log odds ratio for association of childhood cats and adult wheeze in sensitized subjects and prevalence of childhood cats by center. $r = -0.488$.

more adult asthma among nonatopic subjects. Among the atopic, dog keeping in childhood was related to reduced risk for adult hay fever. These associations were consistent across the ECRHS, including centers with great differences in prevalence of symptoms, habits of pet-keeping, and sociocultural conditions. The associations of cat and dog ownership with adult asthma and hay fever differed substantially according to allergic disposition,

whereas subjects who had birds in childhood had more adult respiratory symptoms independent of atopic status. Each pet showed different associations with asthma and hay fever. This is plausible, because the animal species have different allergenic and microbial properties and interact with children at different ages. These findings add to the evidence that early life contact with animals does influence the development of the immune system and the

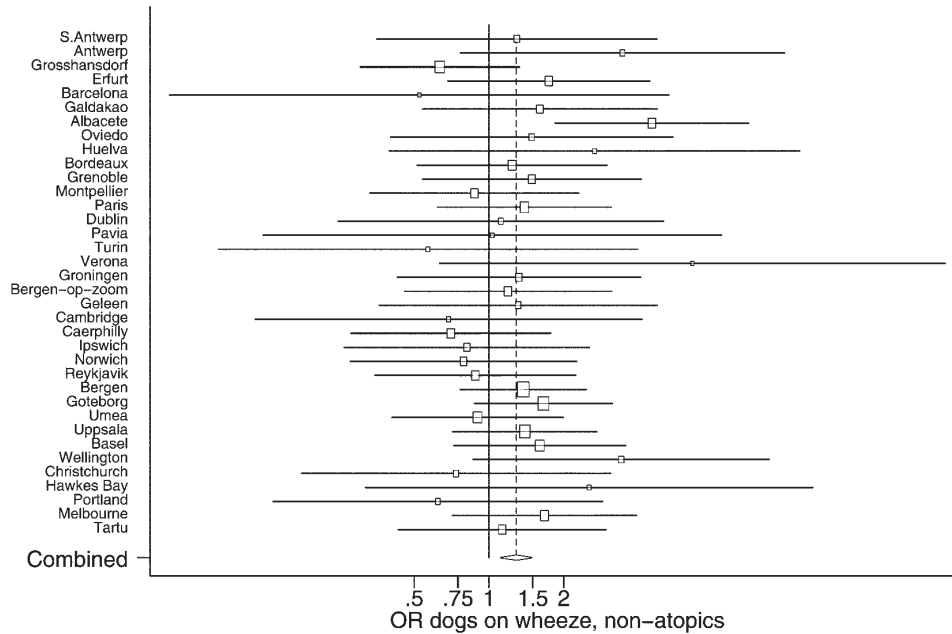


FIG 2. Odds ratios for the association of childhood dogs and adult wheeze in nonsensitized subjects by center. Adjustment within center for other childhood pets, adult pets, parental and sibling allergy, own and parental smoking, number of siblings, age, sex, and occupation. For each center, *horizontal lines* indicate 95% CI. For combined odds ratio, *diamond* indicates 95% CI from model, with center as random effect. The size of each square is proportional to the sample size.

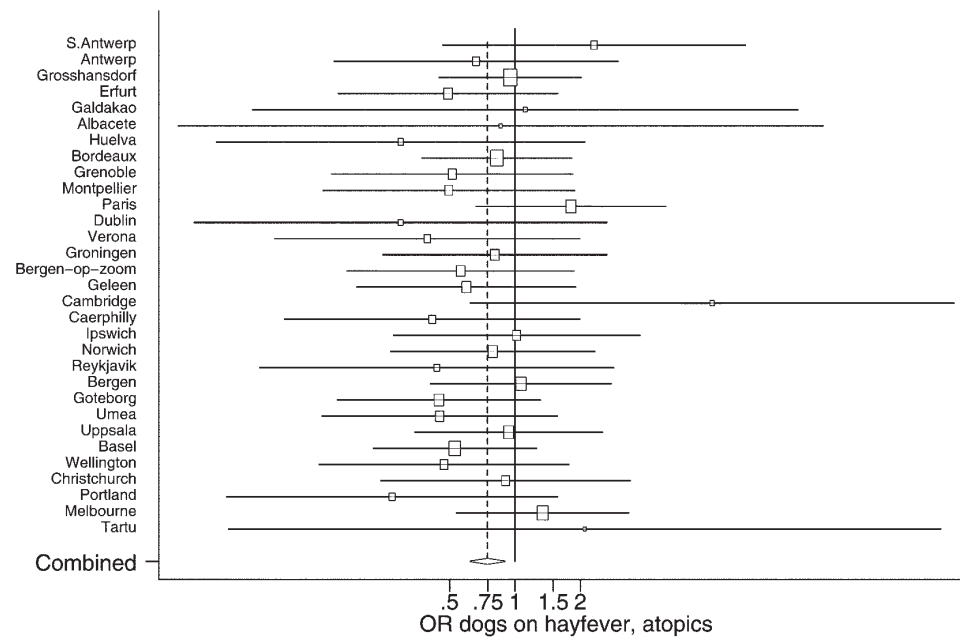


FIG 3. Odds ratios for the association of childhood dogs and adult hay fever in nonsensitized subjects by center. Adjustment within center for other childhood pets, adult pets, parental and siblings allergy, own and parental smoking, number of siblings, age, sex, and occupation. For each center, *horizontal lines* indicate 95% CI. For combined odds ratio, *diamond* indicates 95% CI from model, with center as random effect. The size of each square is proportional to the sample size.

TABLE V. Childhood and current adult pet-keeping as related to wheeze and hay fever at age 20-44 years, in 4514 subjects with atopic sensitization (specific IgE to house dust mite, cat, grass, and/or mold) and 9407 subjects without

	Wheeze					Hay fever				
	Nonatopic subjects		Atopic subjects		P†	Nonatopic subjects		Atopic subjects		P†
	Percent	OR	Percent	OR		Percent	OR	Percent	OR	
		(95% CI)*		(95% CI)*			(95% CI)*		(95% CI)*	
Childhood cat										
No	17	1	28	1		14	1	48	1	
Yes	21	1.06 (0.93-1.20)	37	1.28 (1.10-1.48)	.014	16	1.02 (0.90-1.17)	50	1.02 (0.88-1.17)	.3
Childhood dog										
No	16	1	29	1		15	1	50	1	
Yes	23	1.28 (1.13-1.46)	35	1.01 (0.87-1.17)	.032	16	0.98 (0.86-1.13)	47	0.85 (0.73-0.98)	.001
Childhood bird										
No	17	1	30	1		15	1	51	1	
Yes	21	1.13 (1.00-1.27)	34	1.18 (1.02-1.36)	.9	16	1.07 (0.94-1.21)	46	0.83 (0.81-1.06)	.06
Adult cat										
No	18	1	31	1		15	1	48	1	
Yes	22	1.07 (0.93-1.23)	35	0.95 (0.80-1.12)	.3	18	1.04 (0.90-1.21)	52	1.06 (0.90-1.25)	.9
Adult dog										
No	18	1	31	1		15	1	48	1	
Yes	25	1.31 (1.14-1.51)	37	1.01 (0.85-1.21)	.038	17	1.04 (0.88-1.22)	51	1.12 (0.94-1.33)	.9
Adult bird										
No	19	1	32	1		16	1	49	1	
Yes	19	0.96 (0.80-1.15)	30	0.89 (0.72-1.11)	.5	14	1.02 (0.83-1.25)	46	1.09 (0.88-1.35)	.9

Boldfaced odds ratios refer to associations with $P < .05$.

OR, Odds ratio.

*Odds ratios with 95% CI as estimated by logistic regression adjusting for parental allergy, siblings allergy, parental smoking, number of siblings, age, sex, current smoking, current occupation, and study center.

† P values for interactions of effect of pets on symptom according to atopy.

airways, with the potential to prevent or promote subsequent disease, even in adulthood.

Methodologic considerations

The major problem in the interpretation of analyses of pets and allergy, is that the study subjects cannot be randomly assigned with regard to pet-keeping. People choose whether and what kind of pet to keep on the basis of a range of motives. Doctors in many countries expect allergy to be a main determinant in this choice, whereas the literature gives contradictory information.^{5,34,35} If families with allergy tend to avoid keeping pets, this should have been reflected in apparent "protective" effects of cats and dogs on both asthma and hay fever among predisposed subjects. We did not find such evidence for selective avoidance of pets during childhood, possibly because there was little focus on allergen avoidance during the period when our subjects were children (born 1945-1972). Furthermore, subjects who had gotten rid of a childhood pet because of symptoms would still report having had the pet. In agreement with other studies,^{10,13} allergic disease in siblings or parents was not an important determinant for pet-keeping in childhood compared with the strong effects of sociocultural factors (Table III).

With regard to adult pet-keeping, however, the results must be interpreted with caution, because there were indications of complex selection phenomena (Table VI). Cats were more strongly related to adult asthma in sensitized subjects who had kept cats only in childhood, possibly indicating that those who got symptoms from their child-

hood cat avoided keeping cats when adults. (Alternately, subjects who stopped keeping a cat might have lost their tolerance and developed more symptoms related to community exposure.) Adult cat keeping was not associated with wheeze, not even among the cat sensitized, possibly because of selective avoidance. Childhood dog owners seemed to keep dogs when adults despite respiratory symptoms, compatible with investigations showing that people are reluctant to get rid of their dog even when it causes symptoms.³⁵ Less respiratory symptoms in those who kept a bird only as adults might indicate that adult subjects with asthma avoided getting birds unless they had kept them in childhood (a protective effect from keeping birds during adult life seems unlikely).

Recall bias is another problem, but a pet is an important feature of childhood that people are likely to remember accurately. The cross-sectional design of the study is a weakness, because our measure of exposure is very crude, whereas the biologic influence of pet contact is expected to be specific with regard to time and dose of exposure. Our analyses can therefore not reveal very distinct patterns and might underestimate true associations.

The inheritable susceptibility to asthma and allergy is well known, but direct genetic markers are not available. In this study, the presence of atopic sensitization was used as a measure of allergic predisposition, thereby characterizing the subject's own immunologic constitution based on confirmed production of specific IgE. This measure is not influenced by information bias and is feasible in clinical consulting if further research supports this approach.

TABLE VI. Age of pet-keeping as related to adult respiratory symptoms, asthma medication, and hay fever in 9088 nonatopic subjects and 4374 atopic subjects with complete information

	Wheeze		Wheeze,† breathlessness		Wheeze without cold		Asthma medication		Hay fever	
	Nonatopic subjects	Atopic subjects	Nonatopic subjects	Atopic subjects	Nonatopic subjects	Atopic subjects	Nonatopic subjects	Atopic subjects	Nonatopic subjects	Atopic subjects
	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*
Cat, child, and adult	1.11 (0.93-1.33)	1.14 (0.91-1.42)	1.13 (0.89-1.43)	1.15 (0.89-1.49)	1.06 (0.84-1.33)	0.94 (0.73-1.21)	0.92 (0.60-1.64)	0.95 (0.65-1.37)	1.07 (0.89-1.30)	1.05 (0.85-1.31)
Cat, only childhood	1.06 (0.92-1.21)	1.43 (1.22-1.67)	1.09 (0.91-1.31)	1.36 (1.12-1.64)	0.87 (0.73-1.04)	1.26 (1.06-1.51)	0.91 (0.56-1.46)	1.34 (1.02-1.77)	1.07 (0.92-1.23)	1.04 (0.89-1.21)
Cat, only adulthood	1.08 (0.86-1.35)	1.26 (0.97-1.63)	1.16 (0.86-1.56)	1.20 (0.87-1.64)	1.13 (0.86-1.49)	1.24 (0.93-1.66)	0.79 (0.35-1.81)	0.83 (0.51-1.37)	1.11 (0.87-1.41)	1.13 (0.88-1.46)
Dog, child and adult	1.69 (1.40-2.04)	1.07 (0.85-1.35)	1.64 (1.29-2.09)	1.03 (0.79-1.35)	1.80 (1.42-2.27)	1.20 (0.93-1.55)	1.85 (1.01-3.41)	1.10 (0.75-1.60)	1.06 (0.86-1.31)	0.95 (0.75-1.19)
Dog, only childhood	1.26 (1.10-1.44)	1.00 (0.85-1.17)	1.19 (0.99-1.43)	1.06 (0.87-1.28)	1.37 (1.15-1.63)	1.02 (0.85-1.22)	1.34 (0.82-2.19)	1.02 (0.77-1.36)	0.98 (0.85-1.14)	0.84 (0.72-0.98)
Dog, only adulthood	1.24 (0.98-1.59)	0.95 (0.71-1.26)	1.04 (0.73-1.47)	1.15 (0.83-1.60)	1.29 (0.95-1.76)	1.00 (0.73-1.38)	1.65 (0.76-3.57)	1.33 (0.84-2.10)	0.95 (0.73-1.24)	1.10 (0.84-1.46)
Bird, child and adult	1.15 (0.91-1.45)	1.15 (0.88-1.51)	1.12 (0.83-1.51)	1.19 (0.87-1.63)	1.07 (0.80-1.43)	1.26 (0.93-1.70)	0.95 (0.41-2.23)	1.02 (0.62-1.69)	1.08 (0.84-1.40)	1.00 (0.77-1.30)
Bird, only childhood	1.09 (0.96-1.24)	1.17 (1.01-1.36)	1.11 (0.94-1.32)	1.13 (0.95-1.34)	1.02 (0.87-1.20)	1.10 (0.93-1.30)	1.02 (0.66-1.56)	1.13 (0.87-1.46)	1.08 (0.95-1.24)	0.93 (0.81-1.08)
Bird, only adulthood	0.81 (0.60-1.10)	0.77 (0.53-1.12)	0.60 (0.37-0.96)	0.55 (0.33-0.91)	0.72 (0.48-1.08)	0.78 (0.51-1.20)	1.02 (0.35-2.92)	0.94 (0.50-1.79)	1.05 (0.77-1.44)	1.12 (0.80-1.58)

Boldfaced odds ratios refer to associations with $P < .05$.

OR, Odds ratio.

*Odds ratios with 95% CIs as estimated by logistic regression adjusting for parental allergy, siblings allergy, parental smoking, number of siblings, age, sex, current smoking, current occupation, and study center. Reference groups: no cat/no dog/no bird.

Cats: Symptoms, sensitization, and tolerance

Several studies indicate that keeping a cat during childhood might confer protection against becoming sensitized to cats^{5,6,9,36,37} and to other common aeroallergens,³ particularly among predisposed subjects.^{3,5,36} High-dose cat exposure might induce tolerance in some individuals^{23,24} through production of IgG4 rather than IgE, stimulated by the T_H2 cytokine IL-4.²⁴ We found that in subjects who did not become sensitized (ie, who developed tolerance), keeping cats during childhood did not make any difference with regard to later respiratory symptoms. When sensitization did occur in those who kept cats during childhood, the risk of adult asthma was increased. A stronger effect among the sensitized was also found in a study of adults³⁸ relating current cat allergen level with respiratory symptoms. In 1 study of children, exposure to cats increased the risk of wheeze in the children of asthmatic mothers but reduced the risk in the children of mothers without asthma.¹¹ However, a net protective effect was found in the total cohort,¹² and a protective effect of cats was also found in another cohort of high-risk children.⁹ The discrepancy between these studies of children and our findings in adults could be related to the difference in age span but also to differences in community level of allergen exposure. Increased asthma risk in sensitized subjects who had kept cats in

childhood was restricted to subjects who grew up in areas in which the public exposure to cat was limited. In areas in which >60% of the study subjects kept cats, there was no increase in asthma risk among those who had kept a cat during childhood, and there was even an indication of a protective effect. Our study included only a small number of areas with very high community prevalence of pets, thus we could not determine with certainty whether the OR of childhood cats and adult asthma with further increasing community prevalence of childhood cats tended toward 1 or 0. An OR of 1 would mean that pet-keeping at home did not add to the risk related to high exposure in the community, whereas an association tending toward 0 (as indicated by Fig 1, B) would mean that high exposure at home offered relative tolerance toward high public exposure.

Dogs: Antiallergic but pro-inflammatory?

Dogs kept in childhood, previously shown to protect against allergic sensitization,³ also seemed to protect against adult hay fever in the sensitized population. Protective effects of dogs with regard to atopic sensitization are similarly reported in several studies of children,^{7,12,13,39} particularly in high-risk children.^{7,12} However, among the nonatopic subjects of our study, dog ownership was associated with a substantial increase in risk for adult respiratory symptoms. There was evidence of a

cumulative effect with a 70% increase in wheeze related to dog keeping in both childhood and adulthood. These findings were highly significant, consistent across 36 different populations, and robust to different methods of analysis. The association was similar in never-smokers, and was thus not caused by uncontrolled confounding by smoking. There are no comparable studies of adults. Nafstad et al⁷ showed more bronchial hyperresponsiveness related to dog keeping in infants, but other studies of children show protective effects of dogs on wheeze also in subjects without allergic predisposition.^{13,39}

Microbial challenge could possibly explain the protective effects of dogs on allergic sensitization and on allergic symptoms in sensitized subjects, as well as the demonstrated adverse effects of dogs on adult asthma. Dogs often have close physical contact with people, especially with very small children, nuzzling them in the face and licking their hands. The dog's fur might carry microbes from soil. Dogs, as opposed to cats, might thus provide a wide microbial exposure early in life that might possibly promote a nonallergic immunologic maturation during this sensitive age window. However, in nonsensitized subjects who do not need this additional microbial stimulation because they already have a competent nonallergic immune system, the harmful consequences of microbial challenge might be dominant. Both harmful and protective effects of dogs could be mediated through the bacterial product endotoxin, which is found in increased levels in homes with dogs.⁴⁰ The pro-inflammatory effects of these substances and the related increase in respiratory symptoms are well known,²⁵ whereas exposure during the early stages of immune priming seem to confer protection against allergy.^{41,42} A recent study showed less atopic but more nonatopic asthma related to increasing levels of endotoxin.⁴¹ However, in another study, the protective effect of exposure to dogs was independent of endotoxins,¹² suggesting a role for other mediators. The microbial closeness of the dog with human beings^{26,27} could also increase the possibility for lower airways infections predisposing to asthma.^{43,44} Harmful effects of pro-inflammatory substances and infections from dogs are likely to increase with age. An age-dependent balance of beneficial and harmful effects of dogs could explain the cumulative effect of dog exposure in this study and the different results in children and adults. This view is supported by a meta-analysis showing protective effects of pets in studies of younger children but harmful effects in studies of older children.¹

Birds: Nonspecific pro-inflammatory?

Bird keeping in childhood was found to increase the risk for adult respiratory symptoms independent of allergic disposition. Adult occupational exposure to poultry is known to increase respiratory symptoms.^{45,46} Rees et al⁴⁶ showed that this was unrelated to sensitization, which is in accordance with our study of childhood exposure to pet birds. Melsom et al¹⁴ showed increased asthma in children living in households with poultry kept indoors. A direct toxic or airways irritant effect from ammonia or

other substances in bird manure is a possible explanation. Childhood exposure could cause adult symptoms by an impact during critical stages of lung development.

CONCLUSION

This study showed complex associations of childhood pets and adult asthma and hay fever. Childhood exposure to cats, previously shown to protect against allergic sensitization, had no influence on adult asthma in those who did not become sensitized but was related to increased risk for adult asthma among the sensitized. However, when the community exposure to cats was high during childhood, keeping a cat at home represented no additional asthma risk. Whether in this case cat keeping could offer protection against adult asthma, indicating tolerance toward allergic symptoms in already sensitized subjects, needs further investigation. Dogs kept in childhood, previously shown to protect against allergic sensitization, seemed to also protect against hay fever symptoms in atopic subjects. However, for those who were not atopic a dog kept in childhood or during adult life was associated with a considerably increased risk of adult respiratory symptoms. Dogs might possibly stimulate a nonallergic immunologic maturation, but at the same time promote nonallergic asthma through alternative inflammatory mechanisms or transmission of infections. The choice of keeping dogs in families with children might thus have substantial long-term consequences for allergic disease, and further research is needed. There were clear differences related to atopic status, a feasible and potentially useful marker of immunologic constitution. These results should be a step toward individual clinical advice about pet-keeping on the basis of phenotype.

We thank the Norwegian Asthma and Allergy Foundation for their support and help with the study.

REFERENCES

1. Apelberg BJ, Aoki Y, Jaakkola JJ. Systematic review: exposure to pets and risk of asthma and asthma-like symptoms. *J Allergy Clin Immunol* 2001;107:455-60.
2. Noertjojo K, Dimich-Ward H, Obata H, Manfreda J, Chan-Yeung M. Exposure and sensitization to cat dander: asthma and asthma-like symptoms among adults. *J Allergy Clin Immunol* 1999;103:60-5.
3. Svanes C, Jarvis D, Chinn S, Burney P. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;103:415-20.
4. Sunyer J, Anto JM, Kogevinas M, Barcelo MA, Soriano JB, Tobias A, et al. Risk factors for asthma in young adults. Spanish Group of the European Community Respiratory Health Survey. *Eur Respir J* 1997;10:2490-4.
5. Roost HP, Kunzli N, Schindler C, Jarvis D, Chinn S, Perruchoud AP, et al. Role of current and childhood exposure to cat and atopic sensitization. European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;104:941-7.
6. Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy* 1999;29:611-7.
7. Nafstad P, Magnus P, Gaarder PI, Jaakkola JJ. Exposure to pets and atopy-related diseases in the first 4 years of life. *Allergy* 2001;56:307-12.
8. Withers NJ, Low L, Holgate ST, Clough JB. The natural history of respiratory symptoms in a cohort of adolescents. *Am J Respir Crit Care Med* 1998;158:352-7.

9. Perzanowski MS, Ronmark E, Platts-Mills TA, Lundback B. Effect of cat and dog ownership on sensitization and development of asthma among preteenage children. *Am J Respir Crit Care Med* 2002;166:696-702.
10. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA* 2002;288:963-72.
11. Celedon JC, Litonjua AA, Ryan L, Platts-Mills T, Weiss ST, Gold DR. Exposure to cat allergen, maternal history of asthma, and wheezing in first 5 years of life. *Lancet* 2002;360:781-2.
12. Litonjua AA, Milton DK, Celedon JC, Ryan L, Weiss ST, Gold DR. A longitudinal analysis of wheezing in young children: the independent effects of early life exposure to house dust endotoxin, allergens, and pets. *J Allergy Clin Immunol* 2002;110:736-42.
13. Remes ST, Castro-Rodriguez JA, Holberg CJ, Martinez FD, Wright AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol* 2001;108:509-15.
14. Melsom T, Brinch L, Hessen JO, Schei MA, Kolstrup N, Jacobsen BK, et al. Asthma and indoor environment in Nepal. *Thorax* 2001;56:477-81.
15. Braun-Fahrlander C. The role of the farm environment and animal contact for the development of asthma and allergies. *Clin Exp Allergy* 2001;31:1799-803.
16. Sporik R, Platts-Mills TA. Allergen exposure and the development of asthma. *Thorax* 2001;56 Suppl 2:ii58-63.
17. Pearce N, Douwes J, Beasley R. Is allergen exposure the major primary cause of asthma? *Thorax* 2000;55:424-31.
18. Prescott SL, Jones CA. Cord blood memory responses: are we being naive? *Clin Exp Allergy* 2001;31:1653-6.
19. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259-60.
20. Holt PG, Macaubas C, Prescott SL, Sly PD. Microbial stimulation as an aetiological factor in atopic disease. *Allergy* 1999;54 Suppl 49:12-6.
21. Martinez FD, Holt PG. Role of microbial burden in aetiology of allergy and asthma. *Lancet* 1999;354 Suppl 2:II12-5.
22. Matricardi PM, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M, et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000;320:412-7.
23. Custovic A, Hallam CL, Simpson BM, 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.
24. 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.
25. Douwes J, Pearce N, Heederik D. Does environmental endotoxin exposure prevent asthma? *Thorax* 2002;57:86-90.
26. Tan J. Human zoonotic infections transmitted by dogs and cats. *Arch Intern Med* 1997;157:1933-43.
27. Copperman SM. Cherchez le chien: household pets as reservoirs of persistent or recurrent streptococcal sore throats in children. *NY State J Med* 1982;82:1685-7.
28. Baldini M, Vercelli D, Martinez FD. CD14: an example of gene by environment interaction in allergic disease. *Allergy* 2002;57:188-92.
29. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954-60.
30. Burney P, Malmberg E, Chinn S, Jarvis D, Luczynska C, Lai E. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1997;99:314-22.
31. Classification of occupations. London: Office of population censuses and surveys. HMSO; 1980.
32. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
33. Stata Statistical Software, Release 7.0. College Station (TX): Stata Corporation.
34. Anyo G, Brunekreef B, de Meer G, Aarts F, Janssen NA, van Vliet P. Early, current and past pet ownership: associations with sensitization, bronchial responsiveness and allergic symptoms in school children. *Clin Exp Allergy* 2002;32:361-6.
35. AVMA guidelines for responding to clients with special needs. AVMA Committee on the Human-Animal Bond. *J Am Vet Med Assoc* 1995;206:961-76.
36. Braback L, Kjellman NI, Sandin A, Bjorksten B. Atopy among schoolchildren in northern and southern Sweden in relation to pet ownership and early life events. *Pediatr Allergy Immunol* 2001;12:4-10.
37. Henriksen AH, Holmen TL, Bjermer L. Sensitization and exposure to pet allergens in asthmatics versus non-asthmatics with allergic rhinitis. *Respir Med* 2001;95:122-9.
38. Gehring U, Heinrich J, Jacob B, Richter K, Fahlbusch B, Schlenvoigt G, et al. Respiratory symptoms in relation to indoor exposure to mite and cat allergens and endotoxins. Indoor Factors and Genetics in Asthma (INGA) Study Group. *Eur Respir J* 2001;18:555-63.
39. Hölcher B. Exposure to pets and allergies in children. *Pediatr Allergy Immunol* 2002;13.
40. Heinrich J, Gehring U, Douwes J, Koch A, Fahlbusch B, Bischof W, et al. Pets and vermin are associated with high endotoxin levels in house dust. *Clin Exp Allergy* 2001;31:1839-45.
41. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869-77.
42. Gehring U, Bischof W, Fahlbusch B, Wichmann HE, Heinrich J. House dust endotoxin and allergic sensitization in children. *Am J Respir Crit Care Med* 2002;166:939-44.
43. Buijs J, Egbers MW, Lokhorst WH, Savelkoul HF, Nijkamp FP. Toxocara-induced eosinophilic inflammation. Airway function and effect of anti-IL-5. *Am J Respir Crit Care Med* 1995;151:873-8.
44. Chan PW, Anuar AK, Fong MY, Debruyne JA, Ibrahim J. Toxocara seroprevalence and childhood asthma among Malaysian children. *Pediatr Int* 2001;43:350-3.
45. Radon K, Danuser B, Iversen M, Jorres R, Monso E, Opravil U, et al. Respiratory symptoms in European animal farmers. *Eur Respir J* 2001;17:747-54.
46. Rees D, Nelson G, Kielkowski D, Wasserfall C, da Costa A. Respiratory health and immunological profile of poultry workers. *S Afr Med J* 1998;88:1110-7.
47. Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997;99:763-9.
48. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998;101:587-93.
49. Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von Mutius E, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. *Lancet* 2000;356:1392-7.
50. Hesselmar B, Aberg B, Eriksson B, Aberg N. Allergic rhinoconjunctivitis, eczema, and sensitization in two areas with differing climates. *Pediatr Allergy Immunol* 2001;12:208-15.
51. Ronmark E, Jonsson E, Platts-Mills T, Lundback B. Incidence and remission of asthma in schoolchildren: report from the obstructive lung disease in northern Sweden studies. *Pediatrics* 2001;107:E37.

APPENDIX

Principal participants

Coordinating Center (London). P. Burney, S. Chinn, C. Luczynska, D. Jarvis, E. Lai.

Project Management Group. P. Burney (Project leader) S. Chinn, C. Luczynska, D. Jarvis, P. Vermeire (Antwerp); H. Kesteloot (Leuven); J. Bousquet (Montpellier); D. Nowak (Hamburg); the late J. Prichard (Dublin); R. de Marco (Verona); B. Rijcken (Groningen); J. M. Anto (Barcelona); J. Alves (Oporto); G. Boman (Uppsala); N. Nielsen (Copenhagen); P. Paoletti (Pisa).

Participating Centers. *Austria:* W. Popp (Vienna); *Australia:* M. Abramson, J. Raven, J. Rolland (Melbourne); *Belgium:* P. Vermeire, F. van Bastelaer (Antwerp South, Antwerp Central); *Estonia:* R. Jõgi (Tartu); *France:* J. Bousquet J. Knani (Montpellier); F. Neukirch, R. Liard (Paris); I. Pin, C. Pison (Grenoble); A. Taytard (Bordeaux); *Germany:* H. Magnussen, D. Nowak (Hamburg); H. E. Wichmann, J. Heinrich (Erfurt); *Greece:* N.

Papageorgiou, P. Avarlis, M. Gaga, C. Marossis (Athens); *Iceland*: T. Gislason, D. Gislason (Reykjavik); *Ireland*: J. Prichard, S. Allwright, D. MacLeod (Dublin); *Italy*: M. Bugiani, C. Bucca, C. Romano (Turin); R. de Marco Lo Cascio, C. Campello (Verona); A. Marinoni, I. Cerveri, L. Casali (Pavia); *Netherlands*: B. Rijcken, A. Kremer (Groningen, Bergen-op-Zoom, Geleen); *New Zealand*: J. Crane, S. Lewis (Wellington, Christchurch, Hawkes Bay); *Norway*: A. Gulsvik, E. Omenaas (Bergen); *Portugal*: J. A. Marques, J. Alves (Oporto); *Spain*: J. M. Antó, J. Sunyer, F. Burgos, J. Castellsagué, J. Roca, J. B. Soriano, A. Tobías (Barcelona); N. Muniozguren, J. Ramos González,

A. Capelastegui (Galdakao); J. Castillo, J. Rodriguez Portal (Seville); J. Martinez-Moratalla, E. Almar (Albacete); J. Maldonado Pérez A. Pereira, J. Sánchez (Huelva); J. Quiros, I. Huerta, F. Pavo (Oviedo); *Sweden*: G. Boman, C. Janson, E. Björnsson (Uppsala); L. Rosenhall, E. Norrman, B. Lundbäck (Umeå); N. Lindholm, P. Plaschke (Göteborg); *Switzerland*: U. Ackermann-Liebrich, N. Künzli, A. Perruchoud (Basel); *United Kingdom*: M. Burr, J. Layzell (Caerphilly); R. Hall (Ipswich); B. Harrison (Norwich); J. Stark (Cambridge); *United States*: S. Buist, W. Vollmer, M. Osborne (Portland).