

Original article

Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis

Background: Exposure to pets has been implicated as a risk factor for asthma. However, this relation has been difficult to assess in individual studies because of the large potential of selection bias. We sought to examine the association between exposure to furry pets and asthma and allergic rhinitis by means of a meta-analysis.

Methods: We retrieved studies published in any language by searching systematically Medline (1966–March 2007), Embase, LILACS and ISI Proceedings computerized databases, and by examining manually the references of the original articles and reviews retrieved. We included cohort and case-control studies reporting relative risk estimates and confidence intervals of exposure to cats, dogs and unspecified furry animals and subsequent asthma and allergic rhinitis. We excluded cross-sectional studies and those studies that did not measure exposure but rather sensitization to pets.

Results: Thirty-two studies were included. For asthma, the pooled relative risk related to dog exposure was 1.14 (95% CI 1.01–1.29), that related to exposure to any furry pet was 1.39 (95% CI 1.00–1.95). Among cohort studies, exposure to cats yielded a relative risk of 0.72 (95% CI 0.55–0.93). For rhinitis, the pooled relative risk of exposure to any furry pet was 0.79 (95% CI 0.68–0.93).

Conclusions: Exposure to cats exerts a slight preventive effect on asthma, an effect that is more pronounced in cohort studies. On the contrary, exposure to dogs increases slightly the risk of asthma. Exposure to furry pets of undermined type is not conclusive. More studies with exact measurement of exposure are needed to elucidate the role of pet exposures in atopic diseases.

B. Takkouche¹, F.-J. González-Barcala², M. Etmann³, M. FitzGerald³

¹Department of Preventive Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain; ²Department of Pneumology, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain; ³Center for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute, and The Lung Centre, Vancouver General Hospital, Vancouver, BC, Canada

Key words: allergic rhinitis; asthma; cats; dogs; meta-analysis; pets.

Dr Bahi Takkouche
Department of Preventive Medicine
Faculty of Medicine
University of Santiago de Compostela
15782 Santiago de Compostela
Spain

Accepted for publication 27 February 2008

Asthma is a frequent disease, the prevalence of which varies more than 15-fold among countries worldwide (1). In Europe, the UK (20.7%) and Ireland (15.2%) have the highest rates, whereas Eastern European countries have the lowest (2).

In a similar fashion to the variation in prevalence of asthma, exposure to pets shows significant variations worldwide, being most frequent in Western countries. In the US, 39% of the households have a dog and 34% a cat (3). In the UK, about half of the households own a pet (4), whereas in Australia this proportion reaches 63% (5). On the contrary, pet keeping at home is rare to virtually nonexistent in the majority of Arab and African countries (6). Recently, Saudi Arabia has even prohibited pet possession (7).

Exposure to pet allergens has been implicated as a risk factor for asthma. However, this relation has been difficult to assess in individual studies because of the large potential of selection bias (8). In some studies, it has been shown that subjects with asthma refrain from having pets at home (8). This may lead to the erroneous

conclusion that pet ownership provides a protective effect, mainly in cross-sectional studies but also in other studies where exposure timing is not determined with precision.

Recent reviews, essentially narrative in nature, have commented on the association between exposure to pets and asthma or atopy (8–10). The only quantitative review focused on studies published in the 1990s only, mainly included cross-sectional studies and did not consider pets separately (8). So far, no comprehensive meta-analysis is available. We, therefore, summarized the scientific evidence and carried out a meta-analysis on exposure to pets and risk of asthma, following the MOOSE guidelines for meta-analyses of observational studies (11).

Methods

Data sources and searches

We conducted a computerized Medline search from 1966 to March 2007 to identify potentially eligible studies. We applied the following

algorithm both in Medical Subject Heading and in free text words: (ASTHMA OR RHINITIS OR RESPIR*) AND (CAT* OR DOG* OR PET* OR ANIMAL* OR FURRY) AND (CASE-CONTROL OR CASE-REFERENT OR RETROSPECTIVE OR COHORT OR FOLLOW-UP OR PROSPECTIVE). To check whether every article on the topic was retrieved, we performed a second search, introducing the words 'asthma', 'rhinitis', 'cats' and 'pets' in an unstructured fashion. We used similar strategies to search Embase (1980–2007) and LILACS databases (Latin America and Caribbean). We searched meeting abstracts using the ISI Proceedings database from its inception in 1990–2007. We also examined the references of every article retrieved and those of recent reviews of asthma and pets (8–10). We considered including any relevant article, independent of the language of the publication. Unpublished studies were not considered. All searches were carried out independently by an epidemiologist and a pneumologist (BT and FJGB) and results were merged.

Study selection

Studies were included if they met the following criteria: (i) presented original data from case-control or cohort studies, (ii) the outcome of interest was asthma or rhinitis. Other atopic manifestations were not considered, (iii) the exposure of interest was ownership of cats, dogs or other furry pets, (iv) provided relative risk estimates and their confidence intervals or provided enough data to calculate them (raw data, *P*-value or variance estimate).

Because they are beyond the scope of this meta-analysis, we excluded studies that used single asthma symptoms as an outcome, such as wheezing, and did not establish a diagnosis of asthma. For the same reason, we did not consider those studies that dealt with sensitization to pets. In some instances, sensitization is used by authors either as a proxy for exposure or as an outcome and is generally measured through IgE or skin tests (9).

If data were duplicated in more than one study, the most recent one was included in the analysis. When relative risks of different pets were available in the same publication, we considered each pet separately.

We developed a questionnaire and recorded study name, year of publication, study design, sample size (cases and controls or cohort size), type of controls for case-control studies (hospital or population controls), variables used for adjustment or matching, and association measures that compared exposed subjects with unexposed. Because of their inadequacy to assess causation, cross-sectional studies were discarded from this meta-analysis.

Quality assessment

As no universal scale is available for measuring quality of observational studies, we followed the recommendations of the MOOSE guidelines and assessed the quality of key components of design separately rather than generating a single aggregate score (11). Following this recommendation, we assessed study quality on the basis of the following five criteria labeled as 'yes' or 'no': (i) whether the target population was clearly defined (yes) or on the contrary, based on convenient sampling of subjects (no), (ii) whether asthma diagnosis included clinical features and flow rate and/or reversal after treatment (yes) or was based on clinical examination only (no), (iii) whether exposure assessment included measurement of pet allergens at home (yes) or was based on questionnaire only (no), (iv) (yes) or else (no), and, finally, (v) whether results were adjusted for age, sex and other potential confounders (yes), or else (no). Throughout this assessment, when the information on a specific item was not provided by the authors, we graded this item as 'no'.

Within each item, we calculated two pooled odds ratios: one for those studies that were labeled 'yes' and another for those labeled 'no'. As a secondary analysis, we carried out a pooled analysis on those studies that fulfilled more than three criteria and compared with those that scored 3 or less. The complete protocol for quality scoring is available upon request.

Data synthesis and analysis

We weighted the study-specific adjusted log odds ratios for case control studies and log relative risks for cohort studies by the inverse of their variance to compute a pooled relative risk and its 95% confidence interval. We presented both fixed and random effects pooled estimates, but used preferentially the latter when heterogeneity was present. The fixed effects model assumes that there is no between-study variance, i.e. that the results of the studies used in the meta-analysis are homogeneous and that their variation is because of sampling only. The random effects model, on the contrary, assumes that study results are heterogeneous. The random effects model yields pooled results that are less precise in nature (have wider confidence intervals) but are closer to the true value in case heterogeneity exists.

We used a version adapted to small samples of the DerSimonian and Laird Q test to check for heterogeneity (12). The null hypothesis of this test is the absence of heterogeneity. To quantify this heterogeneity, we calculated the proportion of the total variance as a result of between-study variance (*Ri* statistic) (12). To further explore the origin of heterogeneity, we restricted the analysis to subgroups of studies defined by study characteristics such as case-control/cohort design and type of controls (hospital-based or population-based).

We used funnel plots to assess publication bias visually. As funnel plots have several limitations and represent only an informal approach to detect publication bias (13), we further carried out formal testing using the test proposed by Egger (14). All analyses were performed with the software HEPIMA[®] version 2.1.3 (15) and STATA version 8.0 (StataCorp LP, College Station, TX, USA).

Results

Our search strategy retrieved 3311 references, but only 32 different articles met our inclusion criteria (16–47). The large majority of these references were excluded because they did not provide data on exposure to pets, they presented cross-sectional data, failed to present any measure of uncertainty of the relative risk, or because they presented data on wheezing, bronchitis, sensitization or atopy but not on asthma or allergic rhinitis and thus, did not fulfill our inclusion criteria (48–53).

We finally included 19 case-control studies and 13 cohort studies carried out in 19 countries. One case-control study provided data on only allergic rhinitis and not on asthma (47).

Asthma and exposure to cats

The 18 case-control studies (including 5887 cases and 4222 controls) and 13 cohort studies were published between 1985 and 2006 (Tables 1 and 2). Fourteen case-control studies used population controls and four used hospital controls.

Table 1. Relative risks of asthma according to exposure to furry pets in case-control studies

Source	Population	Cat	Dog	Any pet	Adjustment	Cases/controls
Daigler 1991 (16)	Children	–	–	1.82 (1.05–3.15)	Age, sex, prematurity, history of infections, parental asthma, allergies	137/246
Gelber 1993 (17)	Adults	1.22 (0.33–4.52)	–	–	Age, sex	114/114
Infante-Rivard 1993 (18)	Children 3–4 years	–	–	1.05 (0.79–1.38)	Age, residence, family history of allergy, eczema	457/457
Leen 1994 (19)	Children	–	–	0.64 (0.36–1.15)	Not explained	134/118
Fagbule 1994 (20)	Children	–	–	117.5 (46.9–256.5)	Age, sex, socio-economic status	140/140
Lindfors 1995 (21)	Children 1–4 years	0.76 (0.55–1.05)	0.93 (0.67–1.29)	0.76 (0.55–1.05)	Age, sex, parental asthma	159/318
Strachan 1995 (22)	Children	1.64 (1.09–2.47)	1.27 (0.85–1.89)	1.61 (1.25–2.08)	Age, sex, housing tenure, use of gas for cooking, smoking habits of parents	441/429
Kane 1999 (23)	Adults	–	–	1.58 (0.99–2.54)	Not explained	167/161
Wickens 1999 (24)	Children 7–9 years	1.42 (0.97–2.08)	–	–	Age, sex, sheepskin use, use of waterbed, age of mattress, social class, parents' asthma	233/241
Gehring 2001 (25)	Adults	1.59 (0.35–7.08)	–	–	Age, sex, education, smoking, season, region	222/215
Addo-Yobo 2001 (26)	Children 15 years	1.69 (0.68–4.20)	–	–	Age, sex	50/50
Moraes 2001 (27)	Children	0.23 (0.10–0.51)	–	–	Age, socio-economic status, exposure to allergens, smoking habits of parents	59/104
Zheng 2002 (28)	Children	1.2 (0.7–2.0)	1.3 (0.9–1.7)	1.5 (1.0–2.3)	Age, sex, ethnicity, parents' history of allergy, duration of breast feeding	403/806
Anyo 2002 (29)	Children	–	–	1.11 (0.82–1.51)	Age, sex, area, foreign descent, parents' asthma, education, siblings, smoking	2700/NS
El-Sharif 2003 (30)	Children	–	3.24 (1.09–9.56)	5.27 (1.10–25.3)	Sex, school, family history of asthma, environmental factors, total and specific IgE	99/252
Oryszczyn 2003 (31)	Adults	–	–	1.70 (1.27–2.28)	Age, sex, centre, season	187/243
Al-Mousawi 2004 (32)	Children 9–16 years	3.67 (3.60–3.74)	–	–	Age, sex, other not explained	160/303
Surdu 2006 (33)	Children	–	–	0.73 (0.29–1.85)	Age, sex	25/25

The fixed effect pooled relative risk for cat exposure was 3.52 (95% CI: 3.46–3.59) but the large amount of heterogeneity between studies explains that the random effects estimate was of opposite sign (RR = 0.87, 95% CI, 0.52–1.44). The amount of heterogeneity decreased considerably when we restricted our analysis to cohort studies, group in which exposure to cats shows a protective effect against subsequent asthma (RR = 0.72, 95% CI: 0.55–0.93). On the contrary, heterogeneity did not subside in the case-control group of studies, including after stratification by type of controls (hospital vs population) and the random effects pooled relative risk is inconclusive: 1.23 with 95% CI: 0.65–2.53.

Restricting the analysis to those 12 studies that were carried out on children only did not alter the results (21, 22, 24, 26–28, 32, 34, 39, 42, 44, 46). We did not observe any meaningful changes in the results when we carried out the quality analysis and stratified the results consequently. Globally, there was no heterogeneity between studies of high quality compared with between low-quality studies.

The funnel plot was distorted by one influential point: the study by Al-Mousawi et al. (32) which showed an

exceptionally high RR with a narrow confidence interval. When this study was excluded, there was no evidence of publication bias (*P*-value of Egger's symmetry test: 0.42).

Interestingly, when we excluded the studies carried out among Arab and African populations that provided data on exposure to cats (26, 32), among which pet keeping at home is very infrequent, the fixed-effects RR turned protective and similar to that observed for cohort studies (RR = 0.88, 95% CI 0.79–0.98). These two studies yielded a pooled relative risk of 3.67 with 95% CI: 3.60 to 3.74.

Asthma and exposure to dogs

Nine studies were available on dog ownership and asthma (21, 22, 28, 30, 39, 41, 42, 44, 45), four case-control and five cohort studies. There was no heterogeneity between study-specific effects, and thus, fixed effects pooled estimates were similar if not identical to random effects estimates.

Globally, dog exposure increases slightly the risk of asthma with RR's between 1.10 and 1.20 and confidence

Table 2. Relative risks of asthma according to exposure to furry pets in cohort studies

Source	Population	Cat	Dog	Any pet	Adjustment	Cases/cohort size
Horwood 1985 (34)	Children	0.72 (0.44–1.20)	–	–	Not explained	109/1056
Sigurs 1995 (35)	Infants	–	–	0.6 (0.18–2.25)	Age, sex residence	12/140
Norrman 1998 (36)	Children 14 years	–	–	0.5 (0.2–1.1)	Not explained	225/909
Tariq 1998 (37)	Birth	–	–	0.87 (0.63–1.20)	Not explained	246/1218
Lau 2000 (38)	Birth	1.20 (0.71–2.02)	–	–	Age, social status, family history of atopy	57/1314
Smedje 2001 (39)	Children	0.46 (0.30–0.70)	1.04 (0.71–1.52)	–	Age, sex, history of atopy, smoking	109/1347
Litonjua 2001 (40)	Birth	0.20 (0.03–1.48)	–	–	Maternal age, smoking, race, income, education, lower respiratory tract illness	13/222
Nafstad 2001 (41)	Birth	0.7 (0.4–1.5)	1.1 (0.6–1.9)	0.7 (0.5–1.1)	Age, sex, parental atopy, birth weight, smoke exposure, mother's age, education	278/2531
Perzanowski (42) 2002	Children	0.55 (0.25–1.21)	1.2 (0.6–1.8)	–	Age, sex, parental history of allergy, birth weight, respiratory infection, dampness	73/3431
Rönmark 2002 (43)	Children	–	–	0.89 (0.54–1.48)	Age, sex, parental asthma, birth weight, mother's smoking, breastfeeding, dampness	91/3525
McConnell 2002 (44)	Children	0.9 (0.6–1.3)	1.4 (1.0–2.0)	1.6 (1.0–2.5)	Age, sex, ethnicity, community of residence	265/3535
Almqvist 2003 (45)	Birth	0.89 (0.75–1.07)	1.03 (0.86–1.23)	–	Age, sex, heredity of allergy, maternal smoking, maternal age, socio-economic index	250/4089
de Meer 2004 (46)	Children	0.17 (0.04–0.77)	–	–	Age, sex, family atopy, number of sibs, smoking, dust exposure, wheeze	22/224

Table 3. Pooled relative risks (RR) and 95% confidence intervals (CI) of asthma and pet exposure

	Number of studies	RR (95% CI) fixed effects	RR (95% CI) Random effects	Ri†	Q test P-value
Cat exposure					
All studies	18	3.52 (3.46–3.59)	0.87 (0.52–1.44)	1.00	0.00001
Children only studies*	12	3.58 (3.52–3.65)	0.86 (0.46–1.61)	1.00	0.00001
Case-control studies	9	3.62 (3.55–3.69)	1.23 (0.65–2.53)	1.00	0.00001
Cohort studies	9	0.80 (0.70–0.92)	0.72 (0.55–0.93)	0.62	0.03
Arab/African studies excluded	16	0.88 (0.79–0.98)	0.82 (0.65–1.04)	0.72	0.00001
Dog exposure					
All studies	9	1.13 (1.02–1.26)	1.14 (1.01–1.29)	0.13	0.33
Children only studies*	7	1.20 (1.05–1.38)	1.21 (1.03–1.41)	0.18	0.30
Case-control studies	4	1.20 (1.00–1.44)	1.23 (0.93–1.63)	0.53	0.11
Cohort studies	5	1.10 (0.96–1.26)	1.10 (0.96–1.26)	0.00	0.67
Arab/African studies excluded	8	1.12 (1.01–1.25)	1.12 (1.01–1.25)	0.00	0.61
Any pet exposure					
All studies	18	1.24 (1.13–1.37)	1.39 (1.00–1.95)	0.91	0.00001
Children only studies*	13	1.28 (1.14–1.44)	1.57 (0.99–2.48)	0.93	0.00001
Case-control studies	12	1.38 (1.23–1.54)	1.80 (1.14–2.83)	0.93	0.00001
Cohort studies	6	0.90 (0.74–1.10)	0.88 (0.64–1.19)	0.53	0.07
Anyo (29) excluded	17	1.26 (1.14–1.40)	1.41 (0.98–2.04)	0.92	0.00001
Arab/African studies excluded	16	1.15 (1.04–1.27)	1.09 (0.91–1.32)	0.69	0.00001

*Birth cohorts and adult population excluded.

†Proportion of total variance as a result of between-study variance

intervals that reach statistical significance (Table 3). We did not observe any substantial change in the results when we excluded the only available study carried out in a population with a low pet-keeping frequency (30), nor

when we restricted our analysis to pediatric studies. The funnel plot (Figure 1) and Egger's regression test (P -value: 0.27) did not provide any evidence of publication bias.

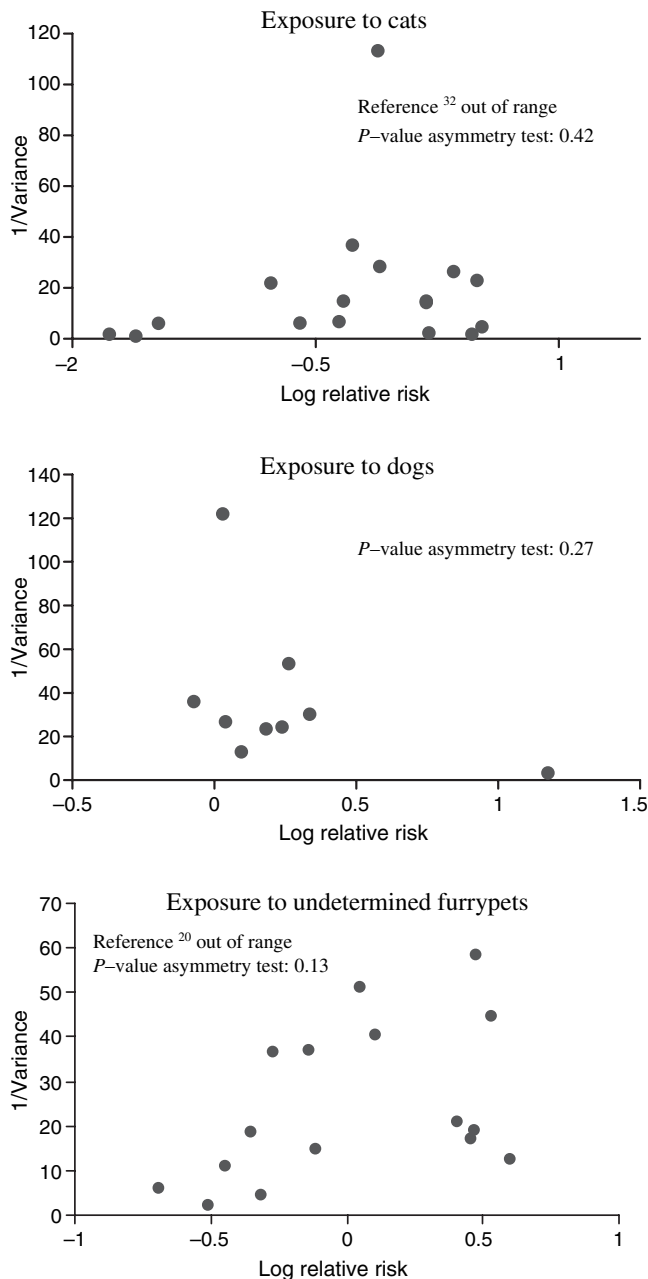


Figure 1. Funnel plots of log relative risk vs inverse variance of log relative risk.

Asthma and exposure to any furry pet

We retrieved 18 articles that presented data on exposure to any furry pet (generally, cats and dogs) and asthma (16, 18–23, 28–31, 33, 35–37, 41, 43, 44), which included 12 case-control and six cohort studies. Globally, there was a considerable amount of heterogeneity between studies. This heterogeneity decreased dramatically among cohort studies when we stratified by design and when we excluded studies carried out among populations with low pet-keeping frequency ($R_i = 0.53$ and 0.69 , respectively)

Table 4. Relative risks of rhinitis according to exposure to furry pets

Source	Cat	Dog	Any pet
Case-control studies			
Anyo 2002(29)	–	–	0.84 (0.71–1.01)
Fasce 2005(47)*	0.77 (0.50–1.17)	–	–
Cohort studies			
Norrman 1998 (36)	–	–	0.4 (0.2–0.9)
Tariq 1998 (37)	–	–	0.9 (0.53–1.52)
Nafstad 2001 (41)	0.5 (0.2–1.4)	0.8 (0.4–1.6)	0.6 (0.4–1.0)

*This study was carried out on a population of children, and used 124 cases and 245 controls. The analysis was adjusted for age, sex, family history of atopy and siblings. Details on the rest of the studies are available in Tables 1 and 2.

(20, 30). The results of this analysis were inconclusive. The pooled RR among cohort studies is compatible with an absence of effect ($RR = 0.88$, 95% CI: 0.64 – 1.19) in a similar fashion to the pooled result of studies in which populations with low pet-keeping frequency were excluded ($RR: 1.09$, 95% CI: 0.91 – 1.32). On the contrary, when all studies were taken into account, or when the analysis was limited to case-control studies or pediatric studies, there is an indication of an increase in the risk of asthma, although with a large amount of heterogeneity (Table 3). The results did not display any meaningful variation when we stratified the analysis by quality items nor when excluded the large case-control study by Anyo et al.(29). Further, we did not find any evidence of publication bias (P -value of Egger's symmetry test: 0.13).

The two studies carried out among low pet-keeping populations (20, 30) yielded a pooled relative risk of 26.89 with 95% CI: 1.29 to 561.37 .

Rhinitis

Only five studies that measured risk of rhinitis were available (Table 4). The two studies that measured the risk among subjects exposed to cats yielded a pooled relative risk of 0.69 (95%CI: 0.41 – 1.16). Among subjects exposed to any furry pet (four studies), the RR was 0.79 (95% CI: 0.68 – 0.93) with no heterogeneity.

Discussion

Our results indicate that, globally, exposure to cats exerts a preventive effect against the development of asthma. The results may be deceptive at first sight if one focuses on fixed effects results, as these results are in apparent opposition to those of the random effects. In fact, heterogeneity between effects exists essentially among case-control studies but to a much lesser extent among cohort studies. As case-control studies are much more prone to bias than cohort studies, results referring to the latter reflect probably better the real effect.

On the contrary to cat ownership, exposure to dogs seems to increase the risk of asthma. Exposure to

undetermined furry pets is inconclusive, with relative risk estimates slightly higher than one, but with large heterogeneity, except among cohort studies. As this group includes mainly studies with exposure to both cats and dogs, the effect observed is probably the result of a mixture of the effects exerted by each pet category.

Globally, it seems that frequency of pet keeping is an important effect modifier. Exposure to pets is a strong risk factor for asthma in those countries where pets are not frequently kept at home for cultural or religious reasons. It has been hypothesized that high exposure to cat allergen may induce tolerance in individuals (54). It is then plausible that a low frequency of pet-keeping leads to an absence of this tolerance. However, these results should be interpreted with caution because of the small number of studies carried out in countries with a low prevalence of pet ownership. In addition, exposure to pets at home may be different from exposure outside of the home. Furthermore, it is difficult to exclude the possibility of the existence of a genetic or other environmental risk factor among these populations. Family inheritance may also be a confounder of the relation between pets and asthma. Only a few studies were adjusted for this factor in the analysis.

The differences in the effects between dog and cat exposure may have several explanations. It is likely that sensitization to dog allergens requires a shorter exposure time and lower dose than sensitization to cats (55). Moreover, cat allergens are ubiquitous and may be found in environments where cats are absent (56, 57), as they can be carried by clothes (58). Another reason is that pet avoidance subsequent to asthma symptoms was observed for cats during childhood and adulthood but not for dogs (59). Further, Fel d 1 the major cat allergen belongs to the group of secretoglobins, whereas Can f 1, the major dog allergen, belongs to the family of lipocalins that presents different biochemical and pathogenic characteristics (60, 61). Last, some pets produce both allergen and endotoxin or bacterial exposures (62), while others may not.

As for allergic rhinitis, although the limited number of studies included in our meta-analysis does not allow for firm conclusions, one can observe a protective pattern.

Our meta-analysis may be subject to several limitations. Recall bias may have distorted the results in case-control studies as shown by the large difference in pooled results between case-control and cohort studies. In the large majority of the studies, measurement of exposure to pets throughout studies was made by questionnaire, which allows for a qualitative assessment of the exposure only. However, this shortcoming was not confirmed by our quality analysis that did not find evidence of any large difference in effects between groups of studies with different exposure assessments.

Further, residual confounding (confounding from unknown variables that is not eliminated by adjustment), as in any meta-analysis of observational studies, may have introduced considerable bias. Genetic factors may be included among these variables. This meta-analysis is limited to those studies with a diagnosis of asthma and allergic rhinitis. The fact that we excluded studies the outcome of which was wheezing or unspecified atopy was likely to influence our results. However, we consider that asthma, wheezing and atopy are distinct entities and that they should not be mixed in the same meta-analysis.

In conclusion, our results show that exposure to cats may have a protective role in asthma occurrence. Exposure to dogs increases the risk slightly, while ownership of undetermined furry pets provides inconclusive results so far. Further studies in which exposure is measured in a more detailed fashion are needed.

Acknowledgments

Dr Takkouche's work in meta-analysis is funded by "CIBER en Epidemiología y Salud Pública" (CIBER-ESP), Spain. ME is funded by a Canadian Institutes of Health Research postdoctoral fellowship award. Dr. Fitzgerald is a Michael Smith Foundation for Health Research Distinguished Scholar and a BC Lung/Canadian Institute of Health Research Scientist. There is no specific funding for this study.

References

1. Weinmayr G, Weiland SK, Björkstén B, Brunekreef B, Büchele G, Cookson WOC et al. Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Resp Crit Care Med* 2007;**176**:564–574.
2. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; **351**: 1225–1232.
3. The humane Society of the United States. U.S. Pet Ownership Statistics, January 5th, 2007. Available at: http://www.hsus.org/pets/issues_affecting_our_pets/pet_overpopulation_and_ownership_statistics/us_pet_ownership_statistics.html; accessed 5 October 2007.
4. Pet Food Manufacturer's Association. Pet Statistics & Pet Ownership Trends. Available at: http://www.pfma.com/public/petownership_stats.htm; accessed on October 5th, 2007.
5. Pet Net. Pet Statistics. Available at: <http://www.petnet.com.au/petstatistics.asp>; accessed on October 5th, 2007.
6. Al-Mousawi MSH, Behbehani N, Arifhodzic N, Lovel H, Woodcock A, Custovic A. Community exposure to environmental allergens in Kuwait: the levels of allergens in public places. *Allergy* 2001;**12**:1237–1238.

7. MSNBC. December 18th, 2006. Cats and dogs banned by Saudi religious police. Available at: <http://www.msnbc.msn.com/id/14738358/#storyContinued>; accessed on October 5th, 2007.
8. Apelberg BJ, Aoki Y, Jaakkola JJK. Systematic review: exposure to pets and risk of asthma and asthma-like symptoms. *J Allergy Clin Immunol* 2001;**107**:455–460.
9. Simpson A, Custovic A. Pets and the development of allergic sensitization. *Curr Allergy Asthma Rep* 2005;**5**: 212–220.
10. Ahlbom A, Backman A, Bakke J, Foucard T, Halken S, Kjellman NIM et al. "NORDPET" pet indoors – a risk factor for or protection against sensitization/allergy. A Nordic interdisciplinary review of the scientific literature concerning the relationship between the exposure to pets at home, sensitisation and the development of allergy. *Indoor Air* 1998;**8**:219–235.
11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008–2012.
12. Takkouche B, Cadarso-Suarez C, Spiegelman D. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. *Am J Epidemiol* 1999;**150**:206–215.
13. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. Chichester: John Wiley & Sons, 2000. 115
14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J* 1997;**315**:629–634.
15. Costa-Bouzas J, Takkouche B, Cadarso-Suarez C, Spiegelman D. HEpiMA: software for the identification of heterogeneity in meta-analysis. *Comput Methods Programs Biomed* 2001;**64**:101–107.
16. Daigler GE, Markelle SJ, Cummings M. The effect of indoor air pollutants on otitis media and asthma in children. *Laryngoscope* 1991;**101**:293–296.
17. Gelber LE, Seltzer LH, Bouzoukis JK, Pollart SM, Chapman MD, Platts-Mills TAE. Sensitization and exposure to indoor allergens as risk factors for asthma among patients presenting to hospital. *Am Rev Respir Dis* 1993;**147**: 573–578.
18. Infante-Rivard C. Childhood asthma and indoor environment risk factors. *Am J Epidemiol* 1993;**137**:834–844.
19. Leen MG, O'Connor T, Kelleher C, Mitchell EB, Loftus BG. Home environment and childhood asthma. *Ir Med J* 1994;**87**:142–144.
20. Fagbule D, Ekanem EE. Some environmental risk factors for childhood asthma: a case-control study. *An Trop Paediatr* 1994;**14**:15–19.
21. Lindfors A, Wickman M, Hedlin G, Pershagen G, Rietz H, Nordvall SL. Indoor environmental risk factors in young asthmatics: a case-control study. *Arch Dis Child* 1995;**73**: 408–412.
22. Strachan DP, Carey IM. Home environment and severe asthma in adolescence: a population based case-control study. *Br Med J* 1995;**311**:1053–1056.
23. Kane MP, Jaén CR, Tumiel LM, Bearman GML, O'Shea R. Unlimited opportunities for environmental interventions with inner-city asthmatics. *J Asthma* 1999;**36**:371–379.
24. Wickens K, Pearce N, Siebers R, Ellis I, Patchett K, Sawyer G et al. Indoor environment, atopy and the risk of asthma in children in New Zealand. *Pediatr Allergy Immunol* 1999;**10**:199–208.
25. 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. *Eur Respir J* 2001;**18**:555–563.
26. Addo-Yobo EOD, Custovic A, Taggart SCO, Craven M, Bonnie B, Woodcock A. Risk factors for asthma in urban Ghana. *J Allergy Clin Immunol* 2001;**108**:363–368.
27. Moraes LSL, Barros MD, Takano OA, Assami NMC. Fatores de risco, aspectos clínicos e laboratoriais da asma em crianças. *J Pediatr (Rio J)* 2001;**77**:447–454.
28. Zheng T, Niu S, Lu B, Fan X, Sun F, Wang J et al. Childhood asthma in Beijing, China: a population-based case-control study. *Am J Epidemiol* 2002;**156**:977–983.
29. Anyo G, Brunekreef B, de Meer G, Aarts F, Janssen NAH, 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**:361–366.
30. El-Sharif N, Abdeen Z, Barghuthy F, Nemery B. Familial and environmental determinants for wheezing and asthma in a case-control study of school children in Palestine. *Clin Exp Allergy* 2003;**33**:176–186.
31. Oryszczyn MP, Annesi-Maesano I, Charpin D, Kauffman F. Allergy markers in adults in relation to the timing of pet exposure: the EGEA study. *Allergy* 2003;**58**:1136–1143.
32. Al-Mousawi MSH, Lovel H, Behbehani N, Arifhodzic N, Woodcock A, Custovic A. Asthma and sensitization in a community with low indoor allergen levels and low pet-keeping frequency. *J Allergy Clin Immunol* 2004;**114**:1389–1394.
33. Surdu S, Montoya LD, Tarbell A, Carpenter DO. Childhood asthma and indoor allergens in Native American in New York. *Environ Health* 2006;**5**:22.
34. Horwood LJ, Fergusson DM, Hons BA, Shannon FT. Social and familial factors in the development of early childhood asthma. *Pediatrics* 1985;**75**:859–868.
35. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Björkstén B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics* 1995;**95**:500–505.
36. Norrman E, Nyström L, Jönsson E, Stjernberg N. Prevalence and incidence of asthma and rhinoconjunctivitis in Swedish teenagers. *Allergy* 1998;**53**:28–35.
37. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factor for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998;**101**:587–593.
38. 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. *Lancet* 2000;**356**:1392–1397.
39. Smedje G, Norbäck D. Incidence of asthma diagnosis and self-reported allergy in relation to the school environment – a four year follow-up study in schoolchildren. *Int J Tuberc Lung Dis* 2001;**5**:1059–1066.
40. Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Exposure to cockroach allergen in the home is associated with incident doctor-diagnosed asthma and recurrent wheezing. *J Allergy Clin Immunol* 2001;**107**:41–47.
41. Nafstad P, Magnus P, Gaarder PI, Jaakkola JJK. Exposure to pets and atopy-related diseases in the first 4 years of life. *Allergy* 2001;**56**:307–312.
42. Perzanowski MS, Rönmark E, Platts-Mills TAE, Lundbäck 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.

43. Rönmark E, Platts-Mills TAE, Lundbäck B, Perzanowski MS. Incidence rates and risk factors for asthma among school children: a 2 year follow-up report from the Obstructive Lung Disease in Northern Sweden (OLIN) studies. *Respir Med* 2002;**96**:1006–1013.
44. McConnell R, Berhane K, Gilliland F, Islam T, Gauderman WJ, London SJ et al. Indoor risk factors for asthma in a prospective study of adolescents. *Epidemiology* 2002;**13**:288–295.
45. Almvist C, Egmar AC, Hedlin G, Lundqvist M, Nordvall SL, Pershagen G et al. Direct and indirect exposure to pets – risk of sensitization and asthma at 4 years in a birth cohort. *Clin Exp Allergy* 2003;**33**:1190–1197.
46. de MeerG, Toelle BG, Ng K, Tovey E, Marks GB. Presence and timing of cat ownership by age 18 and the effect on atopy and asthma at age 28. *J Allergy Clin Immunol* 2004;**113**:433–438.
47. Fasce L, Tosca MA, Silvestri M, Olcese R, Pistorio A, Rossi GA. “Early” cat ownership and the risk of sensitization and allergic rhinitis in Ligurian children with respiratory symptoms. *Ann Allergy Asthma Immunol* 2005;**94**:561–565.
48. Salo PM, Xia J, Johnson A, Li Y, Avol EL, Gong J et al. Indoor allergens, asthma, and asthma-related symptoms among adolescents in Wuhan, China. *Ann Epidemiol* 2004;**14**:543–550.
49. Rylander E, Pershagen G, Eriksson M, Nordvall L. Parental smoking and other risk factors for wheezing bronchitis in children. *Eur J Epidemiol* 1993;**9**:517–526.
50. Tamay Z, Akcay A, Ones U, Guler N, Kilic G, Zencir M. Prevalence and risk factors for allergic rhinitis in primary school children. *Int J Pediatr Otorhinolaryngol* 2007;**71**:463–471.
51. Remes ST, Castro-Rodríguez JA, Holberg CJ, Martínez FD, Wright AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol* 2001;**108**:509–515.
52. 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**:781–782.
53. 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**:963–972.
54. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001;**357**:752–756.
55. Liccardi G, D’Amato G, Canonica GW, Hrabina M, Piccolo A, D’Amato M et al. Direct and prolonged exposure to dogs does not influence the degree of skin prick test positivity to dog allergen. *J Invest Allergol Clin Immunol* 2005;**15**:167–171.
56. Heissenhuber A, Heinrich J, Falhlbush B, Borte M, Wickmann HE, Bolte G. Health impacts of second-hand exposure to cat allergen Fel d 1 in infants. *Allergy* 2003;**58**:154–157.
57. Custovic A, Taggart SC, Woodcock A. House dust mite and cat allergen in different indoor environments. *Clin Exp Allergy* 1994;**24**:1164–1168.
58. D’Amato G, Liccardi G, Russo M, Barber D, D’Amato M, Carreira J. Clothing is a carrier of cat allergens. *J Allergy Clin Immunol* 1997;**99**:577–578.
59. Svanes C, Zock JP, Antó J, Dharmage S, Norbäck D, Wjst M et al. Do asthma and allergy influence subsequent pet keeping? An analysis of childhood and adulthood. *J Allergy Clin Immunol* 2006;**118**:691–698.
60. Virtanen T. Lipocalin allergens. *Allergy* 2001;**56**:48–51.
61. Kaiser L, Grönlund H, Sandalova T, Ljunggren HG, van Hage-Hamsten M, Achour A et al. The crystal structure of the major cat allergen Fel d 1, a member of the secretoglobulin family. *J Biol Chem* 2003;**278**:37730–37735.
62. Campo P, Kalra HK, Levin L, Reponen T, Olds R, Lummus ZL et al. Influence of dog ownership and high endotoxin on wheezing and atopy during infancy. *J Allergy Clin Immunol* 2006;**118**:1271–1278.