Exposure to Cats and Dogs, and Symptoms of Asthma, Rhinoconjunctivitis, and Eczema

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Background: Associations between exposure to cats and dogs and respiratory and allergic outcomes in children have been reported in affluent countries, but little is known about such associations in less-affluent countries.

Methods: The International Study of Asthma and Allergies in Childhood, phase 3 was carried out in children aged 6–7 years and adolescents aged 13–14 years across the world. Questions about cats and dogs in the home were included in an additional questionnaire. Using logistic regression, we investigated the association between such exposures and symptoms of asthma, rhinoconjunctivitis, and eczema. Adjustments were made for sex, region of the world, language, gross national income per capita, and 10 other covariates.

Results: Among children (6–7 years of age), cat exposure in the first year of life was associated with current symptoms of asthma, wheeze, rhinoconjunctivitis, and eczema, especially in less-affluent countries. Among adolescents (13–14 years of age), we found a positive association between exposure to cats or dogs and symptom prevalence in more-affluent and less-affluent countries. The global multivariate odds ratios for children with complete covariate data were 1.17 (95% confidence interval = 1.08–1.29) for current symptoms of asthma, 1.13 (1.05–1.23) for rhinoconjunctivitis, and 1.38 (1.26–1.52) for eczema. Smaller odds ratios were found for exposure to only dogs. Exposure to only cats was associated with eczema.

Conclusion: Early-life exposure to cats is a risk factor for symptoms of asthma, rhinoconjunctivitis, and eczema in 6- to 7-year-old children, especially in less-affluent countries. Current exposure to cats and dogs combined, and only to dogs, is a risk factor for symptom reporting by 13- to 14-year-old adolescents worldwide.

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The relation between exposure to cats and dogs and childhood asthma, rhinoconjunctivitis, and eczema is complicated. Cats and dogs produce allergens to which children may become sensitized; some sensitized children may subsequently develop allergic diseases of the lower and upper airways and/or the skin. Symptoms may be related to nonallergic mechanisms such as inflammation caused by endotoxin, as well. In addition, several studies have shown that early exposure to dogs is associated with reduced development of allergic disease, later in childhood. Development of tolerance to early-life allergen exposure, or immune system modulation by bacterial endotoxin, or other microbial exposures have been suggested to explain such observations. A complicating factor in studies that show a "protective effect" of pets is that allergy in the family may stimulate parents to not have pets, or to remove them after disease has become manifest; such behavior could lead to reverse causation (allergy leading to reduced pet exposure), rather than pet exposure, actually protecting children from allergic disease.

Most studies on cat and dog exposure in children have been conducted in developed countries; it is not clear to what extent the findings can be extrapolated to children in other parts of the world. A few studies have addressed the relationship between cat and dog exposure and childhood symptoms in less-affluent populations, and these have found largely positive relation (in contrast with studies from developed countries). As an example, a case-control study among 6- to 10-year-old children conducted in a suburb of Beijing found an odds ratio (OR) of 1.5 (95% confidence interval [CI] = 1.0–2.3) for asthma in relation to having both a dog and a cat at home.[1] Another Chinese study, this one among adolescents, found increased reporting of persistent cough and wheeze, when cats and dogs were reported in the household, especially before age 6 years.[2] A study from Bulgaria among 2- to 8-year-old children found positive associations between having a cat or dog in the home at birth and current wheezing, rhinitis on pet contact, and eczema; the OR for current pet keeping and wheeze was 1.26 (95% CI = 1.01–1.56).[3]

We present findings on cat and dog exposure from the third phase of the International Study of Asthma and Allergies in Childhood (ISAAC phase three), a questionnaire-based assessment conducted in 1,187,496 children from 238 centers, in 98 countries in all parts of the world. The analyses are restricted to 6- to 7-year-old children (206,332) and 13- to 14-year-old (329,494) adolescents for whom data on exposure to cats and dogs were collected.

METHODS

ISAAC phase three is a repetition and expansion of the first phase of ISAAC, which documented large differences in the prevalence of childhood symptoms of asthma, rhinitis, and eczema across the world.[4–5]

As in the first phase, parents of children aged 6–7 years (referred to here as "children") completed the questionnaires at home, whereas 13- to 14-year-old individuals (referred to as "adolescents") completed the written questionnaire at school. Schools were randomly selected from defined geographical areas. Centers obtained ethical approval from their local ethics committee, or for the minority of centers that did not have an ethics committee, some other approving body such as The Ministry of Health. The method of consent was determined by the local Ethics Committee. Centers obtained their own funding. Further details on protocol and symptom definition have been published previously.[4,6–8]

In ISAAC phase three, an optional environmental questionnaire was administered, in addition to the symptom questionnaire, to test a number of specific etiologic hypotheses.[4] The environmental questionnaire included questions on diet, heating and cooking fuels, exercise, exposure to farm animals and pets, family size, birth order, family socioeconomic status, use of antibiotics and antipyretics, breast-feeding, birth weight, immigrant status, environmental tobacco smoke, and frequency of truck traffic in street of residence. The written questionnaire was translated from English, according to the ISAAC phase three protocol[4] into Arabic, Chinese, English, Hindi, Indonesian, Portuguese, Spanish, and numerous other local languages. These were back translated to English and assessed.[9] The complete questionnaire can be found on the Study Web site www.isaac.auckland.ac.nz.

The questions considered here are as follows:

- In the past 12 months, have you had a cat in your home (y/n)?
- In the past 12 months, have you had a dog in your home (y/n)?

These questions were posed to parents of the children and to the adolescents themselves. Parents of the children were also asked the following questions on early-life exposure:

- Did you have a cat in your home during the first year of your child's life (y/n)?
- Did you have a dog in your home during the first year of your child's life (y/n)?

A detailed definition of the outcomes used in this analysis is given in the eAppendix (http://links.lww.com/EDE/A599).

ORs were calculated using generalized linear mixed models (GLMM) for a binomial distribution and logit link, with the centers modeled as a random effect. The analyses on all study participants were adjusted for sex, region of the world, language, and gross national income per capita (GNI) of the country.

In addition to the combined analyses, analyses were conducted after stratification for sex and per capita income. Countries were categorized as "more-affluent" or "less-affluent," using a 2001 per capita income value of $9,205 as the cut point; this value separates "high-income" countries from the "low," "lower-middle," and "upper-middle income" countries, according to the World Bank's Classification.[10]

Finally, fully adjusted analyses (generalized linear mixed models) were conducted to check whether associations between animal exposure and symptoms were confounded by certain other variables in the environmental questionnaire such as maternal education, cooking fuel, maternal and paternal smoking, television watching, exercise, siblings (older and younger), fast food, truck-traffic exposure, and paracetamol use. Details of the definitions of these variables can be found on the Study Web site www.isaac.auckland.ac.nz. Centers were treated as simple random effects, and region was included in the model as a fixed effect to account for the differences in level between regions.

In a further sensitivity analysis, centers were stratified into above- or below-median current cat or dog exposure, separately for more- and less-affluent countries. This was done because an analysis of the European Community Respiratory Health Survey data suggested that associations between individual cat exposure and health outcomes were more easily found in areas with low community prevalence of cats, where personal exposure is better represented by personal cat ownership than in areas with high cat prevalence where exposure is more ubiquitous.[11]

The final worldwide data set comprised 144 centers from 61 countries with 388,811 children aged 6–7 years and 233 centers from 97 countries with 798,685 adolescents aged 13–14 years. Centers that had not administered the environmental questionnaire were then excluded from the data set, leaving a final data set of 72 centers in 30 countries with 206,332 children and 122 centers from 54 countries with 361,599 adolescents. For inclusion in this analysis, centers were required to have at least 70% of participants with data on reported animal exposure; adolescents in 8 centers were excluded because they did not meet this criterion.

RESULTS

There were 206,332 children (aged 6–7 years) from 72 centers in 30 countries, and 329,494 adolescents (aged 13–14 years) from 114 centers in 49 countries included in the

TABLE 1. Frequency of Reported Cat and Dog Exposure in the Households of Children and Adolescents by Region of the World, ISAAC Phase Three

				Cat		Dog	
Region	**No. Countries**	**No. Centers**	**No. Children**	**Now %**	**First Year %**	**Now %**	**First Year %**
			Ages 6–7 yrs				
All centers	30	72	206,332	16	12	25	20
Africa	1	1	2,354	11	7	17	16
Asia-Pacific	6	9	32,175	11	9	19	19
Eastern Mediterranean	3	5	15,040	12	11	3	2
Indian subcontinent	1	14	42,594	9	10	9	10
Latin America	7	18	49,332	17	11	47	33
North America	2	2	3,940	22	18	38	29
Northern and Eastern Europe	5	6	15,097	20	11	29	26
Oceania	1	4	10,776	52	43	321	29
Western Europe	4	13	35,024	13	10	21	17
			Ages 13–14 yrs				
All centers	49	114	329,494	28		41	
Africa	8	10	27,787	40		35	
Asia-Pacific	7	15	49,669	23		32	
Eastern Mediterranean	4	7	21,267	17		7	
Indian Sub-Continent	1	16	43,931	19		18	
Latin America	10	29	82,262	31		67	
North America	3	3	6,466	27		42	
Northern and Eastern Europe	7	10	29,997	29		38	
Oceania	4	8	19,259	60		56	
Western Europe	5	16	48,856	24		38	

analyses of cat and dog in the home (exposure). Table 1 shows the wide range of reported percentages of cat and dog exposure by area of the world. Cat exposure was highest in Oceania and the lowest in the Eastern Mediterranean and the Indian subcontinent; dog exposure was highest in Latin America and lowest again in the Eastern Mediterranean. Prevalences of cat and dog ownership were lowest in the first year of life, higher for current exposure in the children, and highest for current exposure in the adolescents, likely signifying a progression of acquiring pets as children get older. The rank order of cat and dog ownership for the various parts of the world was similar for the children and the adolescents.

Table 2 shows the association between cat exposure in the first year of life and symptoms that were investigated in the children. In the fully adjusted analysis, current symptoms of asthma (wheeze) and rhinoconjunctivitis, but not eczema, were positively associated with cat exposure in the first year of life. Adjusted associations with current cat exposure, and with dog exposure in the first year and currently, were close to null (eTables 1–3, http://links.lww.com/EDE/A599). For most analyses of cat and dog exposure, ORs adjusted only for sex, region of the world, language, and per capita income were higher than similarly adjusted ORs for children with complete covariate data, indicating that missing values did not occur at random. In comparison, the additional effect of full adjustment for all additional covariates was marginal.

Table 3 shows the association between current cat exposure and symptoms for the adolescents. In the fully adjusted analysis, current cat exposure was positively associated with current symptoms of asthma, rhinoconjunctivitis, and eczema, with ORs ranging from 1.08 to 1.29. Ever having reported asthma, hay fever, and eczema were not associated with cat.

Table 3 also shows the association between current dog exposure and symptoms among the adolescents. In the fully adjusted analysis, current dog exposure was positively associated with current symptoms of asthma, rhinoconjunctivitis, and eczema, with ORs ranging from 1.07 to 1.25. A reported diagnosis of hay fever and severe symptoms of hay fever were not associated with exposure to dogs.

The strongest associations were found when adolescents having both a cat and a dog at home were compared with adolescents who had neither. The ORs were 1.17 (1.08–1.29) for current wheeze, 1.13 (1.05–1.23) for rhinoconjunctivitis, and 1.38 (1.26–1.52) for eczema.

The analyses in Tables 2, 3 were repeated after stratification of the centers into centers those from more- and less-affluent countries (eTables 4–6, http://links.lww.com/EDE/A599). As-

TABLE 2. Association Between Cat in the Home in the First Year of Life and Symptoms of Asthma, Rhinoconjunctivitis, and Eczema in Children Ages 6–7 yrs

	OR (95% CI)		
Symptoms	Adjusted[a] (All Children)	Adjusted[b] (Children With Complete Covariate Data)	Fully Adjusted[c]
Asthma			
Current wheeze	1.30 (1.23–1.36)	1.19 (1.10–1.28)	1.17 (1.09–1.26)
Current, severe	1.30 (1.21–1.40)	1.15 (1.04–1.27)	1.12 (1.01–1.23)
Ever	1.22 (1.16–1.29)	1.14 (1.06–1.23)	1.12 (1.04–1.21)
Rhinoconjunctivitis			
Current	1.19 (1.13–1.27)	1.10 (1.01–1.19)	1.09 (1.00–1.18)
Current, severe	1.63 (1.37–1.94)	1.43 (1.08–1.89)	1.34 (1.02–1.77)
Hay fever			
Ever	1.17 (1.10–1.24)	1.10 (1.02–1.20)	1.10 (1.01–1.19)
Eczema			
Current	1.21 (1.14–1.28)	1.09 (1.01–1.18)	1.09 (1.01–1.17)
Current, severe	1.57 (1.36–1.81)	1.19 (0.97–1.48)	1.13 (0.92–1.39)
Ever	1.11 (1.05–1.17)	1.04 (0.97–1.12)	1.05 (0.98–1.13)

[a]Adjusted for sex, region of the world, language, and gross national income per capita (GNI).
[b]Adjusted for sex, region of the world, language, and GNI. Including only centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed.
[c]Analysis including centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Adjusted for sex, region of the world, language, GNI, cooking fuel, maternal education, current maternal and paternal smoking, exercise, television viewing, consumption of fast food, current paracetamol use, older and younger siblings, and truck traffic in street of residence.

sociations between cat in the home in the first year of life, and symptoms in the children were stronger in less-affluent countries for wheeze and eczema but not for rhinoconjunctivitis. Among the adolescents, associations in less-affluent countries were stronger only for eczema. When analyzed in 4 categories of affluence (according to the World Bank's 4 categories[10]), associations tended to become stronger with decreasing affluence, but estimates were less precise (results not shown).

In a sensitivity analysis, centers were stratified into those above and below the median current cat exposure, separately for more- and less-affluent countries. When having a cat in the home in the first year of life was examined among children, low cat prevalence centers in both more- and less-affluent countries were associated with much higher ORs for the current symptoms of asthma than in high cat-presence countries; much higher ORs for current symptoms of rhinoconjunctivitis and eczema were found only in the less-affluent countries (Table 4). Differences for dog exposure at either period and for current cat exposure were less pronounced, although of 36 comparisons between high and low cat or dog presence centers, only 4 showed a higher OR in high cat or dog presence centers compared with low cat or dog presence centers (results not shown).

Table 5 shows that, among adolescents, there was no association of cat or dog exposure with wheeze and with rhinoconjunctivitis in centers having above-median levels of cat or dog exposure in the home, whereas in centers with below-median levels of cat or dog exposure, there was a clear association between these symptoms and cat or dog exposure. This was observed in both more- and less-affluent countries. For eczema, this pattern was observed only in less-affluent countries. In this analysis, cat and dog exposures were combined, as in the analyses presented in Tables 3 and 5 the patterns of association were generally the same.

Mutual adjustment for cat and dog exposures did not change these findings. Adjustment for farm animal exposure during pregnancy or in the first year of life (data available for children only) also did not change the findings (results not shown). There was some heterogeneity in associations among centers from various parts of the world but without systematic patterns (results not shown). There was no difference for boys and girls (results not shown). Data were neither available to check for effect modification by family income nor available on parental history of disease or on asthma medication use.

If relationships between cat or dog exposure in the home and symptoms are masked in areas with high levels of cat or dog ownership, one might expect a positive relation at the ecologic level, ie, more symptoms in centers with high levels of cat or dog ownership. The figure presents an anal-

TABLE 3. Association Between Cat or Dog in the Home Currently and Current Symptoms of Asthma, Rhinoconjunctivitis, and Eczema in Adolescents 13–14 yrs

	OR (95% CI)		
Symptoms	**Adjusted[a] (All Children)**	**Adjusted[b] (Children With Complete Covariate Data)**	**Fully Adjusted[c]**
	Cat		
Asthma			
Current wheeze	1.14 (1.09–1.18)	1.11 (1.05–1.18)	1.09 (1.02–1.15)
Current (video)	1.18 (1.11–1.24)	1.15 (1.06–1.24)	1.10 (1.02–1.19)
Current, severe	1.25 (1.20–1.32)	1.24 (1.15–1.33)	1.17 (1.09–1.26)
Ever	1.08 (1.05–1.12)	1.00 (0.95–1.06)	0.99 (0.93–1.04)
Rhinoconjunctivitis			
Current	1.16 (1.12–1.21)	1.11 (1.05–1.18)	1.08 (1.02–1.15)
Current, severe	1.23 (1.12–1.36)	1.26 (1.09–1.46)	1.16 (1.01–1.35)
Hay fever			
Ever	1.08 (1.04–1.13)	1.06 (0.99–1.13)	1.06 (0.99–1.13)
Eczema			
Current	1.22 (1.16–1.28)	1.27 (1.19–1.36)	1.23 (1.15–1.32)
Current, severe	1.41 (1.29–1.54)	1.41 (1.24–1.60)	1.29 (1.14–1.47)
Ever	1.10 (1.06–1.15)	1.06 (0.99–1.14)	1.06 (0.99–1.13)
	Dog		
Asthma			
Current wheeze	1.15 (1.11–1.20)	1.16 (1.09–1.23)	1.10 (1.04–1.16)
Current (video)	1.18 (1.12–1.25)	1.16 (1.08–1.26)	1.10 (1.02–1.19)
Current, severe	1.24 (1.18–1.30)	1.28 (1.20–1.37)	1.18 (1.10–1.27)
Ever	1.12 (1.09–1.16)	1.14 (1.09–1.20)	1.11 (1.06–1.17)
Rhinoconjunctivitis			
Current	1.16 (1.12–1.20)	1.13 (1.07–1.19)	1.07 (1.01–1.13)
Current, severe	1.34 (1.21–1.47)	1.23 (1.07–1.41)	1.11 (0.97–1.28)
Hay fever			
Ever	1.04 (1.00–1.08)	1.02 (0.96–1.08)	1.00 (0.94–1.06)
Eczema			
Current	1.21 (1.16–1.27)	1.22 (1.14–1.30)	1.16 (1.08–1.24)
Current, severe	1.32 (1.20–1.45)	1.37 (1.20–1.57)	1.25 (1.09–1.43)
Ever	1.09 (1.05–1.13)	1.08 (1.01–1.15)	1.06 (1.00–1.13)

[a]Adjusted for sex, region of the world, language, and gross national income per capita (GNI).
[b]Adjusted for sex, region of the world, language, and GNI. Including only centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed.
[c]Analysis including centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Adjusted for sex, region of the world, language, GNI, cooking fuel, maternal education, current maternal and paternal smoking, exercise, television viewing, consumption of fast food, current paracetamol use, older and younger siblings, and truck traffic in street of residence.

ysis of this relation, suggesting that, current wheeze in children was higher in centers with high levels of cat ownership in the first year of life compared with areas that had low levels of exposure.

DISCUSSION

We found positive relationships between cat in the home in the first year of life and childhood symptoms of current asthma (wheeze) rhinoconjunctivitis, and eczema among children, especially in less-affluent centers and in centers with a low presence of cats. Positive relationships were also found among adolescents between combined current cat and dog exposure and exposure only to dogs, and these symptoms. These relationships were not different between more- and less-affluent countries.

The strengths of the ISAAC study are worldwide coverage, the use of standardized and validated methods of symptom reporting, large numbers of centers, and large numbers of participants. Limitations include the reliance on self-completed questionnaires and the absence of objective

TABLE 4. Associations Between Cat in the Home During the First Year of Life and Current Symptoms of Asthma, Rhinoconjunctivitis, and Eczema in Children Aged 6–7 yrs, Stratified by Regional SES[a] and Center Prevalence of Current Cat Exposure. Multiple Regression Analyses in Children With Complete Covariate Data

					Asthma (Wheeze)	Rhinoconjunctivitis	Eczema
SES of Region	Current Cat Prevalence %	No. Countries	No. Centers	No. Children	OR[b] (95% CI)	OR[b] (95% CI)	OR[b] (95% CI)
Cat in the first year of life in > median current cat prevalence centers							
More affluent	29.6	4	10	19691	1.09 (0.99–1.21)	1.09 (0.97–1.22)	0.98 (0.88–1.09)
Less affluent	13.3	8	10	24617	1.15 (0.99–1.33)	0.97 (0.82–1.16)	1.14 (1.00–1.30)
Cat in the first year of life in < median current cat prevalence centers							
More affluent	4.4	2	9	22163	1.36 (1.08–1.71)	1.01 (0.77–1.32)	1.20 (0.92–1.55)
Less affluent	5.7	6	15	31297	1.41 (1.14–1.73)	1.38 (1.10–1.73)	1.55 (1.22–1.97)

[a]World Bank classification for 2001.
[b]Fully adjusted analysis including centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Adjusted for sex, region of the world, language, gross national income per capita, cooking fuel, maternal education, current maternal and paternal smoking, exercise, television viewing, consumption of fast food, current paracetamol use, older and younger siblings, and truck traffic in street of residence.

TABLE 5. Associations Between Having Both Cat and Dog Currently in the Home and Current Symptoms of Asthma, Rhinoconjunctivitis, and Eczema in Adolescents 13–14 yrs, Stratified by Regional SES[a] and by Center Prevalence of Current Exposure to Cats or Dogs. Multiple Regression Analyses in Children With Complete Covariate Data

				Asthma (Wheeze)	Rhinoconjunctivitis	Eczema
SES of Region	No. Countries	No. Centers	No. Children	OR[b] (95% CI)	OR[b] (95% CI)	OR[b] (95% CI)
Centers with > median current cat and dog prevalence[c]						
All centers	18	27	61966	1.11 (1.00–1.24)	1.10 (0.99–1.22)	1.41 (1.24–1.60)
More affluent	2	4	8519	1.14 (0.85–1.51)	1.09 (0.80–1.47)	1.39 (1.01–1.90)
Less affluent	16	23	53447	1.11 (0.99–1.25)	1.09 (0.97–1.22)	1.41 (1.22–1.62)
Centers with < median current cat and dog prevalence[c]						
All centers	18	37	87922	1.29 (1.12–1.48)	1.21 (1.06–1.37)	1.36 (1.17–1.59)
More affluent	5	13	34668	1.29 (1.06–1.57)	1.16 (0.96–1.39)	1.15 (0.91–1.46)
Less affluent	13	24	53254	1.29 (1.06–1.58)	1.24 (1.05–1.47)	1.57 (1.28–1.92)

[a]World Bank classification for 2001.
[b]Fully adjusted analysis including centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Adjusted for sex, region of the world, language, gross national income per capita, cooking fuel, maternal education, current maternal and paternal smoking, exercise, television viewing, consumption of fast food, current paracetamol use, older and younger siblings, and truck traffic in street of residence.

measurements of exposure, symptom status, and allergic sensitization. Furthermore, no data on avoidance behaviors were collected. Also, because this is a prevalence study, we could not differentiate between exacerbation of existing symptoms and new-onset symptoms.

Could these results have been produced by bias? It is possible that parents of children with symptoms, or adolescents with symptoms themselves, over-report exposure to cats or dogs, as this exposure is widely discussed in the media and by physicians, in at least some parts of the world, as having a possible association with allergic symptoms. However, relationships tended to be stronger in less-affluent countries and in areas with low exposure to cats or dogs in the home, where awareness of cats or dogs as a risk factor for symptoms is probably less. By focusing the main analyses on centers for which at least 70% of the invited children had full covariate data, the potential for selection bias was reduced. Not all centers chose to include the environmental questionnaire. We did not detect any systematic difference in symptom prevalence between centers that did and did not include the environmental questionnaire. There was little evidence of confounding by the individual- or community-level confounders that were assessed in these analyses, although we cannot exclude a possible influence of unmeasured or inadequately measured confounders.

We did note that effect estimates tended to be smaller, when restricted to centers for at least 70% of the children had full covariate data. A detailed analysis of missing values by center and covariate showed that missing values were much more of an issue in less-affluent than in more-affluent countries. In the analyses presented for the children, for example, we lost 3 of 22 centers in the more-affluent countries, but 24 of 49 centers in the less-affluent countries. Further analysis shows that, in the more-affluent countries, ORs did not change at all after

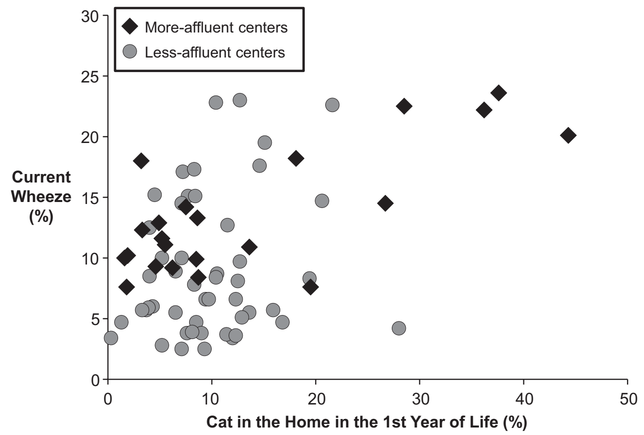

FIGURE. Prevalence of cat in the home in the first year of life and current wheeze, children aged 6–7 years.

restriction and adjustment, whereas they did change in the less-affluent countries (eTable 7, http://links.lww.com/EDE/A599).

Furthermore, we found that in the majority of the centers where missing values led to exclusion, this was because values were missing for number of siblings. Perhaps, when parents were asked "How many older (younger) siblings does your child have?" those with only one child did not answer this question. In China, for instance, where many families have only one child, the percentage missing was high. When we repeated the analysis, ignoring the questions on siblings, we lost 2 centers (down from 3) in more-affluent countries and 11 (down from 24) in less-affluent countries. We re-ran the analyses for some selected end points (current wheeze, rhinitis, and eczema among children in relation to having had a cat in the first year of life). The results were unchanged in the more-affluent countries, and for wheeze and eczema, a rather smaller attenuation of the ORs in the less-affluent countries (eTable 8, http://links.lww.com/EDE/A599). These sensitivity analyses show that the differences in effect estimates between more and less-affluent countries was likely larger in reality than in the fully adjusted analysis.

The effect of cat and dog exposure on the development of allergic disease remains controversial.[12–15] Few studies have been conducted in less-affluent countries, and so these countries are underrepresented in the cited reviews. The few studies on dog ownership and symptoms cited in the most recent review[12] found positive associations, as did our study. Detailed analyses of prospective birth cohort studies in Australia and the Netherlands have suggested some protective effects of early cat or dog exposure on subsequent allergic sensitization, but not on development of asthma.[16,17] Pet avoidance can invert the associations between current symptoms and current pet ownership.[18] In our study, however, we found that associations were generally positive, suggesting that, worldwide, pet avoidance may not be a major factor. Prospective birth cohort studies are needed also in less-affluent countries to shed more light on these complex patterns of association.

Few studies conducted in less-affluent countries have addressed the relationship between pet exposure and childhood symptoms of asthma, rhinoconjunctivitis, and eczema. A study from Turkey reported significant positive associations between unspecified pet exposure and symptoms of wheeze, rhinitis, and eczema among children aged 6–12 years.[19] The most frequently reported pets were birds, followed by cats, fish, and dogs; thus, no conclusions are possible about the specific contributions of cats and dogs to these associations. A study from the United Arab Emirates found significant relationships between unspecified pet exposure and wheeze, rhinitis, and eczema among children aged 6–14 years.[20] Pet exposure was reported by 40% of households, with cats (15%) being most common. A study from India compared 60 severely and 60 mildly asthmatic children with 60 nonasthmatic controls who were, on average, 10 years old; exposure to cats or dogs was reported for 18%, 10%, and 7% of these children, respectively, suggesting a strong positive association between cat or dog exposure and asthma severity.[21] Two studies from Saudi Arabia among children aged 6–15 years found strong positive associations between pet exposure and asthma.[22,23] Type of pet was not specified; cats, birds, and poultry were all mentioned. A small case-control study from Malaysia found no association between cat or dog at home and asthma.[24] However, children with asthma in that study were significantly more often found to be seropositive for *Toxocara*, an infection associated with especially, cat contact. A study from Beijing found 1.5 (95% CI = 1.0–2.3) times more asthma in children having both a dog and a cat at home, compared with children without pets.[1] Associations with cat-only or dog-only exposure were less pronounced as in our study. Another large Chinese study among >10,000 children aged 2–13 years found significantly more wheeze (but not rhinitis) in children having cats or dogs at home.[25] Associations with cat-only or dog-only exposure were less pronounced, as in our study. Results from a Bulgarian study were already mentioned.[3] An ISAAC study in Brazil found a positive association between current, but not early, pet exposure and asthma prevalence in children aged 6–7 years,[26] but the pets were not specified. The evidence from less-affluent countries, gleaned from a variety of cross-sectional and case-control studies, seems to support positive associations between pet exposure and childhood wheeze in these countries. Results for rhinitis and eczema have been reported from fewer studies.

Our stratified analysis of associations by high or low community prevalence of cats and dogs gave intriguing results. Associations with wheeze and rhinoconjunctivitis were found only in centers with below-median cat or dog exposure in the home. This suggests that, in areas with high cat or dog prevalence, exposure to cats and dogs (and the substances they produce) is ubiquitous and therefore contrasts in exposure do not depend as much on whether a dog or cat is present in the household. This is in line with a European study among adults in which an association between keeping cats in childhood and asthma in atopic subjects was found only in centers with a below-median prevalence of cat ownership.[11]

It is unlikely that allergic sensitization to cats or dogs explains the associations seen in our study. ISAAC phase two showed that especially, in less-affluent countries, only a very small fraction of wheeze, rhinoconjunctivitis, and eczema could be attributed to allergic sensitization, to all tested allergens combined.[27–29] Other mechanisms could involve exposure to endotoxin, which has been found to be positively associated with nonatopic wheeze in farm children in some studies.[30] Early-life exposure to endotoxin was associated with wheeze between the ages of 1 and 7 years in a birth cohort in Boston, United States.[31] Pets may also lead to helminth infections in children, such infections have been shown to be associated with wheeze, rhinitis, and eczema in studies from less-affluent countries.[24,32–34]

In our analysis of cat and dog exposure in children aged 6–7 years, we did not find that combined cat and dog exposure was more strongly associated with symptoms than exposure to only cats or only dogs. The strongest relation in the younger age group was found for cat exposure and wheeze, irrespective of dog exposure. This could mean that associations change with age, cat exposure being more important early in life, and combined cat and dog and dog-only exposure becoming more important in the teenage years. As we are interpreting results from a cross-sectional study, we cannot rule out the possibility that associations may also change with time.

We conclude that early-life exposure to cats is a risk factor for symptoms of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years. Current exposure to cats and dogs combined, and to dogs only, is a risk factor for symptom reporting by adolescents.

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