Pet exposure and risk of atopic dermatitis at the pediatric age: A meta-analysis of birth cohort studies

Claudio Pelucchi, ScD,[a] Carlotta Galeone, PhD,[a,b] Jean-François Bach, MD, DSc,[c,d] Carlo La Vecchia, MD,[a,b] and Liliane Chatenoud, ScD[a]   *Milan, Italy, and Paris, France*

Background: Findings on pet exposure and the risk of atopic dermatitis (AD) in children are inconsistent.
Objective: With the aim to summarize the results of exposure to different pets on AD, we undertook a meta-analysis of epidemiologic studies on this issue.
Methods: In August 2012, we conducted a systematic literature search in Medline and Embase. We included analytic studies considering exposure to dogs, cats, other pets, or pets overall during pregnancy, infancy, and/or childhood, with AD assessment performed during infancy or childhood. We calculated summary relative risks and 95% CIs using both fixed- and random-effects models. We computed summary estimates across selected subgroups.
Results: Twenty-six publications from 21 birth cohort studies were used in the meta-analyses. The pooled relative risks of AD for exposure versus no exposure were 0.72 (95% CI, 0.61-0.85; $I^2 = 46\%$; results based on 15 studies) for exposure to dogs, 0.94 (95% CI, 0.76-1.16; $I^2 = 54\%$; results based on 13 studies) for exposure to cats, and 0.75 (95% CI, 0.67-0.85; $I^2 = 54\%$; results based on 11 studies) for exposure to pets overall. No heterogeneity emerged across the subgroups examined, except for geographic area.
Conclusion: This meta-analysis reported a favorable effect of exposure to dogs and pets on the risk of AD in infants or children, whereas no association emerged with exposure to cats. (J Allergy Clin Immunol 2013;132:616-22.)

The hygiene hypothesis has been proposed as a possible explanation for the apparent increasing prevalence of allergic diseases, including atopic dermatitis (AD), registered during the last decades in several high-income countries.[1] This hypothesis assumes that a reduced exposure to infectious agents in early life can affect the development of the immune system, leading to increased susceptibility to allergic and autoimmune disorders.[1,2]

Along these lines, regular contact with animals and thus increased exposure to microbial products, including endotoxins, in pregnancy or during early life (ie, before the inception of asthma and allergies) has been linked to reduced atopic sensitization[3] and then to various allergic diseases.[4-11] In particular, a decreased risk of asthma and hay fever, but not AD, emerged in children of farmers,[9] pointing toward a favorable role of exposure to livestock and related bacterial components.[12] In a large birth cohort study from Germany, the development of asthma was not related to cat and mite allergen exposure in the first years of life or to cat ownership, although sensitization to mite and cat allergens was associated with indoor exposure.[13] Another study conducted in a rural setting considered the role of pets.[10] This found an inverse relation between dog exposure at interview and diagnoses of asthma and hay fever, although the associations were somewhat attenuated after allowing for livestock exposure. On the other hand, only an intensive exposure to cats, but not to pets in general, was found to prevent asthma in a population of schoolchildren not living on a farm.[11]

Earlier reviews and meta-analyses tried to summarize the role of exposure to pets on asthma and rhinitis. A meta-analysis reported that exposure to dogs, but not cats, increased the risk of asthma, whereas exposure to any furry pet decreased the risk of rhinitis by approximately 20%.[14] However, this meta-analysis included prevalence studies and was criticized on this and other bases.[15] A subsequent systematic review indicated that most birth cohort studies report no effect of early-life pet exposure on the development of asthma and that conflicting findings emerged across different study designs and methods of assessment of pet exposure.[15,16] Similarly, no effect on asthma or allergic rhinitis in children aged 6 to 10 years was found in a recent pooled analysis of birth cohort studies.[17]

Various, mainly narrative reviews have also been conducted on AD, which is often the first clinical step in the atopic pathway, reporting a possible inverse relation with early pet exposure.[18,19] Several birth cohort studies have recently provided new results on the relation between exposure to pets, mainly dogs or cats, and the risk of AD in children.[5,7,20-25] Thus there is the need to quantify the role of exposure to different pets on the cause of AD by using a meta-analytic approach and to examine the association in selected subgroups to address potential methodological shortcomings or underlying factors, if any were present, explaining the relation. In particular, likely confounding roles of family history of allergic diseases through an effect of pet avoidance, as well as of social class and maternal smoking habits, have been reported.[26,27]

With the aim to summarize the information on the relation between exposure to various pets and AD in infants and children and to address the role of several covariates, we conducted a formal systematic review and a meta-analysis of epidemiologic studies on the issue.

METHODS

This systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reporting meta-analysis of observational studies.[28] We registered this review in the International Prospective Register of Systematic Reviews (PROSPERO, registration no. CRD42012002908), describing in advance the aims and methods of our investigation.[29]

In August 2012 we performed a systematic literature search of the Medline and Embase databases for cohort and case-control studies reporting data on exposure to pets and AD in infants and children. The following search string, restricted to the English language, was used in PubMed: "(case-control OR cohort OR prospective OR retrospective) AND (eczema OR dermatitis) AND (pregnancy OR pregnant OR child OR children OR infant OR adolescent) AND (animals OR pets OR dogs OR cats)." A similar combination was adopted for the Embase search.

Two review team members (C.P. and C.G.) retrieved and independently assessed the potentially relevant articles and checked the reference lists of all articles of interest to obtain other pertinent publications. Abstracts and unpublished studies were not included. No studies were excluded *a priori* for weakness of design or data quality, and we did not assign quality scores to the studies. Each publication identified was included in the analysis if the following criteria were met: (1) cohort or case-control studies considering exposure to dogs, cats, other pets, or pets overall (ie, pet keeping or regular contacts with pets) during pregnancy, infancy, and/or childhood; (2) AD assessment performed during infancy or childhood (ie, ≤12 years of age); and (3) reported estimates of odds ratios (ORs) and corresponding 95% CIs or information sufficient to calculate them for occurrence of AD. We excluded studies that were (1) cross-sectional; (2) focused on measures of pet exposure other than pet keeping (eg, sensitization to dogs or cats and pet allergens/endotoxins measured in the mattress, at home, or at school); (3) studies reporting outcomes in adolescents or adults; and (4) studies focused on the prognosis of AD.

We collected data on the number of subjects with and without the disease in the exposed (ie, to dogs, cats, other pets, or pets overall) and nonexposed groups; risk estimates (crude and/or adjusted ORs, hazard ratios, or rate ratios, hereafter collectively defined as relative risks [RRs]) and the corresponding 95% CIs at any available age end point. Furthermore, we abstracted information on potential sources of heterogeneity or bias across studies, including details on the population enrolled (ie, children with a family history of atopic diseases or unselected children), geographic area, period or periods of pet exposure, outcome assessors, covariate or covariates adjusted for in the statistical models, and subgroup analyses. Discrepancies between review team members were discussed and resolved.

We pooled the RR estimates of each study according to exposure to different pets. For those studies providing only frequency (or percentage) distributions, we calculated unadjusted ORs and their 95% CIs from the outcome distribution of exposed and nonexposed children, as reported in the publications. When multiple estimates from the same study (from ≥1 publications) were available, we included in the main meta-analysis the one study that fulfilled the following ordered criteria: (1) outcome assessment occurring at an earlier age[4,5,22,30,31]; (2) outcome assessment over a time period, rather than at a given end point (eg, AD up to age 1 year was preferred to AD at age 1 year)[4]; (3) pet exposure occurring at an earlier age[32,33]; (4) risk estimate adjusted for the largest number of the terms family history of allergic diseases, parental education/income, parental smoking[34,35]; and (5) exposure to any pet rather than to "dog or cat" only.[36]

We calculated summary RR estimates of AD by using both fixed-effects models with the inverse variance method (ie, computing an average effect by weighting the log OR of each study according to the inverse of the sampling variance) and random-effects models, which consider both within- and between-study variations by using the DerSimonian and Laird method.[37-39] We presented RRs from random-effects models that assume that the exposure effects observed in the studies are a random sample from a distribution of exposure effects, thus yielding a more global and conservative estimate.[39] Furthermore, random-effects models have the advantage of increasing the accuracy of the exposure estimates because the information from the study error stratum is used in addition to that from the residual stratum. Heterogeneity between estimates was assessed by using the χ^2 test and defined as a P value of less than .10, and inconsistency was measured by using the I^2 statistic.[40] We also computed summary estimates in several subgroups, including geographic area, family history of allergic disease, age and period of outcome assessment, period of exposure, and adjustment for family history of allergic disease, parental education/income, or parental smoking. In stratified analyses we presented RRs from random-effects models because the number of studies and hence the power of the heterogeneity test was low. We used meta-regression to test heterogeneity between subgroups for study-level, 2-strata covariates or a heterogeneity test otherwise.[41] The presence of publication bias was assessed by examining the funnel plot and applying the tests proposed by Begg and Mazumdar[42] and Egger et al.[43] All the statistical analyses were performed with STATA software (version 11; StataCorp, College Station, Tex).

RESULTS

Fig 1 shows the selection process of publications in a flowchart. Overall, 307 publications were identified in PubMed and 93 in Embase. By examining the title and abstract, approximately three fourths of the articles were excluded as irrelevant (eg, studies of food allergies, atopic or dermatologic diseases other than AD, sensitization to several allergens, dust mite exposures, and treatment/prognosis and review articles). Furthermore, 20 of the retained publications were present in both databases, leaving 94 unique publications for full-text examination. The review of the reference lists of these publications led to the identification of 7 additional reports, for a total of 101 articles. After in-depth consideration, 72 publications were excluded (mostly because they lacked data for pets or analyzed outcomes other than AD, were cross-sectional studies, or lacked data from original studies). Thus there were 29 publications that reported original data on pet exposure and the risk of AD from cohort studies. These were the basis for our meta-analysis. Three of 29 publications[44-46] reported duplicate data with other articles and thus were not used in the overall meta-analysis or in subgroup investigations. These publications were thus not presented in this review.

Table E1 in this article's Online Repository at www.jacionline. org summarizes the main characteristics of the 26 selected publications reporting data on exposure to pets and risk of AD.[4-7,20-25,30-36,47-55] A few articles were multiple publications from the same studies, and therefore data were available from a total of 21 investigations. All of them were birth cohort studies conducted since 1989[36] in various areas of Europe (14 studies, 6 of which were from Scandinavian countries alone), the United States (3 studies), Oceania (3 studies), and Japan (1 study). With reference to pet exposures considered in these 21 studies, 15 reported data for exposure to dogs, 13 to cats, and 11 to pets (we included in the latter category also those studies reporting data for exposure to "dog or cat" only because those were by far the most common domestic animals kept in the populations examined). Results for exposure to other domestic animals were scanty, and thus the subsequent quantitative meta-analyses were restricted to dogs, cats, and pets overall.

Fig 2 reports the results from each study, as well as overall results, by using a random-effects model for the relation between
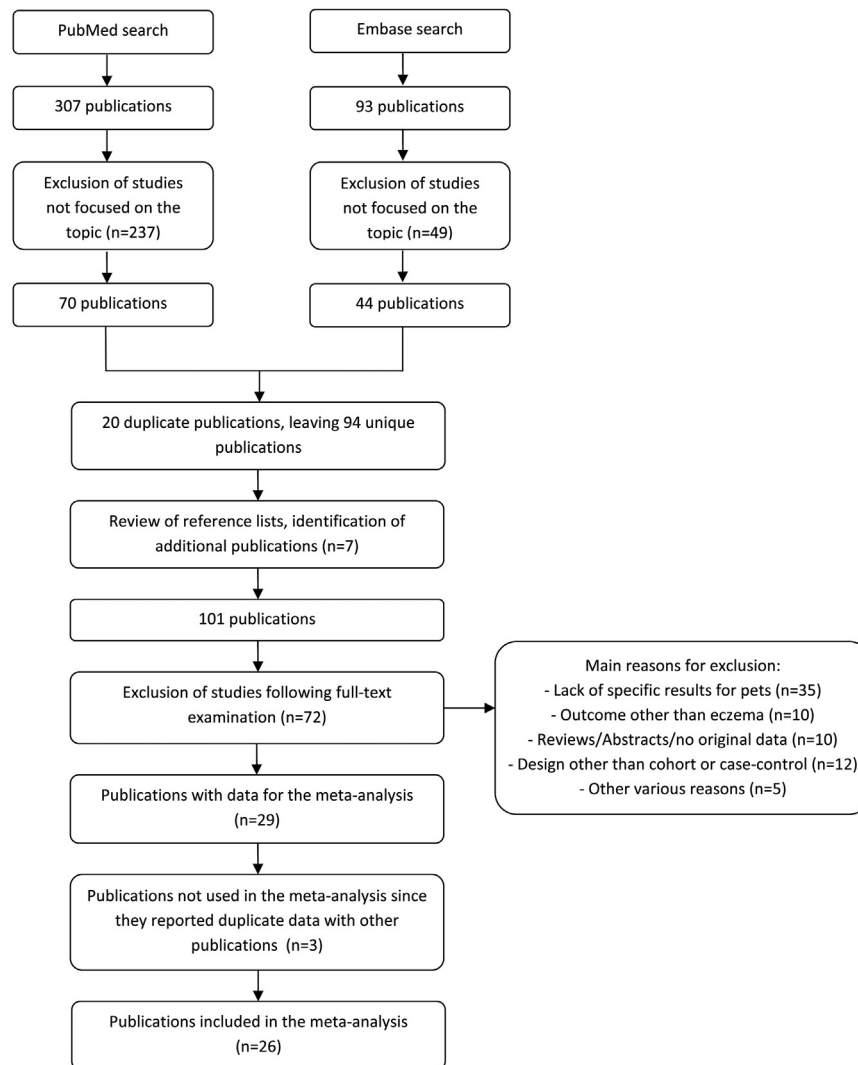
FIG 1. Flowchart for search and selection of publications for the meta-analysis.

exposure to dogs (Fig 2, *A*), cats (Fig 2, *B*), and pets overall (Fig 2, *C*) and the risk of AD in infants or children. Twelve of 15 RRs for dog exposure were below unity. The pooled RR of AD for exposure versus no exposure to dogs was 0.72 (95% CI, 0.61-0.85), with moderate inconsistency observed between studies ($I^2 = 46\%$). When we used a fixed-effects model, the pooled RR was not materially affected (RR, 0.73; 95% CI, 0.65-0.82). With reference to cat exposure, 6 of 13 RRs of AD were below unity. When we pooled the estimates, the RR for exposure versus no exposure to cats was 0.94 (95% CI, 0.76-1.16). Moderate inconsistency emerged between studies ($I^2 = 54\%$). By using a fixed-effects model, the pooled RR was unchanged, and the CI was narrower (RR, 0.94; 95% CI, 0.82-1.08). Six of 7 studies of any pet exposure (vs no pet exposure) and 3 of 4 studies of dog or cat exposure (vs no dog or cat exposure) found RRs of AD of below unity. The corresponding pooled RRs were 0.78 (95% CI, 0.72-0.85; $I^2 = 22\%$) and 0.66 (95% CI, 0.40-1.06; $I^2 = 78\%$), with no significant heterogeneity between subgroups ($P = .66$). Pooling all 11 estimates for pet exposure, the overall RR of AD was 0.75 (95% CI, 0.67-0.85). For the latter analysis, moderate inconsistency between studies was found ($I^2 = 54\%$).

When we performed the analysis of all 11 studies using a fixed-effects model, the pooled RR was 0.80 (95% CI, 0.75-0.84).

Table I reports the pooled RRs of AD for exposure to dogs, cats, and pets among several subgroups. No major differences emerged across the subgroups examined. Even if the within-group heterogeneity was moderate or high for several strata (ie, for dog exposure, the I^2 value was >60% in ≥1 subgroup for 8/10 strata considered), point estimates remained consistent between strata. In particular, significant heterogeneity was found only between subgroups of geographic areas for the relation between dog exposure ($P = .005$) and pet exposure ($P = .02$) and AD and subgroups of age at outcome assessment for the relation between pet exposure and AD ($P = .04$), although for the latter, no trend in risk was observed. Furthermore, a borderline significant heterogeneity emerged across different study designs in the analysis of dog exposure ($P = .051$) and AD. Inconsistency within subgroups was high (ie, approximately 70%) between studies not adjusted for major potential covariates and absent between adjusted studies when we considered the relation between dog exposure and AD. The opposite finding (ie, no inconsistency between
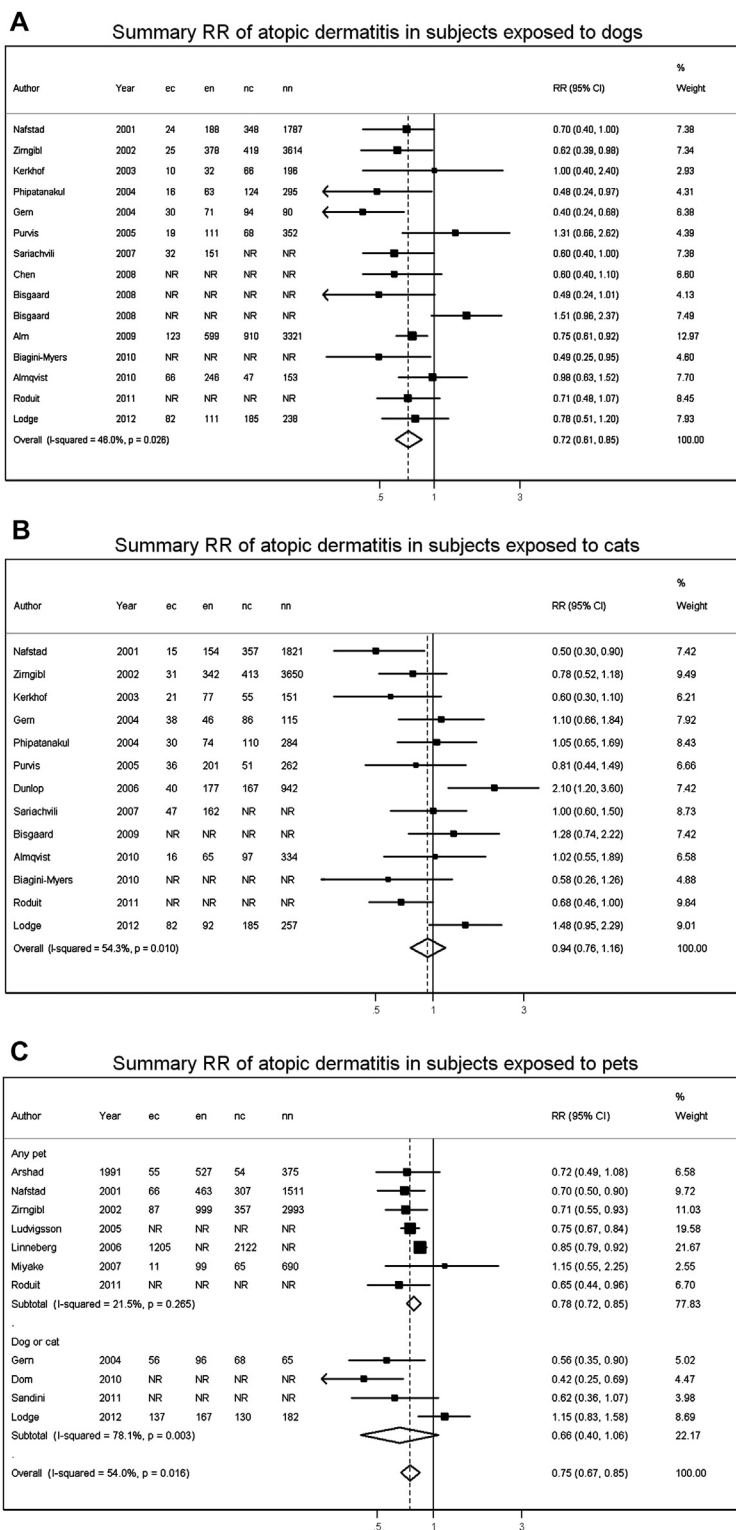
A Summary RR of atopic dermatitis in subjects exposed to dogs

Author	Year	ec	en	nc	nn	RR (95% CI)	% Weight
Nafstad	2001	24	188	348	1787	0.70 (0.40, 1.00)	7.38
Zirngibl	2002	25	378	419	3614	0.62 (0.39, 0.98)	7.34
Kerkhof	2003	10	32	68	196	1.00 (0.40, 2.40)	2.93
Phipatanakul	2004	18	63	124	295	0.48 (0.24, 0.97)	4.31
Gern	2004	30	71	94	90	0.40 (0.24, 0.68)	6.38
Purvis	2005	19	111	68	352	1.31 (0.66, 2.62)	4.39
Sariachvili	2007	32	151	NR	NR	0.60 (0.40, 1.00)	7.38
Chen	2008	NR	NR	NR	NR	0.60 (0.40, 1.10)	6.60
Bisgaard	2008	NR	NR	NR	NR	0.49 (0.24, 1.01)	4.13
Bisgaard	2008	NR	NR	NR	NR	1.51 (0.96, 2.37)	7.49
Alm	2009	123	599	910	3321	0.75 (0.61, 0.92)	12.97
Biagini-Myers	2010	NR	NR	NR	NR	0.49 (0.25, 0.95)	4.60
Almqvist	2010	66	246	47	153	0.98 (0.63, 1.52)	7.70
Roduit	2011	NR	NR	NR	NR	0.71 (0.48, 1.07)	8.45
Lodge	2012	82	111	185	238	0.78 (0.51, 1.20)	7.93
Overall (I-squared = 46.0%, p = 0.026)						0.72 (0.61, 0.85)	100.00

B Summary RR of atopic dermatitis in subjects exposed to cats

Author	Year	ec	en	nc	nn	RR (95% CI)	% Weight
Nafstad	2001	15	154	357	1821	0.50 (0.30, 0.90)	7.42
Zirngibl	2002	31	342	413	3650	0.78 (0.52, 1.18)	9.49
Kerkhof	2003	21	77	55	151	0.60 (0.30, 1.10)	6.21
Gern	2004	38	46	86	115	1.10 (0.66, 1.84)	7.92
Phipatanakul	2004	30	74	110	284	1.05 (0.65, 1.69)	8.43
Purvis	2005	36	201	51	262	0.81 (0.44, 1.49)	6.66
Dunlop	2006	40	177	167	942	2.10 (1.20, 3.60)	7.42
Sariachvili	2007	47	162	NR	NR	1.00 (0.60, 1.50)	8.73
Bisgaard	2009	NR	NR	NR	NR	1.28 (0.74, 2.22)	7.42
Almqvist	2010	16	65	97	334	1.02 (0.55, 1.89)	6.58
Biagini-Myers	2010	NR	NR	NR	NR	0.58 (0.26, 1.26)	4.88
Roduit	2011	NR	NR	NR	NR	0.68 (0.46, 1.00)	9.84
Lodge	2012	82	92	185	257	1.48 (0.95, 2.29)	9.01
Overall (I-squared = 54.3%, p = 0.010)						0.94 (0.76, 1.16)	100.00

C Summary RR of atopic dermatitis in subjects exposed to pets

Author	Year	ec	en	nc	nn	RR (95% CI)	% Weight
Any pet							
Arshad	1991	55	527	54	375	0.72 (0.49, 1.08)	6.58
Nafstad	2001	66	463	307	1511	0.70 (0.50, 0.90)	9.72
Zirngibl	2002	87	999	357	2993	0.71 (0.55, 0.93)	11.03
Ludvigsson	2005	NR	NR	NR	NR	0.75 (0.67, 0.84)	19.58
Linneberg	2006	1205	NR	2122	NR	0.85 (0.79, 0.92)	21.67
Miyake	2007	11	99	65	690	1.15 (0.55, 2.25)	2.55
Roduit	2011	NR	NR	NR	NR	0.65 (0.44, 0.96)	6.70
Subtotal (I-squared = 21.5%, p = 0.265)						0.78 (0.72, 0.85)	77.83
Dog or cat							
Gern	2004	56	96	68	65	0.56 (0.35, 0.90)	5.02
Dom	2010	NR	NR	NR	NR	0.42 (0.25, 0.69)	4.47
Sandini	2011	NR	NR	NR	NR	0.62 (0.36, 1.07)	3.98
Lodge	2012	137	167	130	182	1.15 (0.83, 1.58)	8.69
Subtotal (I-squared = 78.1%, p = 0.003)						0.66 (0.40, 1.06)	22.17
Overall (I-squared = 54.0%, p = 0.016)						0.75 (0.67, 0.85)	100.00

FIG 2. Summary RRs of AD in subjects exposed to dogs **(A)**, cats **(B)**, and pets overall **(C)**. In Fig 2, *A*, 2 studies from Bisgaard et al[30] are reported. Both results are extracted from Bisgaard et al, which are from the COPSAC and MAAS birth cohorts, respectively. The reference category was as follows: no exposure to dogs in Fig 2, *A*; no exposure to cats in Fig 2, *B*; and no exposure to pets (or to dog or cat) in Fig 2, *C*.

unadjusted studies and moderate-to-high inconsistency between adjusted studies) emerged for the relations between cat and pet exposure and AD.

Fig E1 in this article's Online Repository at www.jacionline. org shows the funnel plots of studies on exposure to dogs (Fig E1, *A*), cats (Fig E1, *B*), and pets overall (Fig E1, *C*) and

TABLE I. Summary RRs of AD in relation to exposure to dogs, cats, and pets, according to selected subgroups

Subgroup	Dogs*			Cats			Pets†		
	No. of studies	RR (95% CI)	I^2	No. of studies	RR (95% CI)	I^2	No. of studies	RR (95% CI)	I^2
Geographic area									
Europe	9	0.74 (0.61-0.90)	40%	7	0.88 (0.63-1.23)	69%	8	0.73 (0.66-0.82)	48%
United States	3	0.44 (0.31-0.63)	0%	3	0.97 (0.70-1.34)	0%	1	0.56 (0.35-0.90)	—
Asia/Oceania	3	0.93 (0.70-1.23)	0%	3	1.13 (0.79-1.63)	25%	2	1.15 (0.86-1.54)	0%
Age at outcome assessment (y)									
≤1	10	0.67 (0.53-0.84)	56%	8	0.89 (0.66-1.21)	61%	6	0.74 (0.67-0.81)	0%
>1-≤3	6	0.62 (0.47-0.80)	44%	5	1.01 (0.77-1.32)	50%	6	0.84 (0.73-0.98)	41%
>3	7	0.84 (0.63-1.11)	53%	4	1.05 (0.79-1.40)	0%	4	0.75 (0.53-1.07)	60%
Period of outcome assessment									
At an end point (eg, AD at age 1 y)	5	0.68 (0.42-1.10)	73%	5	0.89 (0.60-1.30)	51%	3	0.70 (0.38-1.27)	84%
Up to an end point (eg, AD by age 1 y)	10	0.69 (0.56-0.84)	52%	9	0.95 (0.74-1.20)	57%	9	0.73 (0.63-0.82)	51%
Period of exposure									
In pregnancy	1	0.71 (0.48-1.07)	—	1	0.68 (0.46-1.00)	—	2	0.80 (0.47-1.37)	48%
At birth	5	0.71 (0.45-1.12)	75%	4	1.02 (0.64-1.63)	70%	3	0.78 (0.52-1.18)	75%
After birth	8	0.66 (0.52-0.84)	32%	6	0.89 (0.72-1.10)	0%	5	0.70 (0.57-0.87)	60%
Adjusted for family history of allergic diseases									
No	7	0.76 (0.53-1.09)	71%	6	0.93 (0.73-1.18)	5%	3	0.64 (0.49-0.84)	0%
Yes	8	0.69 (0.59-0.82)	0%	7	0.97 (0.69-1.36)	71%	7	0.80 (0.72-0.90)	50%
Adjusted for education/income									
No	8	0.77 (0.58-1.02)	67%	7	0.90 (0.74-1.10)	0%	4	0.64 (0.52-0.80)	0%
Yes	7	0.66 (0.54-0.80)	0%	6	0.96 (0.64-1.44)	75%	6	0.81 (0.72-0.91)	53%
Adjusted for parental smoking/exposure to ETS									
No	8	0.69 (0.50-0.95)	69%	5	1.00 (0.78-1.28)	0%	4	0.69 (0.54-0.88)	0%
Yes	7	0.73 (0.62-0.88)	0%	8	0.92 (0.67-1.26)	69%	6	0.79 (0.71-0.89)	55%
Family history of allergic diseases									
No	1	0.80 (0.50-1.40)	—	1	0.60 (0.30-1.20)	—	2	0.79 (0.70-0.90)	0%
Yes	9	0.66 (0.51-0.85)	40%	8	0.95 (0.72-1.27)	45%	5	0.74 (0.57-0.96)	59%
Studies with unselected populations	7	0.87 (0.67-1.13)	63%	5	0.96 (0.67-1.38)	66%	6	0.73 (0.60-0.88)	56%
Study design									
Birth cohort	11	0.70 (0.56-0.87)	61%	8	0.95 (0.70-1.29)	64%	8	0.73 (0.64-0.83)	54%
Birth cohort from other designs (ie, intervention or case-control studies)	5	0.95 (0.75-1.20)	0%	5	0.92 (0.67-1.26)	43%	3	0.82 (0.57-1.18)	69%
Type of diagnosis									
Performed by clinicians/outcome assessors	3	0.86 (0.46-1.59)	49%	3	0.88 (0.57-1.36)	37%	2	0.68 (0.50-0.94)	0%
Reported by parents based on a physician's diagnosis or treatment	5	0.66 (0.54-0.82)	0%	4	0.94 (0.67-1.33)	61%	5	0.84 (0.71-1.00)	48%
Self-reported by parents	5	0.74 (0.53-1.04)	72%	3	0.80 (0.52-1.23)	53%	3	0.67 (0.52-0.85)	59%
Others/mixed types	3	0.59 (0.33-1.07)	73%	4	1.13 (0.70-1.84)	61%	1	0.56 (0.35-0.90)	—
Overall	15	0.72 (0.61-0.85)	46%	13	0.94 (0.76-1.16)	54%	11	0.75 (0.67-0.85)	54%

All ORs were calculated by using random-effects models. The sum of studies in subgroups might be higher or lower than the total number of studies because some studies, in turn, provided results for more than 1 subgroup or did not report selected information.

ETS, Environmental tobacco smoke.

*P value for heterogeneity between subgroups of geographic area was .005.

†P values for heterogeneity between subgroups were .02 for geographic area and 0.04 for age at outcome assessment.

the risk of AD. No evidence of publication bias emerged either by looking at the plots or from Egger and Begg tests for dogs (P = .62 and .15, respectively) and cats (P = .79 and .81, respectively). The funnel plot for pets was moderately asymmetric, but the Egger (P = .18) and Begg (P = .53) tests did not support significant small-study effects.

DISCUSSION

This meta-analysis of birth cohort studies reported an approximately 25% decreased risk of AD for children who experienced exposure to dogs and pets overall, whereas no association emerged with cat exposure. Moderate heterogeneity between studies was reported, and thus results should be considered with caution because global estimates could be influenced by confounding factors not considered in the analyses. There was no evidence of publication bias, notwithstanding the fact that all the identified studies were conducted after the formulation of the hygiene hypothesis in 1989.[2] Furthermore, we considered birth cohort studies only to avoid possible bias deriving from the inclusion of prevalence studies. Thus our findings for AD are apparently different from those for asthma, which showed no clear association with pet exposure[16] or, if any association were present, an increased risk for dog exposure.[14]

The different role played by pet exposure in patients with AD compared with those with asthma and hay fever could be due to the different effects of allergens in these diseases, at least in part.

Furry pet allergens have an important and complex role in the onset of asthma and hay fever, whereas pet allergens are not mainly involved in AD occurrence.

A major issue to be clarified is why a favorable effect on AD emerged for dog and pet exposure but not for cat keeping. The gut microbial communities differ across various mammalian species.[56] In particular, the fecal microbiota of dogs and cats is highly diverse,[57] and it is likely that their skin and mucosal microbiomes differ as well. Thus, contact with dogs and cats can have a different effect on the risk of AD because of the diverse microbial exposures experienced by children living with these animal species. In fact, changes in the (intestinal) colonization pattern during infancy have been related to the increasing allergy prevalence in high-income countries[58] through an effect of the microflora by driving the maturation of the immune system.[59] Increasing evidence supports the latter hypothesis.[60,61]

The stronger inverse association observed in the United States than in European studies for both dog and pet exposure with AD and the lack of association reported in studies from Oceania and Japan are difficult to explain. The prevalence of pet owners, specifically cat owners, in a population might play a role in the variation of risks of allergic diseases (ie, through a community effect).[16,62] However, we observed no clear relation between the prevalence of pet keeping and risk estimates of AD in the identified studies. Differences between populations in handling a dog/pet (eg, kept inside or outside the house and level of animal contact with infants/children) and a role of gene-environment interactions[4,30,63,64] are other tentative explanations for the geographic variation in risks. In any case only a minority of studies were conducted outside Europe, thus limiting the scope for interpretation.

One of the major difficulties in the investigation of the relation between pet exposure and AD is the role of family history of allergic disease. In fact, the presence of allergy in the family, besides increasing the risk of allergic disease in the child, might lead to the avoidance or removal of pets, in particular cats,[65] from the home and thus to reverse causation. We tried to overcome this problem by excluding cross-sectional studies, which are more prone to this problem,[66] using, when available, estimates adjusted for family history of allergy and by means of subgroup analyses. Furthermore, summary estimates were not materially different among studies adjusting or not adjusting for family history of allergy, as well as among studies based on children with a family history of allergy or unselected with respect to the latter factor. However, only a small number of studies provided results among children with no family history of allergy. Another reassuring consideration against the role of reverse causation derives from the different results obtained for dog and cat exposure on AD risk because such bias would be expected to equally affect both relationships[4] or, if any effect is present, to have a larger effect on the relation with cats.

In all 3 meta-analyses of dogs, cats, and pets and AD, results from different studies were moderately heterogeneous, with the I^2 value for inconsistency ranging between 45% and 55%. This might be due to the fact that studies differed widely in their methods; that is, they were conducted among different populations using diverse diagnostic procedures and end points, assessed exposures at various ages, and were adjusted for different covariates. When we considered these aspects in subgroup analyses, however, we could not find any specific factor that adequately explained the inconsistency.

It was not possible to stratify studies directly by adjustment for pet avoidance behavior of parents.[19] To obviate this problem, we used family history of allergy as a proxy variable of pet avoidance. This might be suitable for prospective studies, although some limits of this approach have been previously discussed.[5,26] The number of studies was relatively small, and consequently, the statistical power of some subgroup analyses was limited. For example, our meta-analysis was not informative on the role of maternal pet exposure during pregnancy because only 2 studies had data on the issue.[25,52] We also considered the role of pet exposure on IgE-associated AD, as in our previous meta-analysis of probiotic use,[67] but data were available from 1 cohort study only (reporting ORs of 0.56 [95% CI, 0.28-1.14] at age 2 years and 1.05 [95% CI 0.61-1.81] at age 5 years for exposure to dog or cat).[7]

The favorable effect of dog exposure on AD might be explained by the role of contact with microbial agents during early life, affecting the development of the immune system. Our findings thus provide support to the hygiene hypothesis.

Key messages

- **Exposure to dogs decreased the risk of AD in children by approximately 25%, whereas no association emerged with cat exposure.**
- **The association might be explained by the role of contact with microbial agents during early life, affecting the development of the immune system.**

REFERENCES

1. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002;347:911-20.
2. Strachan DP. Hay fever, hygiene, and household size. BMJ 1989;299:1259-60.
3. Eder W, von Mutius E. Hygiene hypothesis and endotoxin: what is the evidence? Curr Opin Allergy Clin Immunol 2004;4:113-7.
4. Gern JE, Reardon CL, Hoffjan S, Nicolae D, Li Z, Roberg KA, et al. Effects of dog ownership and genotype on immune development and atopy in infancy. J Allergy Clin Immunol 2004;113:307-14.
5. Lodge CJ, Lowe AJ, Gurrin LC, Matheson MC, Balloch A, Axelrad C, et al. Pets at birth do not increase allergic disease in at-risk children. Clin Exp Allergy 2012; 42:1377-85.
6. 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.
7. Sandini U, Kukkonen AK, Poussa T, Sandini L, Savilahti E, Kuitunen M. Protective and risk factors for allergic diseases in high-risk children at the ages of two and five years. Int Arch Allergy Immunol 2011;156:339-48.
8. Brunekreef B, Von Mutius E, Wong G, Odhiambo J, Garcia-Marcos L, Foliaki S. Exposure to cats and dogs, and symptoms of asthma, rhinoconjunctivitis, and eczema. Epidemiology 2012;23:742-50.
9. Von Ehrenstein OS, Von Mutius E, Illi S, Baumann L, Bohm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. Clin Exp Allergy 2000;30:187-93.
10. Waser M, von Mutius E, Riedler J, Nowak D, Maisch S, Carr D, et al. Exposure to pets, and the association with hay fever, asthma, and atopic sensitization in rural children. Allergy 2005;60:177-84.
11. Oberle D, von Mutius E, von Kries R. Childhood asthma and continuous exposure to cats since the first year of life with cats allowed in the child's bedroom. Allergy 2003;58:1033-6.
12. von Mutius E, Braun-Fahrlander C, Schierl R, Riedler J, Ehlermann S, Maisch S, et al. Exposure to endotoxin or other bacterial components might protect against the development of atopy. Clin Exp Allergy 2000;30:1230-4.
13. 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.
14. Takkouche B, Gonzalez-Barcala FJ, Etminan M, Fitzgerald M. Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. Allergy 2008;63:857-64.

15. Chen CM, Heinrich J. Re: Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. Allergy 2009;64:494-5.

16. Chen CM, Tischer C, Schnappinger M, Heinrich J. The role of cats and dogs in asthma and allergy—a systematic review. Int J Hyg Environ Health 2010;213:1-31.

17. Lodrup Carlsen KC, Roll S, Carlsen KH, Mowinckel P, Wijga AH, Brunekreef B, et al. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. PLoS One 2012;7:e43214.

18. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. Curr Probl Dermatol 2011;41:1-34.

19. Langan SM, Flohr C, Williams HC. The role of furry pets in eczema: a systematic review. Arch Dermatol 2007;143:1570-7.

20. Alm B, Aberg N, Erdes L, Mollborg P, Pettersson R, Norvenius SG, et al. Early introduction of fish decreases the risk of eczema in infants. Arch Dis Child 2009;94:11-5.

21. Almqvist C, Garden F, Kemp AS, Li Q, Crisafulli D, Tovey ER, et al. Effects of early cat or dog ownership on sensitisation and asthma in a high-risk cohort without disease-related modification of exposure. Paediatr Perinat Epidemiol 2010;24:171-8.

22. Biagini Myers JM, Wang N, LeMasters GK, Bernstein DI, Epstein TG, Lindsey MA, et al. Genetic and environmental risk factors for childhood eczema development and allergic sensitization in the CCAAPS cohort. J Invest Dermatol 2010; 130:430-7.

23. Bisgaard H, Halkjaer LB, Hinge R, Giwercman C, Palmer C, Silveira L, et al. Risk analysis of early childhood eczema. J Allergy Clin Immunol 2009;123: 1355-60.e5.

24. Dom S, Droste JH, Sariachvili MA, Hagendorens MM, Oostveen E, Bridts CH, et al. Pre- and post-natal exposure to antibiotics and the development of eczema, recurrent wheezing and atopic sensitization in children up to the age of 4 years. Clin Exp Allergy 2010;40:1378-87.

25. Roduit C, Wohlgensinger J, Frei R, Bitter S, Bieli C, Loeliger S, et al. Prenatal animal contact and gene expression of innate immunity receptors at birth are associated with atopic dermatitis. J Allergy Clin Immunol 2011;127:179-185.e1.

26. Almqvist C, Egmar AC, van Hage-Hamsten M, Berglind N, Pershagen G, Nordvall SL, et al. Heredity, pet ownership, and confounding control in a population-based birth cohort. J Allergy Clin Immunol 2003;111:800-6.

27. Eller E, Roll S, Chen CM, Herbarth O, Wichmann HE, von Berg A, et al. Meta-analysis of determinants for pet ownership in 12 European birth cohorts on asthma and allergies: a GA2LEN initiative. Allergy 2008;63:1491-8.

28. 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;283:2008-12.

29. Pelucchi C. Pets exposure and risk of atopic dermatitis in the paediatric age. CRD Register 2012:CRD42012002908. Available at: www.crd.york.ac.uk/prospero/display_record.asp?id=crd42012002908. Accessed April 30, 2013.

30. Bisgaard H, Simpson A, Palmer CNA, Bonnelykke K, McLean I, Mukhopadhyay S, et al. Gene-environment interaction in the onset of eczema in infancy: filaggrin loss-of-function mutations enhanced by neonatal cat exposure. PLoS Med 2008;5:e131.

31. Zirngibl A, Franke K, Gehring U, von Berg A, Berdel D, Bauer CP, et al. Exposure to pets and atopic dermatitis during the first two years of life. A cohort study. Pediatr Allergy Immunol 2002;13:394-401.

32. Chen CM, Morgenstern V, Bischof W, Herbarth O, Borte M, Behrendt H, et al. Dog ownership and contact during childhood and later allergy development. Eur Respir J 2008;31:963-73.

33. Purvis DJ, Thompson JM, Clark PM, Robinson E, Black PN, Wild CJ, et al. Risk factors for atopic dermatitis in New Zealand children at 3.5 years of age. Br J Dermatol 2005;152:742-9.

34. Linneberg A, Simonsen JB, Petersen J, Stensballe LG, Benn CS. Differential effects of risk factors on infant wheeze and atopic dermatitis emphasize a different etiology. J Allergy Clin Immunol 2006;117:184-9.

35. Sariachvili M, Droste J, Dom S, Wieringa M, Vellinga A, Hagendorens M, et al. Is breast feeding a risk factor for eczema during the first year of life? Pediatr Allergy Immunol 2007;18:410-7.

36. Arshad SH. Pets and atopic disorders in infancy. Br J Clin Pract 1991;45:88-9.

37. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

38. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987;9:1-30.

39. Bradburn MJ, Deeks JJ, Altman DG. sbe24: metan—an alternative meta-analysis command. Stata Tech Bull 1998;44:4-15.

40. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

41. Harris RJ, Bradburn MJ, Deeks JJ, Harbord RM, Altman DG, Sterne JAC. Metan: fixed- and random-effects meta-analysis. In: Sterne JAC, editor. Meta-analysis in

Stata: an updated collection from the Stata Journal. College Station (TX): Stata Press; 2009. p. 29-54.

42. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-101.

43. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.

44. Arshad SH, Hide DW. Effect of environmental factors on the development of allergic disorders in infancy. J Allergy Clin Immunol 1992;90:235-41.

45. Benn CS, Melbye M, Wohlfahrt J, Bjorksten B, Aaby P. Cohort study of sibling effect, infectious diseases, and risk of atopic dermatitis during first 18 months of life. BMJ 2004;328:1223.

46. Hagendorens MM, Bridts CH, Lauwers K, van Nuijs S, Ebo DG, Vellinga A, et al. Perinatal risk factors for sensitization, atopic dermatitis and wheezing during the first year of life (PIPO study). Clin Exp Allergy 2005;35:733-40.

47. Bufford JD, Reardon CL, Li Z, Roberg KA, DaSilva D, Eggleston PA, et al. Effects of dog ownership in early childhood on immune development and atopic diseases. Clin Exp Allergy 2008;38:1635-43.

48. Dunlop AL, Reichrtova E, Palcovicova L, Ciznar P, Adamcakova-Dodd A, Smith SJ, et al. Environmental and dietary risk factors for infantile atopic eczema among a Slovak birth cohort. Pediatr Allergy Immunol 2006;17:103-11.

49. Epstein TG, Bernstein DI, Levin L, Khurana Hershey GK, Ryan PH, Reponen T, et al. Opposing effects of cat and dog ownership and allergic sensitization on eczema in an atopic birth cohort. J Pediatr 2011;158:265-71, e1-5.

50. Kerkhof M, Koopman LP, van Strien RT, Wijga A, Smit HA, Aalberse RC, et al. Risk factors for atopic dermatitis in infants at high risk of allergy: the PIAMA study. Clin Exp Allergy 2003;33:1336-41.

51. Ludvigsson JF, Mostrom M, Ludvigsson J, Duchen K. Exclusive breastfeeding and risk of atopic dermatitis in some 8300 infants. Pediatr Allergy Immunol 2005;16:201-8.

52. Miyake Y, Ohya Y, Tanaka K, Yokoyama T, Sasaki S, Fukushima W, et al. Home environment and suspected atopic eczema in Japanese infants: the Osaka Maternal and Child Health Study. Pediatr Allergy Immunol 2007;18:425-32.

53. Phipatanakul W, Celedon JC, Raby BA, Litonjua AA, Milton DK, Sredl D, et al. Endotoxin exposure and eczema in the first year of life. Pediatrics 2004;114:13-8.

54. 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.

55. Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. Clin Exp Allergy 1993;23:504-11.

56. Ley RE, Hamady M, Lozupone C, Turnbaugh PJ, Ramey RR, Bircher JS, et al. Evolution of mammals and their gut microbes. Science 2008;320:1647-51.

57. Handl S, Dowd SE, Garcia-Mazcorro JF, Steiner JM, Suchodolski JS. Massive parallel 16S rRNA gene pyrosequencing reveals highly diverse fecal bacterial and fungal communities in healthy dogs and cats. FEMS Microbiol Ecol 2011;76:301-10.

58. Wold AE. The hygiene hypothesis revised: is the rising frequency of allergy due to changes in the intestinal flora? Allergy 1998;53:20-5.

59. Bjorksten B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. J Allergy Clin Immunol 2001;108:516-20.

60. Russell SL, Gold MJ, Hartmann M, Willing BP, Thorson L, Wlodarska M, et al. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. EMBO Rep 2012;13:440-7.

61. Hill DA, Siracusa MC, Abt MC, Kim BS, Kobuley D, Kubo M, et al. Commensal bacteria-derived signals regulate basophil hematopoiesis and allergic inflammation. Nat Med 2012;18:538-46.

62. Svanes C, Heinrich J, Jarvis D, Chinn S, Omenaas E, Gulsvik A, et al. Pet-keeping in childhood and adult asthma and hay fever: European community respiratory health survey. J Allergy Clin Immunol 2003;112:289-300.

63. Simpson A, John SL, Jury F, Niven R, Woodcock A, Ollier WE, et al. Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. Am J Respir Crit Care Med 2006;174:386-92.

64. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med 2011;365:1315-27.

65. Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills T, Weiss ST. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. Am J Respir Crit Care Med 1999;160:227-36.

66. Hennekens CH, Buring JE. Epidemiology in medicine. Boston: Little, Brown & Co; 1987.

67. Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, et al. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. Epidemiology 2012;23:402-14.
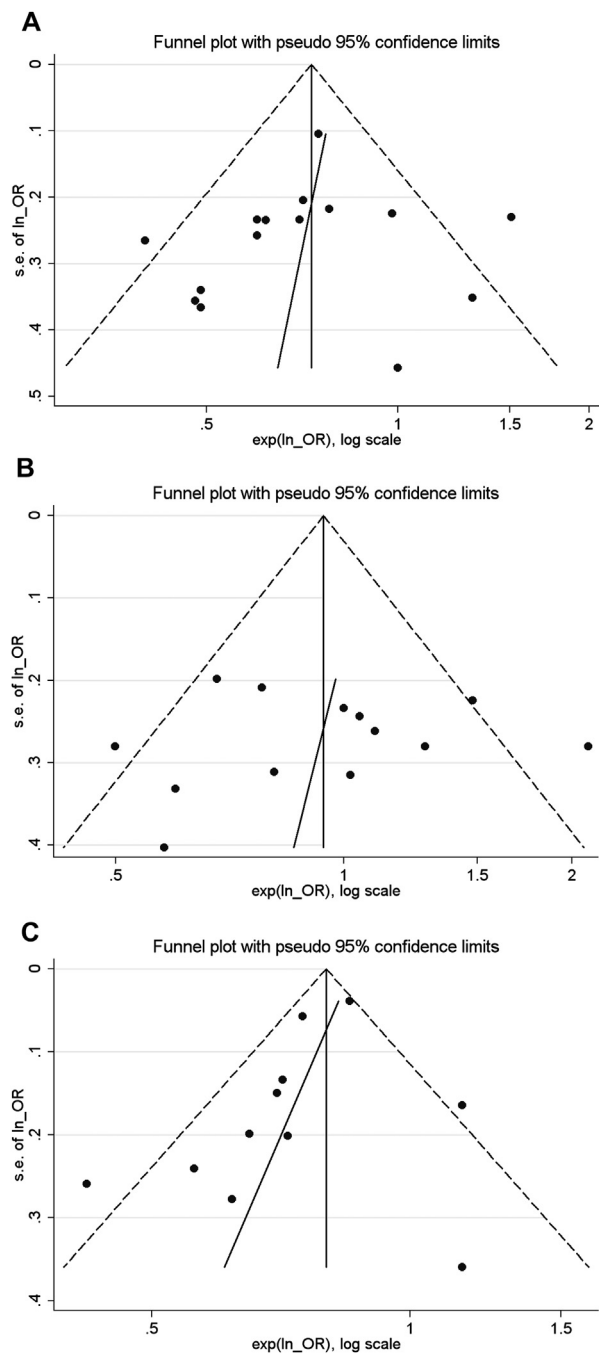
FIG E1. Funnel plots of studies on exposure to dogs **(A)**, cats **(B)**, and pets overall **(C)** and risk of AD.

TABLE E1. Publications from epidemiologic studies on exposure to pets and risk of AD included in the main meta-analysis or in subgroup analysis

Reference	Country	Period of enrollment	Age at follow-up's end	Study design (name)	Pet exposure	Period of exposure assessment	Outcome assessment for AD	Type of diagnosis	No. of subjects	Adjustment factors	Data for subgroups
Alm et al, 2009[20]	Sweden	2003	1 y	Birth cohort (IWS)	1: Dog 2: Cat (NS, NR) 3: Bird 4: Rodent	NR	Up to age 1 y	Self-reported	4,953	None: An adjusted model was used in analysis on dogs, but ORs were not reported.	None
Almqvist et al, 2010[21]	Australia	1997-1999	5 y	Birth cohort (CAPS) from an RCT on house dust mite avoidance and fatty acid intake for the prevention of asthma and allergic diseases	1: Dog 2: Cat	Up to age 5 y	At age 5 y	Presence at inspection or parental report of itchy rash and use of creams/seeking medical care referred to the last 12 mo	516 children with family history of asthma or wheeze and without a cat at prenatal enrollment	1: Sex, older siblings, family history of asthma, maternal smoking during pregnancy, breast-feeding, intervention group 2: Same as 1, plus environmental tobacco smoke	None
Isle of Wight cohort											
Arshad, 1991[36]	United Kingdom	1989-1990	1 y	Birth cohort (Isle of Wight)	Any pet	At age 1 y	At age 1 y	Physical examination	1,111	None	None
Arshad et al, 1993[55]	United Kingdom	1989-1990	2 y	Birth cohort (Isle of Wight)	Dog or cat	At age 2 y	At age 2 y	Physical examination	1,174	None	None
Tariq et al, 1998[54]	United Kingdom	1989-1990	4 y	Birth cohort (Isle of Wight)	Any pet	At age 4 y	At age 4 y	Physical examination	1,218	None	None
CCAAPS cohort											
Biagini Myers et al, 2010[22]	United States	2001-2003	3 y	Birth cohort (CCAAPS)	1: Dog 2: Cat	At age 6-7 mo	At age 1 y; up to age 3 y; at both ages 2 and 3 y	Parental report or positive physical examination	762 children with ≥1 atopic parent	None	None
Epstein et al, 2011[49]	United States	2001-2003	4 y	Birth cohort (CCAAPS)	1: Dog 2: Cat	Up to age 1 y (home visit)	At age 4 y	Parental report	636 children with ≥1 atopic parent	None	African Americans
COPSAC cohort											
Bisgaard, 2008[30]	Denmark and United Kingdom	1998-2001 (COPSAC) 1995-1997 (MAAS)	1 y	Two birth cohorts (COPSAC and MAAS)	1: Dog 2: Both dog and cat (not allowing to compute ORs for "dog or cat")	At birth	Up to age 1 y (hazard ratio)	Clinical examination (COPSAC) or parental report (MAAS)	379 children of mothers with asthma (COPSAC) and 503 unselected children (MAAS)	None	COPSAC and MAAS separately: cat exposure, according to filaggrin mutations

Bisgaard et al, 2009[23]	Denmark	1998-2001	3 y	Birth cohort (COPSAC)	1: Dog 2: Cat	At birth	Up to age 3 y	Physical examination or history of AD collected by the doctor. Hanifin and Rajka criteria	356 children of mothers with asthma	1: NR, based on stepwise selection 2: None	Parental sensitization to dogs
COAST cohort											
Bufford et al, 2008[47]	United States	1998-2000	3 y	Birth cohort (COAST)	1: Dog 2: Cat (NS, NR)	At birth; at age 3 y	Up to age 3 y; at age 3 y	Diagnosed by a physician (by documents or reported by a parent)	275 children with ≥1 parent with respiratory allergy and/or asthma	Ethnicity, older siblings, day care attendance, RSV infection in infancy, smoke exposure in infancy, maternal and paternal history of asthma and allergy, family income, maternal and paternal education	None
Gern et al, 2004[4]	United States	1998-2001	1 y	Birth cohort (COAST)	1: Dog 2: Cat 3: Both dog and cat (allowing to compute ORs for "dog or cat" as well)	At birth	Up to age 1 y; at age 1 y	Diagnosed by a physician (by documents or reported by a parent)	285 children with ≥1 parent with respiratory allergy or asthma	None	Dog exposure by CD14 genotype
GINI cohort											
Chen et al, 2008[32]	Germany	1995-1998 (GINI) 1997-1999 (LISA)	6 y	Birth cohorts (LISA and GINI: the latter is a 2-arm study: 1 interventional and 1 non-interventional)	Dog	Up to age 1 y; up to age 4 y	Between ages 4 and 6 y	Self-report of doctor-diagnosed AD (data on presence of symptoms of AD were also given)	2,083 (GINI1, non-intervention) and 1,632 (GINI2, intervention) children with family history of allergic disease and 2,171 unselected children (LISA)	Sex, parental history of allergy, parental education and study center: Further ORs adjusted for cat ownership and frequent contact with cats were given. Results were unaffected.	None

(Continued)

Reference	Country	Period of enrollment	Age at follow-up's end	Study design (name)	Pet exposure	Period of exposure assessment	Outcome assessment for AD	Type of diagnosis	No. of subjects	Adjustment factors	Data for subgroups
Zirngibl et al, 2002[31]	Germany	1996-1998	2 y	Birth cohort (GINI, a 2-arm study, 1 interventional and 1 non-interventional)	1: Dog 2: Cat 3: Hamster, rabbit, or guinea pig 4: Other 5: Any pet	Up to age 1 y	Up to age 1 y; between ages 1 and 2 y	Parental report of a physician's diagnosis of AD	4,578	Sex, siblings, family history of atopic diseases, parental education and nationality, living surroundings, environmental tobacco smoke, gestational age, breast-feeding, study area, and study group	None
Dunlop et al, 2006[48]	Slovak Republic	1997-1999	1 y	Birth cohort	1: Cat 2: Bird 3: Other furred pet (ie, dog, hamster, guinea pig, rabbit)	NR	Up to age 1 y	Physical examination yielding a SCORAD score >2 or physician's diagnosis reported by parents	1,326	Family history of atopy, parental education, region, residential factors, fuel used for heating and cooking, parental smoking, household exposures, pregnancy factors and infant feeding	None
Kerkhof et al, 2003[50]	The Netherlands	1996-1997	1 y	Birth cohort (PIAMA, intervention arm from a double-blind placebo-controlled trial on preventive effect of mattress covers)	1: Dog 2: Cat	NR	At 1 y (vs never AD)	Physical examination, according to the modified UK Working Party criteria	304 children of mothers with respiratory allergy or asthma	Sex, siblings, day care attendance, birth weight, gestational age, age of mother, region, parental education, parental smoking, and breast-feeding	Cat and dog exposure according to presence or absence of symptoms of AD at 3 mo

Linneberg et al, 2006[34]	Denmark	1997-2002	1.5 y	Birth cohort (DNBC)	Any pet	Up to age 1.5 y	Up to age 1.5 y	Maternal report of a physician's diagnosis of AD and recurrent rash with relevant localization	34,793	Sex older siblings, season of birth, head circumference, birth weight, day care before 6 mo, parental history of allergy, maternal age and occupation, farm residence, family income, gestational age, smoking during pregnancy, and breast-feeding	None
Lodge et al, 2012[5]	Australia	1990-1994	12 y	Birth cohort (MACS) of an RCT on infant formulas	1: Cat 2: Dog 3: Dog or cat	At birth	At age 2 y; at age 7 y; at age 12 y	Doctor consultation for AD or treatment	620 children with ≥1 parent or sibling with history of allergic diseases (359 followed until 12 y of age)	Sex, parental history of asthma, AD, hay fever and atopy, parental smoking status, household carpets, and government assistance	None
Ludvigsson et al, 2005[51]	Sweden	1997-1999	1 y	Birth cohort (ABIS)	Furred pets (ie, dog, cat, or guinea pig)	NR	Up to age 1 y; severe AD (ie, ≥3 AD episodes)	Maternal report	8,346	Siblings, preterm birth, family history of atopy, parental smoking status, maternal education, and breast-feeding	Family history of atopy
Miyake et al, 2007[52]	Japan	2001-1003	2-9 mo	Birth cohort (OMCHS)	Indoor domestic pets (ie, dog, cat, bird, or hamster)	During pregnancy	Up to age 2-9 mo	Maternal report of diagnosis or treatment for AD	865	Sex, older siblings, birth weight, parental history of atopic diseases, maternal age, gestational age, family income, parental education, and time of delivery before second survey	None

(Continued)

Reference	Country	Period of enrollment	Age at follow-up's end	Study design (name)	Pet exposure	Period of exposure assessment	Outcome assessment for AD	Type of diagnosis	No. of subjects	Adjustment factors	Data for subgroups
Nafstad et al, 2001[6]	Norway	1992-1993	4 y	Birth cohort (OBCS)	1: Dog 2: Cat 3: Any pet	At birth	Up to age 6 mo	Parental report	2,347	Sex, older siblings, birth weight, parental history of atopy, gestational age, maternal education, family income, and environmental tobacco smoke	History of atopy in parents
Phipatanakul et al, 2004[53]	United States	1994-1996	1 y	Birth cohort (HAAS)	1: Dog 2: Cat	At age 2-3 mo	Up to age 1 y	Parental report of a diagnosis of AD	498 children with parental history of asthma or allergy	1: Sex, season of birth, paternal history of AD, family income, maternal IgE positivity 2: None	None
Purvis et al, 2005[33]	New Zealand	1995-1997	3.5 y	Birth cohort (ABC, designed as a case–control study of SGA infants, with SGA and AGA infants being sampled with different probabilities of selection)	1: Dog 2: Cat	Up to age 1 y; at age 3.5 y	At age 3.5 y	Physical examination, according to the modified UK Working Party criteria	550	None	None
Roduit et al, 2011[25]	Europe (5 countries)	2002-2005	2 y	Birth cohort (PASTURE-EFRAIM)	1: Dog 2: Cat 3: Any pet	During pregnancy (third trimester)	Up to age 2 y	Parental report of a physician's diagnosis of AD	1,063	Sex, maternal history of atopic diseases, maternal smoking during pregnancy, farming status, and center	Exposure to cats by various subgroups of Toll-like receptor genotypes
Sandini et al, 2011[7]	Finland	2000-2003	5 y	Birth cohort of an RCT of probiotic use	Dog or cat	Up to age 2 y; up to age 5 y	Up to age 2 y; up to age 5 y: Results for IgE-associated AD were also given.	Physical examination	934 children with ≥1 parent with allergic disease	Allocation group (probiotics or placebo) and interaction term (treatment group*presence of dog/cat)	None

PIPO cohort

Sariachvili et al, 2007[35]	Belgium	1997-2001	1 y	Birth cohort (PIPO)	1: Dog 2: Cat	Up to age 1 y	Up to age 1 y	Parental report	976	Sex, siblings, day care attendance, parental history of atopy, maternal education and age, passive smoking of the child, pregnancy duration, active and passive smoking during pregnancy, and use of antibiotics during pregnancy and first year	None
Dom et al, 2010[24]	Belgium	1997-2001	4 y	Birth cohort (PIPO)	Dog or cat	Up to age 4 y, before or at AD onset	Up to age 4 y	Parental report	773	NR	None

Data from the same birth cohorts for the Isle of Wight cohort,[36,54,55] the COPSAC cohort,[23,30] the COAST cohort,[4,47] the CCAAPS cohort,[22,49] and the PIPO cohort.[24,35] The GINI cohort[31,32] had partially overlapping subjects.

AD, Atopic dermatitis; *AGA*, appropriate for gestational age; *NR*, not reported; *NS*, not significant; *RCT*, randomized clinical trial; *RSV*, respiratory syncytial virus; *SGA*, small for gestational age.