

Systematic review: Exposure to pets and risk of asthma and asthma-like symptoms

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Background: Studies of exposure to pets and risk of asthma have yielded conflicting results.

Objectives: We performed a systematic review to synthesize the evidence of the effect of exposure to pets in the home on the risk of asthma and asthma-related symptoms. We also assessed differences between the studies as sources of heterogeneity of the results.

Methods: We conducted a MEDLINE search (until the end of 1999) using the following boolean search command: (asthma[all] OR wheez*[all]) AND (domestic animal*[all] OR pets[all]). The outcome was limited to either diagnosis of asthma or the symptom of wheezing. The exposure of interest was domestic animals in the home. Appropriate temporal relationship was defined as present in studies with either pet keeping within the first 2 years of life, in the past, or exposure to pets preceding the outcome.

Results: Thirty-two of the 217 retrieved articles fulfilled the eligibility criteria. Inappropriate time sequence of the exposure and outcome information was an important source of heterogeneity and an indication of potential selection bias. Therefore we analyzed studies focusing on early exposure or ensuring appropriate temporal sequence. The pooled risk estimates for both asthma (fixed-effects odds ratio, 1.11; 95% CI, 0.98-1.25; heterogeneity, $P = .04$; random-effects odds ratio, 1.09; 95% CI, 0.89-1.34) and wheezing (fixed-effects odds ratio, 1.19; 95% CI, 1.05-1.35; heterogeneity, $P = .03$; random-effects odds ratio, 1.17; 95% CI, 0.95-1.44) indicated a small effect, which was limited to studies with a median study population age of over 6 years (fixed-effects odds ratio, 1.19; 95% CI, 1.02-1.40; heterogeneity, $P = .04$; random-effects odds ratio, 1.15; 95% CI, 0.86-1.56; fixed-effects odds ratio, 1.29; 95% CI, 1.12-1.48; heterogeneity, $P = .31$). In younger children the harmful effect disappeared for wheezing (odds ratio, 0.80; 95% CI, 0.59-1.08; $P = .38$).

Conclusion: Exposure to pets appears to increase the risk of asthma and wheezing in older children. The observed lower risk among exposed than among unexposed young children is consistent with a protective effect in this age group but could also be explained by selection bias. (*J Allergy Clin Immunol* 2001;107:455-60.)

Key words: *Pets, asthma, wheeze, domestic animal, meta-analysis, selection bias*

Indoor allergens from dust mites,¹⁻² cockroaches,³ and pets⁴ have been implicated as potential causes of asthma, but it has been difficult to separate their role as causative factors versus aggravators of symptoms. Sensitization to allergen has been shown to be one of the strongest determinants of asthma, and individuals with a predisposition for atopy are at higher risk.⁵

The association between exposure to pets and the risk of asthma has been difficult to quantify because of issues of study design. Selection bias could be a major source of error. Studies have shown that parents of asthmatic children are more likely to remove pets from the home, biasing the results of prevalence studies.^{6,7} Ahlbom et al⁴ concluded that pet exposure is a strong risk factor in sensitized individuals and recommended that families with an atopic child avoid getting a pet until the child is 2 years old. However, recent literature, taking into account selection mechanisms, has suggested that early exposure to pets may provide a protective effect for children.⁸ The purpose of this systematic review is to synthesize the evidence of the effect of exposure to pets in the home on the risk of asthma and asthma-related symptoms and assess the influence of differences in study design on the results obtained.

METHODS

Selection criteria and data collection

We performed a search of the MEDLINE database using the following boolean search command: (asthma[all] OR wheez*[all]) AND (domestic animal*[all] OR pets[all]).

From this list, we chose only cross-sectional, case-control, or cohort studies, excluding letters, comments, reviews, and ecological studies. The outcome was limited to either diagnosis of asthma, with or without verification of medical records, or the symptom of wheezing. The exposure of interest was domestic animals in the home, assessing exposure to pets through questionnaire or home visit. We did not permit the use of a skin prick test to determine sensitization as the only measure of exposure because sensitization could be influenced by individual characteristics that are related to the propensity for asthma. There was no criterion for the type of animal so long as the pet was kept or allowed to be in the home. The cutoff date for publication was limited by the depth of the MEDLINE database (ie, 1966 through the end of December 1999). The following languages were included: English, French, Spanish, German, and the Scandinavian languages. Appropriate temporal sequence was defined as present in studies with either exposure in the first 2 years of life, exposure in the past, or, in the case of cohort studies, exposure preceding the development of symptoms. For studies of adult populations, early exposure included exposure to pets as a child. In cases in which multiple outcomes were presented, all data that fit the outcome criteria were included. Similarly, we included both early-life and current exposures when applicable.

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Statistical methods

We calculated pooled effect estimates by using both the fixed- and random-effects models. The fixed-effects model was calculated by using the Mantel-Haenszel method, with inverse variances of individual effect estimates as weights.⁹ The random-effects model was calculated by using the method of DerSimonian and Laird.¹⁰ Random-effects estimates tend to be more conservative because they take into account a between-study component of variability in addition to within-study sampling variability. The natural log and standard error of the natural log of effect measures were calculated from the raw data or CIs presented, depending on availability. The authors of studies that presented only qualitative results or lacked CIs were contacted to obtain the data. Fixed- and random-effects models were run on Stata 6.0¹¹ by using the "meta" command.¹² Heterogeneity among studies was tested for by using the Q statistic and χ^2 distribution. Regression was performed by using the "metareg" module.¹³ A funnel plot was created, and publication bias was tested for with the Begg test of the correlation between effect estimates and their variance¹⁴ by using the "metabias" module.¹⁵ In the stratified analyses, where one study could potentially contribute multiple estimates to a single stratum, only one was selected on the basis of the following criteria: asthma over wheezing and cumulative incidence (lifetime) over current prevalence.

RESULTS

Selected studies

The MEDLINE search retrieved 217 articles to which selection criteria were applied. After searching the abstracts, full text, or both of the studies, 32 studies were included in the analysis. Reasons for removal included failure of exposure or outcome to meet the aforementioned criteria, presence of only data for select subpopulations, lack of an appropriate control group (eg, severity of symptoms in asthmatic subjects), and presentation of inconsistent data. We contacted authors of 4 of the studies to obtain complete data and obtained additional information from one author.

Design characteristics

Of the 32 studies included in this analysis, all but 3 were published in the 1990s.¹⁶⁻¹⁸ Furthermore, 9 of the articles were published in 1999.^{8,19-26} Twenty (63%) of the studies were cross-sectional,^{6,7,16,18-21,23-35} whereas 6 were cohort studies,^{8,17,36-39} and 6 were case-control studies.^{22,40-44} The largest number of studies (5) was performed in Great Britain,^{22,36-38,41} followed by the United States^{16,22,24,43} and Sweden.^{8,19,21,42} with 4 studies each. Five of the 32 studies focused exclusively on furred pets,^{21,23,37,39,41} whereas 4 others looked at cats, dogs, or both exclusively.^{8,17,19,42} The remaining studies included pets ranging from cats and dogs to birds, camels, goats, and reptiles, depending on geographic location and cultural customs. Twelve of the 32 studies had solely asthma as the outcome* on the basis of a doctor's diagnosis, as recalled by parents or medical records, or the judgment of the investigator. Ten studies used only the symptom of wheezing as the outcome,[†] whereas 10 others evaluated both outcomes.[‡] Of the 32 studies, 13 included

adjustments or matching for various potential confounders.* These adjustments ranged from demographic factors (race, age, and region) to environmental factors (environmental tobacco smoke and indoor air pollutants) to genetic factors (family history).

Exposure and outcome measures and selection bias

It has been demonstrated that individuals with symptoms of asthma tend to remove pets from the home as a means of controlling their condition.^{6,7} This tendency for asthmatic subjects to remove the exposure may mask or even reverse an association in a cross-sectional analysis and should be regarded as a major threat to validity. Fairly simple ways to reduce the effect of this selection bias include asking about early exposure to pets or asking about motivation for removing pets from the home. For these reasons, the studies in this analysis were graded on their ability to ensure the appropriate temporal sequence. Of the 32 studies, 12 dealt with this issue in the analysis, either by assessing exposure in the past or, in the case of cohort studies, by assessing exposure before disease development.[†] Given a true effect of pet exposure, these studies would be expected to have risk estimates further away from the null value.

Table I shows a stratified analysis of studies that ensured an appropriate temporal relationship versus studies with current exposure and outcome measures of cumulative incidence and current prevalence. Because early childhood asthma or asthma-like symptoms are capable of going into remission, and it is estimated that close to 60% of cases of wheezing may do so,⁴⁵ then the most appropriate outcome measure for studying this association may be cumulative incidence (or life-time prevalence). This association resulted in a fixed-effects model estimate of 1.08 for studies with the appropriate temporal relationship (95% CI, 0.94-1.24; heterogeneity, $P < .01$; random-effects pooled estimate, 1.02; 95% CI, 0.79-1.32). The association between exposure to pets and current prevalence was slightly larger (fixed-effects pooled estimate, 1.13; 95% CI, 0.98-1.31; random-effects, 1.11; 95% CI, 0.85-1.45), with less heterogeneity ($P = .04$). The associations for current exposure showed much greater heterogeneity ($P < .001$), as would be expected because of the varying effects of selection bias. The associations for current exposure were similar in the fixed-effects model (current prevalence, 1.09; 95% CI, 1.03-1.14; lifetime cumulative incidence, 1.09; 95% CI, 0.99-1.20). In the random-effects model the pooled estimate for current prevalence remained significant (1.37; 95% CI, 1.07-1.75; lifetime cumulative incidence, 1.09; 95% CI, 0.77-1.54). However, the use of cumulative incidence is inappropriate in studying the effect of current exposure unless current exposure can be seen as an unbiased surrogate for early exposure.

*References 8, 17-19, 21, 22, 32, 35, 36, 40, 42, 43.

†References 16, 23, 26, 28, 30, 31, 38, 39, 41, 44.

‡References 6, 7, 20, 24, 25, 27, 29, 33, 34, 37.

*References 18, 20, 23-27, 37, 39, 40-43.

†References 6-8, 17, 19, 26, 30, 36, 38, 39, 41, 42.

TABLE I. Pooled measure of effect and its heterogeneity according to the time frame of exposure and outcome

Time of exposure	Outcome definition	Fixed-effects model	Random-effects model	Heterogeneity	
		OR (95% CI)	OR (95% CI)	Q (n)	P value
Preceding disease	Lifetime	1.08 (0.94-1.24)	1.02 (0.79-1.32)	17.6 (7)	<.01
Preceding disease	Current*	1.13 (0.98-1.31)	1.11 (0.85-1.45)	10.1 (5)	.04
Current	Lifetime	1.09 (0.99-1.20)	1.09 (0.77-1.54)	106 (10)	.001
Current	Current	1.09† (1.03-1.14)	1.37† (1.07-1.75)	154 (13)	.001

Asthma and wheezing are combined.

OR, Odds ratio.

*Current prevalence includes the previous 12 months.

†Significance, $P = .05$.

TABLE II. Relation between exposure to pets and the risk of asthma by median age of study population

Stratification	Fixed-effects model	Random-effects model	Heterogeneity	
	OR (95% CI)	OR (95% CI)	Q (n)	P value
No (single stratum)	1.11 (0.98-1.25)	1.09 (0.89-1.34)	13.5 (7)	.04
Two strata				
≤6 y	0.98 (0.80-1.20)	0.99 (0.77-1.27)	2.77 (3)	.25
>6 y	1.19* (1.02-1.40)	1.15 (0.86-1.56)	8.39 (4)	.04
			Model = 11.2	Model $P = .05$

$P = .10$ for comparison between single-stratum and two-strata groups.

OR, Odds ratio.

*Significance, $P < .05$.

TABLE III. Relation between exposure to pets and the risk of wheezing by median age of study population

Stratification	Fixed-effects model	Random-effects model	Heterogeneity	
	OR (95% CI)	OR (95% CI)	Q (n)	P value
No (single stratum)	1.19* (1.05-1.35)	1.17 (0.95-1.44)	12.3 (6)	.03
Two strata				
≤6 y	0.80 (0.59-1.08)	0.80 (0.59-1.08)	0.79 (2)	.38
>6 y	1.29* (1.12-1.48)	1.30* (1.11-1.52)	3.55 (4)	.31
			Model = 4.34	Model $P = .36$

$P = .005$ for comparison between single-stratum and two-stratum groups.

OR, Odds ratio.

*Significance, $P < .05$.

Early-life exposure

In the subsequent analyses we focused on studies that have ensured the appropriate temporal sequence (cross-sectional and case-control studies with past or early exposure and cohort studies). Table II provides the results of a stratified analysis of the association between exposure to pets and asthma. The fixed-effects model produced a non-significant 11% increase in risk (9% for random effects), with a heterogeneity P value of .04. We assessed the potential role of the age of the study population in introducing heterogeneity. The age of 6 years was chosen as a cutoff point because of a hypothesized change in the distribution of incidence at this age. Studies with a younger population showed a pooled effect measure of 0.98 (95% CI, 0.80-1.20) compared with a pooled effect estimate for the older populations of 1.19 (95% CI, 1.02-1.40; random-effects, 1.15; 95% CI, 0.86-1.56). Stratification on median age did not decrease heterogeneity ($P = .05$).

Table III provides similar pooled risk estimates for the outcome of wheezing. The overall pooled effect measure

is more pronounced than that for asthma, although still with a great deal of heterogeneity ($P = .03$). Analysis of the younger populations (≤6 years) showed a fixed-effects estimate of 0.80 (95% CI, 0.59-1.08), whereas slightly older populations (>6 years) produced the opposite effect (fixed-effects pooled estimate, 1.29; 95% CI, 1.12-1.48). The use of this model including age resulted in a reduction of heterogeneity ($P = .36$). In both stratified analyses, the younger study populations tended to be cohort studies, and therefore it is difficult to separate the influence of longitudinal study design from the possibility of effect modification by age. We assessed geographic region, timing of the study, and adjustment for socioeconomic status and family history of allergy as potential sources of heterogeneity; however, none of these factors could sufficiently explain the heterogeneity.

Publication bias

To assess the potential for publication bias, a funnel plot was created and is presented in Fig 1. As a result of

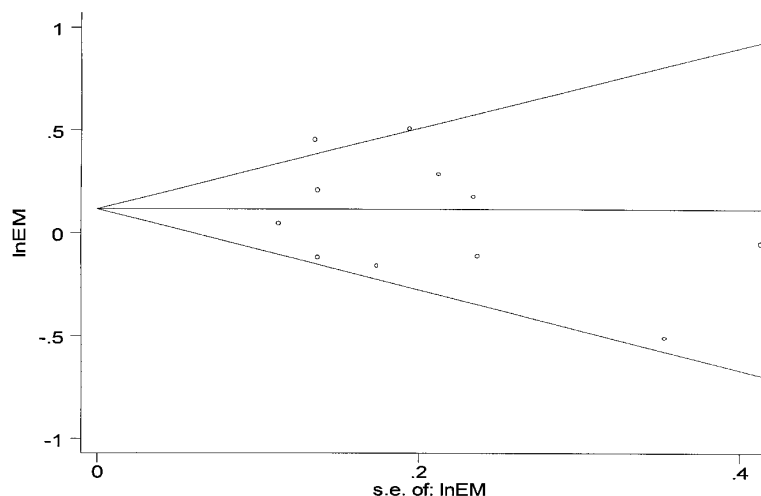


FIG 1. Begg funnel plot for exposure to pets and asthma or wheezing. *lnEM*, Natural log of the effect measure.

random variability, studies that attempt to measure the same association may result in estimates that differ from the underlying *true* value to various degrees, depending on sample size. This distribution of estimates should converge to the true value as the sample size increases and standard error decreases. In the absence of publication bias, we should see a fanning out in both directions as the standard error increases, as shown in Fig 1. If publication bias were a concern (meaning that studies with significant results were more likely to be collected), we would expect a portion of the distribution to be missing. No such pattern was observed in Fig 1.

DISCUSSION

The present analysis indicates that problems related to study design may have compromised some previous studies of the relation between exposure to pets and asthma or related symptoms. Our results showed that restriction to analyses of studies that took into account the potential for bias resulted in a reduction in heterogeneity between studies. Although it is not possible to precisely quantify the risks to children associated with exposure to pets, this analysis showed a slightly elevated risk. This increase in risk appeared stronger for the outcome of wheezing versus asthma, however, with substantial heterogeneity.

There are several potential weaknesses to the meta-analysis. First, it becomes apparent that a great deal of heterogeneity exists among the reported estimates in the association between exposure to domestic animals and the risk of asthma or asthma-related symptoms. It has become common practice to routinely apply the random-effects model as a conservative solution to the heterogeneity problem. We agree with Poole and Greenland⁴⁶ that differences between the studies should primarily be assessed as an explanation for the heterogeneity of the effect measure. In a thorough analysis, the only study characteristics that could explain a portion of the heterogeneity were age of the study population and type of study.

The use of biologically meaningful timing of exposure and outcome influenced the risk estimates. Studies that dealt with appropriate temporality between exposure and outcome tended to measure early-life exposure, whereas the remaining studies assessed current exposure. These differences, as well as the use of lifetime versus current asthma, resulted in different measures of effect. In the previous studies, use of current exposure has been shown to introduce a selection bias. In the present pooled analyses, inclusion of studies making use of current exposure increased the heterogeneity, which is consistent with the varying degrees of selection bias present in those studies. Even with the use of early-life exposure, many studies did not assess avoidance as a result of family history, which, as another source of selection bias, could lead to underestimation of effects. Furthermore, not all of the studies that took into account these selection factors attempted to adjust the results for potential confounders.

The type, duration, and intensity of exposure could introduce more heterogeneity. Only one study attempted to estimate the cumulative exposure by crudely determining the amount of time spent in the presence of pets.⁴² The exposure to pet allergens is influenced by both the type of pet in the home and geographic and cultural customs associated with the role of pets in society. In some cultures children may sleep with or near pets, whereas in other areas they are kept mainly out of the home. A study by Roost et al⁴⁷ showed that keeping cats outdoors was not significantly associated with an increased risk of sensitization, whereas keeping them indoors was related. The type of pet may also differ by geography and culture. Intensity and duration of exposure could only be ascertained through intensive monitoring and recording measures, and therefore exposure misclassification may exist. The use of the skin prick test as an exposure measure was not allowed because sensitization could be influenced by individual characteristics that are related to the propensity for asthma. Sensitization has been shown to be strongly associated with asth-

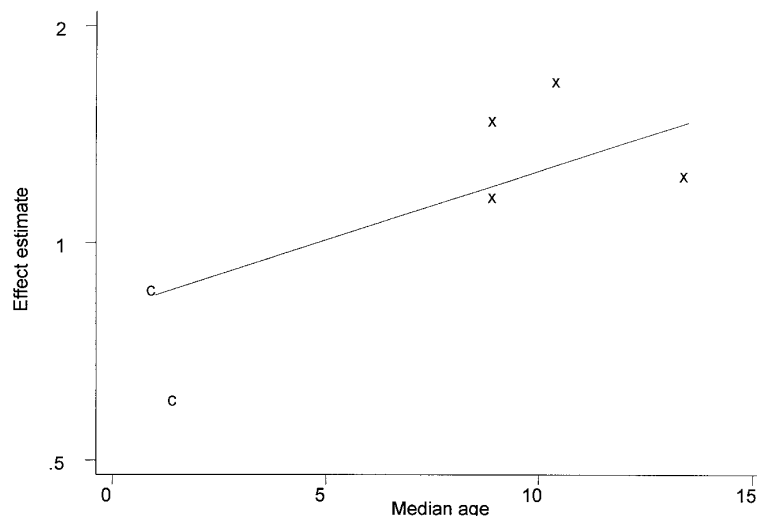


FIG 2. Plot of the effect estimate by median age of study population and type of study for studies of exposure to pets and risk of wheezing. Regression coefficient for median age is 0.044 (95% CI, 0.006-0.082). C, Cohort study; X, other.

ma,^{19,20} but the relationship between exposure and sensitization has been harder to define. In fact, recent literature has shown a negative association between early exposure to cats and sensitization later in life.⁴⁷ On the other hand, it is plausible that sensitization itself indicates susceptibility to the effects of exposure on asthma.

The choice of outcome measure (cumulative incidence versus current prevalence) will also have an effect on the result. Furthermore, this effect is related to the time frame of exposure. Because asthma is a disease that is capable of going into remission,⁴⁸ a measure of point prevalence may not capture all children who had the disease. When early exposure is used, the more appropriate outcome measure would be lifetime cumulative incidence. This will quantify the risk up to a certain age, whereas current prevalence may merely be an underestimation, excluding those who recovered. Conversely, if exposure to pets alters the duration of disease, biologically or through removal and remission, cumulative incidence may not be relevant for describing the risk of asthma at a particular age.

The stratified analysis by age of assessment may suffer from the fact that because the median value of the age range was chosen, many of the populations would overlap in terms of age distribution. Furthermore, the differences in strength of association may be due in part to the fact that cohort studies tended to have short follow-up times and thus younger populations. However, although cohort studies are often perceived to be of stronger validity, there is little reason to expect an effect on the basis of study design in this case. The analytic focus on studies with the appropriate temporal relationship was meant to minimize selection bias caused by removal of pets. Therefore the remaining differences reflected by study design would more likely be due to information bias, possibly relating to issues of recall. However, there is little reason to believe that individuals would have trouble recalling pet

ownership, and in at least one cohort, early pet exposure was assessed at the conclusion of follow-up.⁸

Further analysis showed a statistically significant linear association between age of assessment and strength of association in studies looking at exposure to pets and wheezing (Fig 2). As the median age of the study populations increased, the strength of the association observed in the study increased as well. A similar pattern was seen for publication year as well, and therefore it was not possible to separate its effect from a potential age effect. This relationship could be due to a refocus on particular age groups over time or the results of cohort studies publishing cross-sectional results over time. Nonetheless, studies of individuals in adulthood tend to look at pet exposure as a child, whereas studies of young children tend to get detailed information on exposure within the first year of life. Thus the timing of outcome can be seen as a surrogate for timing and duration of exposure. As a result of this phenomenon, there may be a negative association seen with very early exposure to pets caused either by vaccination-like effects or a selection bias associated with family history of allergy. Studies in which exposure is assessed shortly before outcome may also show a protective effect, most likely caused by selection bias as a result of removal of exposure. It is the time in between these two extremes when a positive association would be seen. Thus timing of exposure and outcome may be seen as potential sources of heterogeneity, either on the basis of biologic differences in effect or compromised validity in some studies.

In conclusion, exposure to pets appears to slightly increase the risk of asthma and wheezing in older children. The observed lower risk of wheezing among exposed than among unexposed young children is consistent with a protective effect in this age group but could also be explained by selection bias (avoidance) related to family history of allergy. Thus it remains possible that a combination of factors in the home environment, including changing habits

with respect to keeping pets, has played a role in the reported increases of asthma in recent years. It is clear that the body of literature on this topic suffers from numerous design flaws. As a whole, very few studies exist that take into account the selection mechanisms, potential for confounding, and appropriate exposure-outcome time frame for the hypothesis being tested. The ideal study would consist of a longitudinal design in which disease status and exposure to pets are assessed at multiple time points.

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