

Effect of Exposure to Cats and Dogs on the Risk of Asthma and Allergic Rhinitis: A Systematic Review and Meta-analysis

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Abstract

Background: Controversies persist regarding whether exposure to cat or dog increases the risk of asthma and allergic rhinitis.

Objective: This meta-analysis aimed to assess the associations between exposure to cats or dogs and the development of asthma and allergic rhinitis.

Methods: A systematic review was performed to identify case-control and cohort studies before May 2019, evaluating the association between exposure to cats and dogs and the risk of asthma and rhinitis. The risk of bias was assessed using the Newcastle–Ottawa Scale. The odds ratios (ORs) and risk ratios (RRs) were pooled for case-control and cohort studies, respectively. Subgroup analyses were performed on prespecified study-level characteristics.

Results: The meta-analysis of 34 cohort studies showed a protective role of exposure to cats [RR: 0.88, 95% confidence interval (CI): 0.77–0.99] or dogs (RR: 0.85, 95% CI: 0.73–0.97) in the development of asthma. The subgroup analysis of birth cohort (RR: 0.74, 95% CI: 0.56–0.93) and children population (RR: 0.83, 95% CI: 0.70–0.96) also suggested a favorable role of exposure to dogs in the development of asthma. Pooled evidence from 13 case-control studies indicated no significant impact of cats (OR: 1.66, 95% CI: 0.39–2.94) and dogs (OR: 1.22, 95% CI: 0.92–1.52) on the development of asthma. A pooled analysis of five cohort studies showed a favorable effect of exposure to cats (RR: 0.60, 95% CI: 0.33–0.86) or dogs (RR: 0.68, 95% CI 0.44–0.90) on the development of allergic rhinitis.

Conclusion: The findings indicated a protective effect of exposure to cats and dogs, especially ownership, on the development of asthma and allergic rhinitis.

Keywords

allergic, rhinitis, asthma, cat, dog, meta-analysis, risk, systematic review, association, exposure

Introduction

Asthma is characterized by recurrent but reversible bronchial obstruction and variable airflow limitation. The first symptoms usually start during childhood.^{1,2} Allergic rhinitis is characterized by pruritus, sneezing, rhinorrhea, and nasal congestion, and is caused by hypersensitivity responses similar to those in allergic asthma.³ Rhinitis and asthma share common pathogenesis, including increased bronchial hyperresponsiveness and reactivity to a variety of stimuli, a predominance of T-helper type 2 inflammation, and tissue eosinophilia.⁴ A growing body of evidence suggests that environmental exposures have a significant impact on the risk of allergic

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sensitization, especially those during the first months of life.⁵ Asthma is the most prevalent chronic respiratory disease worldwide, with an increase in the prevalence of 12.6% from 1990 to 2015.⁶ The prevalence of rhinitis has been estimated to be approximately 10%–30% in adults⁷ and up to 40% in children.^{7,8} Countries with an initially low prevalence of rhinitis showed sharp increases in recent decades.⁹

The domestic house cat (*Felis domesticus*) and dog (*Canis lupus familiaris*) are domesticated, carnivorous mammals valued for their companionship, but they are the pets that are the most commonly involved in allergic diseases.¹⁰ The frequency of ownership of cats and dogs in Europe ranges from 7.2% to 35% and from 5.4% to 35%, respectively.¹¹ Current guidelines across the globe did not reach consensus with regard to cat and dog keeping and asthma management.^{12–15} Several meta-analyses and systematic reviews tried to address the association between pet keeping and the development of asthma.^{16–19} Takkouche et al. revealed that exposure to cats exerts a slight preventive effect on asthma, while exposure to dogs slightly increases the risk of asthma.²⁰ On the other hand, exposure to cats and dogs has no impact on the development of rhinitis.^{20–22} Nevertheless, these studies did not distinguish between the effect of exposure to cat or dog allergen vs. cat or dog ownership, and the effect of exposure during early childhood vs. later.²³ Apelberg et al. tried to determine the effect of exposure to pets at home on the risk of asthma and asthma-related symptoms,¹⁷ but exposure to different pets might have different effects on the risk of asthma.

The effect of environmental exposures can either increase or decrease the risk of developing asthma²⁴ due to the windows of immune development.²⁵ Lodge et al. revealed that perinatal exposure to pets, especially dogs, might reduce the development of asthma.¹⁹ Nevertheless, these results remain conflicting. The present study adds on previous knowledge on the association between exposure to cats or dogs and asthma or rhinitis and updates the evidence based on the most recently published studies.

Methods

Systematic Literature Search

The study was performed according to the Meta-analysis of Observational Studies in Epidemiology guidelines.²⁶ Medline (via PubMed), Web of Science, and Embase were searched for published case-control and cohort studies investigating the association between exposure to cats or dogs and asthma or rhinitis from 1966 to May 2019. Key terms, including asthma OR rhinitis AND cat OR dog AND case-control OR retrospective

OR cohort OR follow-up OR prospective, were used. The search strategy was augmented by reviewing the bibliographies of retrieved studies and even reviews. Two independent investigators performed the literature search and resolved the disagreements by consensus decision.

Inclusion Criteria

Studies meeting the following criteria were included: (a) Patients: diagnosis of asthma or allergic rhinitis, with or without verification of medical records; (b) exposure: ownership of cats or dogs or exposure to cat or dog allergen; (c) Outcome: having extractable data to estimate the relative risk for case-control study and longitudinal study; and (d) Study design: case-control or cohort studies. The study with the most suitable data for the aim was included if more than one study was published from the same population data.

The exclusion criteria were: (a) other atopic diseases; (b) single symptom of asthma or rhinitis, and no diagnosis of asthma or rhinitis; (c) studies dealing with sensitization to pets; (d) studies reported in a language other than English; and (e) cross-sectional study but not case-control study. Three researchers independently screened all records according to the inclusion and exclusion criteria. Any inconsistencies were resolved by discussion among the three authors.

Data Extraction and Quality Assessment

Two investigators independently reviewed the full text of the eligible studies and extracted information into a standardized electronic database, including study name, year of publication, study design, study population (children or adult), exposure (ownership or allergen), cohort (birth or nonbirth), and so forth. The primary outcome was the risk estimate evaluating the association between exposure to cats or dogs and the development of asthma or rhinitis. The latest data were included in the analysis if they were reported in more than one study. The estimates of exposure to cats or dogs were considered independently if they were presented in the same study. Inconsistency was resolved by double-checking the information in original studies.

The methodological quality of the included case-control and cohort studies was quantitatively evaluated according to the Newcastle–Ottawa Scale (NOS) in terms of selection (maximal score of 4), comparability (maximal score of 2), and outcome (maximal score of 3).²⁷ Studies scoring greater than 6 were defined as high quality.

Statistical Analysis

Odds ratios (ORs) for case-control studies and risk ratios (RRs) for cohort studies with their corresponding 95% confidence intervals (CIs) were used to assess the association between exposure to cats or dogs and asthma. Heterogeneity was examined using the Cochran's Q statistic, and a P value of less than 0.01 was considered significant. The I^2 test was also used to quantify heterogeneity (ranging from 0% to 100%). $P < 0.01$ for the Q -test or $I^2 > 50\%$ indicated the existence of heterogeneity across the studies. A random-effects model (DerSimonian–Laird method) was used if marked heterogeneity was found. A subgroup analysis was performed to explore the heterogeneity according to study design, study population, exposure, and cohort population (birth or nonbirth cohort). Funnel plot and Egger's test were used to detect publication bias.^{28,29} All statistical analyses in this meta-analysis were conducted using Stata version 12.0 (Stata Corp, TX, USA).

Results

Characteristics of Included Studies

A total of 3205 potential references were identified from the search of published studies. From them, 1746

duplicate references were excluded, 1127 references were excluded after reviewing titles and abstracts because they did not address the exposure or outcomes, and 307 studies were excluded for not fulfilling the inclusion criteria.

Finally, 49 studies were included in the meta-analysis.^{21,22,30–76} For asthma, 34 of 47 included studies were prospective cohort studies, while 13 of 47 included studies were cross-sectional studies. One case-control study and five cohort studies were included for allergic rhinitis. All of the included studies were of high quality, according to the NOS (Figure 1).

Risk of Asthma and Exposure to Cats

A total of 38 studies addressed the relationship between exposure to dogs and asthma, including 12 case-control studies (Table S1) and 26 cohort studies (Table S2). Pooled estimates from case-control studies indicated a negative association between cat exposure and the development of asthma (OR: 1.66, 95% CI: 0.39–2.94) with significant heterogeneity ($P < 0.001$) (Figure 2) and publication bias ($P = 0.003$) (Figure S1). A stratified analysis by population and exposure suggested similar outcomes (OR for children population: 1.71, 95% CI: 0.33–3.09; OR for adult population: 1.32, 95% CI: –0.46 to 3.10;

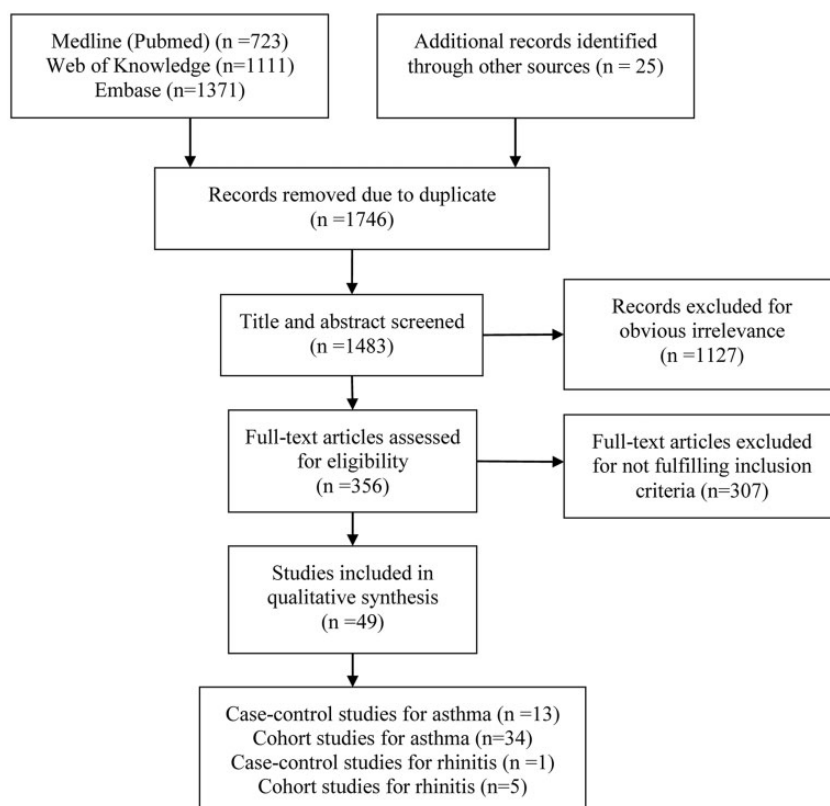


Figure 1. A flow chart of the literature search.

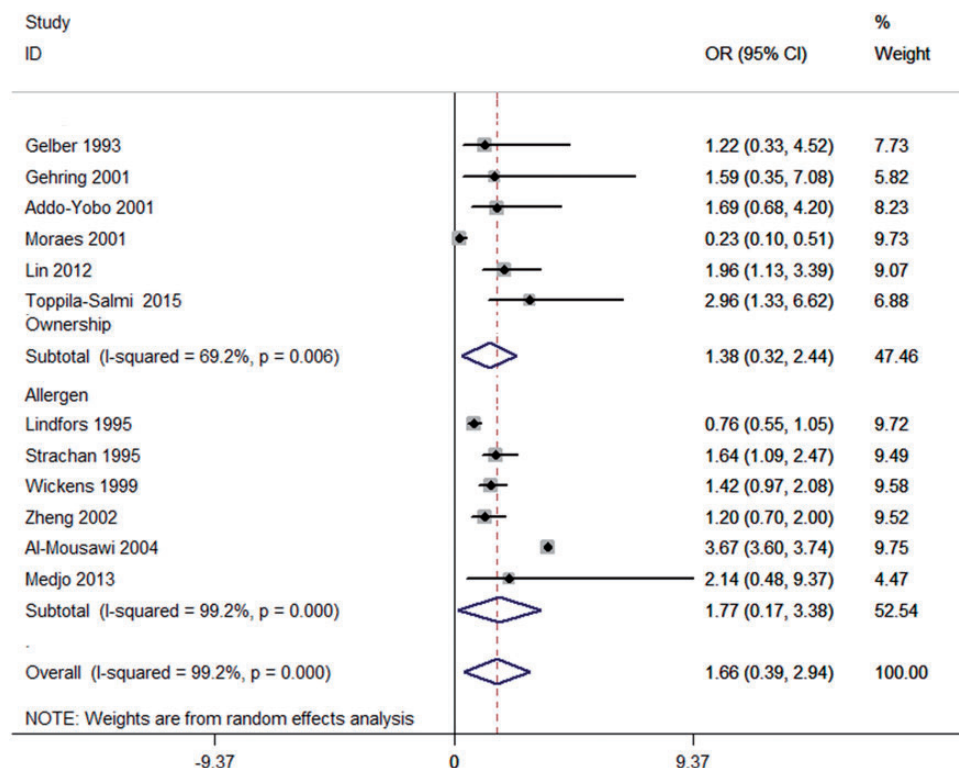


Figure 2. A meta-analysis of case-control studies on the exposure to cats and the risk of asthma categorized by exposure.

OR for ownership of cat 1.78, 95% CI: 0.17–3.38; OR for cat allergen: 1.38, 95% CI: 0.32–2.44) (Table 1).

Compared with case-control studies, pooled estimates from cohort studies indicated a protective effect of exposure to cats on the development of asthma (RR: 0.88, 95% CI: 0.77–0.99) with significant heterogeneity ($P < 0.001$) and without publication bias ($P = 0.452$) (Figures 3 and S2). The subgroup analysis of exposure also showed a protective effect of cat ownership on the development of asthma (RR: 0.83, 95% CI: 0.69–0.97), but a non-significant effect of cat allergen on the risk of asthma (RR: 0.99, 95% CI: 0.76–1.23). The stratified analysis revealed a non-significant effect of cat exposure on the development of asthma in the adult population (RR: 0.97, 95% CI: 0.88–1.06), children population (RR: 0.88, 95% CI: 0.74–1.01), birth cohort (RR: 0.85, 95% CI: 0.68–1.02), and nonbirth cohort (RR: 0.91, 95% CI: 0.75–1.07) (Table 1).

Risk of Asthma and Exposure to Dogs

Thirty studies, including seven case-control studies and 23 cohort studies, focused on the influence of exposure to dogs on the development of asthma. Overall estimates from case-control studies indicated a negative association between exposure to dogs and the development of asthma (OR: 1.22, 95% CI: 0.92–1.52) without heterogeneity ($P = 0.238$) and publication bias ($P = 0.155$)

(Figures 4 and S3). The subgroup analysis revealed an increased risk of asthma for dog allergen (OR: 2.14, 95% CI: 1.19–3.09), but not for dog ownership (OR: 1.10, 95% CI: 0.88–1.32) (Table 1).

Compared with case-control studies, pooled estimates from cohort studies suggested a protective effect of exposure to dogs on the development of asthma (RR: 0.85, 95% CI: 0.73–0.97) with marked heterogeneity ($P < 0.001$) and without publication bias ($P = 0.804$) (Figures 5 and S4). The subgroup analysis suggested an increased risk of asthma in the adult population exposed to dogs (RR: 1.11, 95% CI: 1.01–1.21), but a protective role of this exposure on the development of asthma in the children population (RR: 0.83, 95% CI: 0.70–0.96). The stratified analysis according to the exposure showed a favorable effect of dog ownership (RR: 0.86, 95% CI: 0.73–0.99), but no significant effect of dog allergen (RR: 0.83, 95% CI: 0.45–1.20), on the development of asthma. Similarly, a significant protective effect of dog exposure was identified in the birth cohort (RR: 0.74, 9% CI: 0.56–0.93), but a non-significant effect in the nonbirth cohort (RR: 0.95, 95% CI: 0.81–1.08) (Table 1).

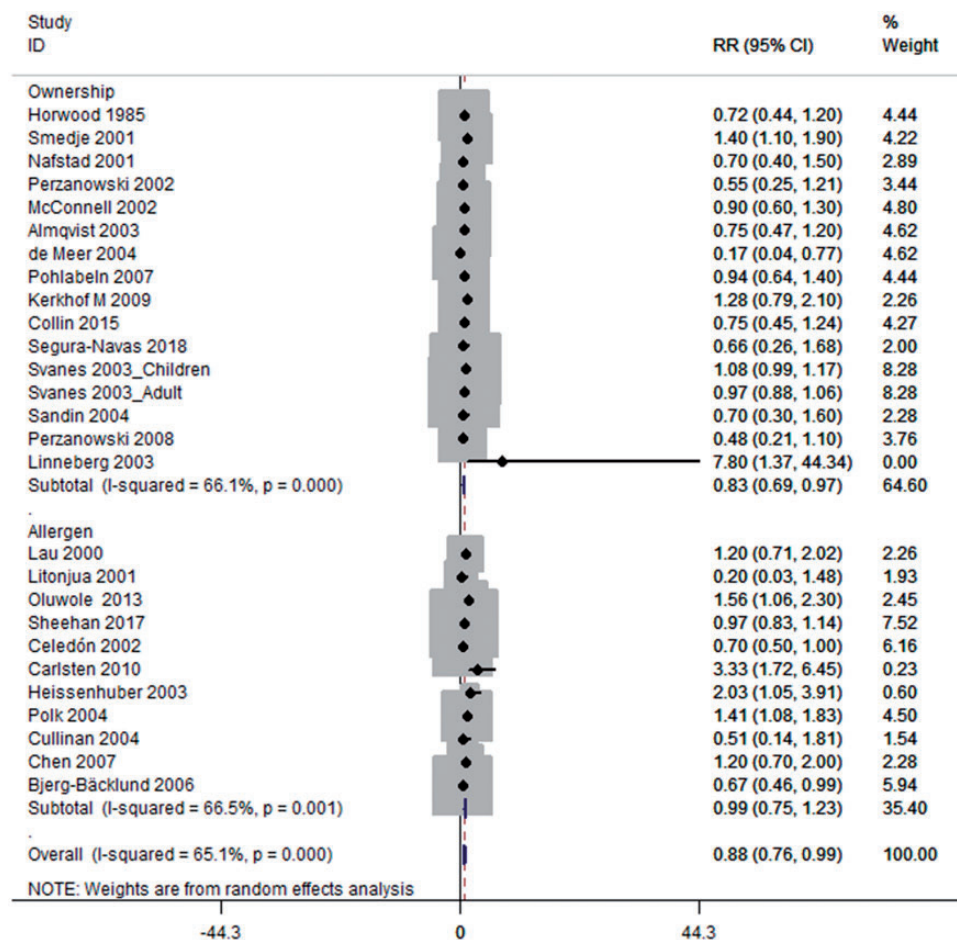
Risk of Allergic Rhinitis and Exposure to Cats or Dogs

The pooled analysis of five cohort studies revealed a protective effect of cat exposure (RR: 0.60, 95%

Table 1. Meta-analysis Summary Statistics for Risks of Asthma According to Exposure to Cat and Dog.

	Cat				Dog			
	No of studies	Fixed effect model	Random effect model	I-squared (%)	No of studies	Fixed effect model	Random effect model	I-squared (%)
Case-control study								
All	12	3.08(3.02–3.15)	1.66(0.39–2.94)	99	7	1.16(0.94–1.37)	1.22(0.92–1.52)	25
Adult	2	1.32(–0.46–3.10)	1.32(–0.46–3.10)	0	–	–	–	–
Children	10	3.09(3.02–3.15)	1.71(0.33–3.09)	99	7	1.16(0.94–1.37)	1.22(0.92–1.52)	25
Allergen	6	0.33(0.13–0.53)	1.38(0.32–2.44)	69	3	2.14(1.19–3.09)	2.14(1.19–3.09)	0
Ownership	6	3.39(3.32–3.46)	1.78(0.17–3.38)	99	4	1.10(0.88–1.32)	1.10(0.88–1.32)	0
Longitudinal study								
All	26	0.96(0.91–1.01)	0.88(0.77–0.99)	65	23	0.93(0.89–0.97)	0.85(0.73–0.97)	72
Adult	3 ^a	0.97(0.88–1.06)	0.97(0.88–1.06)	0	3 ^a	1.11(1.01–1.21)	1.11(1.01–1.21)	0
Children	24 ^a	0.95(0.89–1.01)	0.88(0.74–1.01)	69	21 ^a	0.90(0.85–0.94)	0.83(0.70–0.96)	71
Allergen	11	0.93(0.82–1.03)	0.99(0.76–1.23)	67	4	0.89(0.73–1.05)	0.83(0.45–1.20)	70
Ownership	15	0.97(0.91–1.02)	0.83(0.69–0.97)	66	19	0.93(0.89–0.98)	0.86(0.73–0.99)	74
Birth cohort	15	0.83(0.71–0.95)	0.85(0.68–1.02)	43	12	0.66(0.54–0.79)	0.74(0.56–0.93)	44
Non-birth cohort	11	0.99(0.93–1.04)	0.91(0.75–1.07)	75	11	0.96(0.92–1.01)	0.945(0.81–1.08)	77

^aOne study (Svanes et al.⁷³) include both adult and childhood population.

**Figure 3.** A meta-analysis of cohort studies on the exposure to cats and the risk of asthma categorized by exposure.

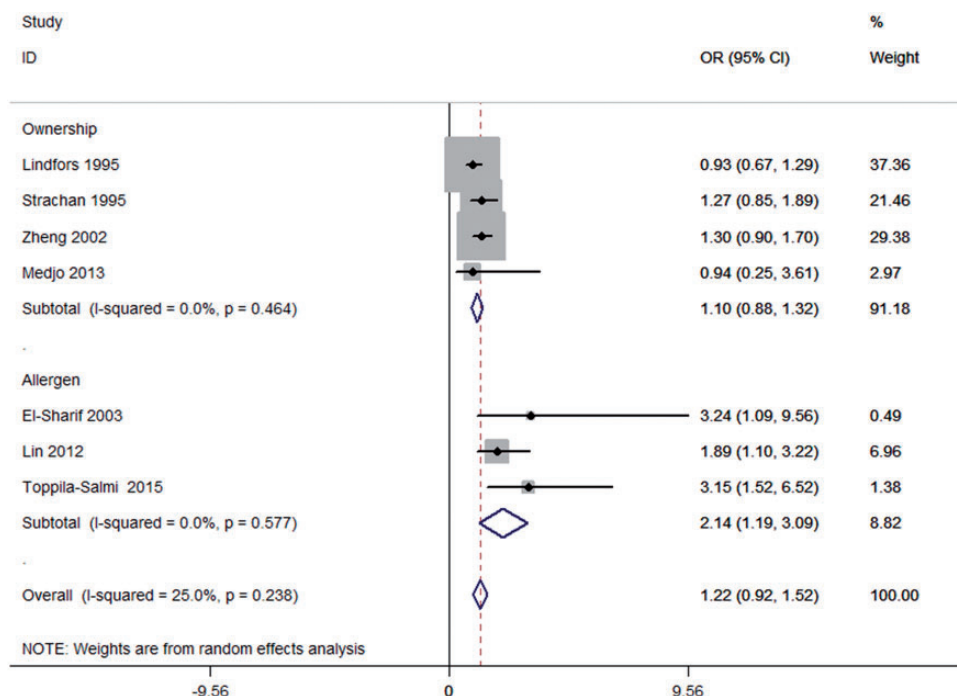


Figure 4. A meta-analysis of case-control studies on the exposure to dogs and the risk of asthma categorized by exposure.

0.33–0.86; $I^2 = 43.6\%$) or dog exposure (RR: 0.68, 95% 0.44–0.90; $I^2 = 0\%$) on the development of rhinitis. Early cat ownership (OR: 0.51, 95% CI: 0.28–0.92), rather than late ownership (OR: 1.19, 95% CI: 0.64–2.20), was associated with a significantly lower risk of allergic rhinitis than never cat ownership²¹ (Table 2).

Discussion

This systematic review and meta-analysis of cohort studies provided evidence that exposure to cats or dogs had a protective role in the development of asthma, especially ownership. In contrast, pooled evidence from case-control studies revealed no association between exposure to cats and dogs and the risk of asthma. The pooled evidence from cohort studies was more reliable to assess the cause-and-effect relationship compared with case-control studies. The publication bias might explain the inconsistent results regarding cats between case-control and cohort studies. Nevertheless, different study designs and a limited number of included studies partly contributed to the conflicting results in dogs. In agreement with a previous study,²⁰ exposure to cats had a protective effect against the risk of asthma, but exposure to dogs might reduce the development of asthma, which was confirmed in a later systematic review of longitudinal studies.¹⁹ The findings of this study challenged the theoretical dogma that allergen exposure induces sensitization, and that continued exposure leads to asthma because accumulating evidence indicated a

protective effect of exposure to cats and dogs.^{77–86} Custovic et al. showed a decreased prevalence of sensitization to cats with high exposure to cat allergen.⁷⁷ Ownby et al. found that the risk of allergic sensitization to multiple allergens at the age of 6–7 years could be reduced if exposure to dogs or cats occurred in the first year of life.⁸⁵ Oryszczyn et al. reported that exposure to pets before asthma onset might protect against allergen sensitization in adulthood.⁸⁴

A previous study indicated that dogs in the home corresponded to dog allergen in the home.⁸⁷ The findings of the present study suggested that the ownership of cats or dogs might have a protective effect on the development of asthma. Exposure to cat allergen can induce modified T-helper-2 cell response without sensitization or risk of asthma, leading to allergy tolerance.⁸⁸ This explained the decreased risk of asthma in children exposed to cats.⁸² In a community where cat sensitization was strongly associated with asthma, owning a cat was protective against both prevalent and incident asthma.⁶⁶ Fall et al. indicated an association between the sex of the dogs and the number of dogs and with a lower risk of childhood asthma in dog-exposed children.⁸⁹ The results showed no significant association between cat or dog allergen and the development of asthma. An allergen avoidance strategy was developed based on the hypothesis that the level of an allergen could reduce the risk of allergen sensitization and then the risk of allergic disease, but it seems that the process of sensitization is independent of the disease process

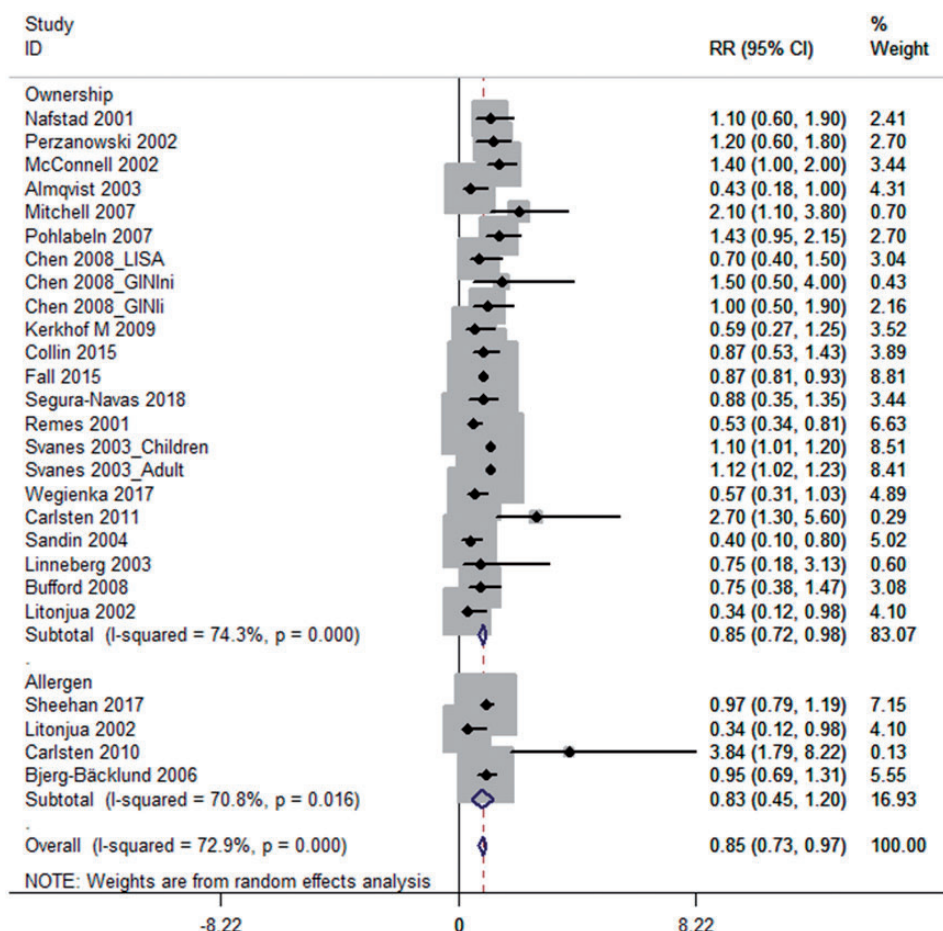


Figure 5. A meta-analysis of cohort studies on the exposure to dogs and the risk of asthma categorized by exposure.

Table 2. Relative Risks of Rhinitis According to Exposure to Cats or Dogs.

Study	Design	Exposure	Cat	Dog	Quality
Fasce et al. ²¹	Case-control	Ownership	Early 0.51 (0.28–0.92) Late 1.19 (0.64–2.20)	–	7
Nafstad et al. ²²	Birth cohort	Ownership	0.5 (0.2–1.4)	0.8 (0.4–1.6)	8
Chen et al. ⁴⁹	Birth cohort	Ownership		LISA 0.5 (0.2–1.2) GINIn 0.8 (0.4–1.6) GINli 0.7 (0.3–1.4)	7
Marinho et al. ⁷⁶	Birth cohort	Ownership	1.14 (0.71–1.83)	1.00 (0.58–1.70)	8
Perzanowski et al. ⁶⁵	Birth cohort	Ownership	0.41 (0.19–0.89)		6
Linneberg et al. ⁵⁹	Non-birth cohort	Ownership	3.34 (0.71–15.80)	0.27 (0.06–1.27)	7

Early: early cat ownership; late: late cat ownership; LISA: LISA study; GINli: GINI interventional; GINIn: GINI non-interventional.

despite a clear association between sensitization and the development of allergic disease.¹²

The present study showed a protective role of dog exposure in the birth cohort, rather than in the nonbirth cohort. It is believed that environmental exposure in the first years of life has the most significant impact on the development of asthma.⁹⁰ Thus, it is reasonable to assume that the development of asthma is greatly

influenced by prenatal environmental factors during gestation.^{91,92} Meanwhile, the findings of the present study showed that exposure to dogs conferred a protective effect on the development of asthma in children but increased the risk of asthma in the adult population. The observation further supported the intuitive notions that maternal environmental risk factors influence the development of the fetal immune system.⁹³

In cats and dogs, two and four lipocalin allergens have been identified with a variety of biologic and immunologic properties, including Fel d 4,⁹⁴ Fel d 7,⁹⁵ Can f 1, Can f 2,⁹⁶ Can f 4,⁹⁷ and Can f 6.^{98,99} These allergens are present everywhere in the indoor environment of homes, regardless of the presence of the animals. Thus, exposure to cats and dogs is inevitable to a certain degree. The findings of the present study indicated a protective role of exposure to cats and dogs, but a different role of these allergen subtypes for asthma remains uncertain. Allergies to furry animals other than cats and dogs are not the topic for the present study and have been extensively reviewed elsewhere.^{100,101}

Allergic rhinitis and asthma both are heterogeneous disorders caused by a wide variety of allergens and with different phenotypes.¹⁰² Both diseases are linked,¹⁰² but specialization in medicine and different medication led to the belief that they are different entities.¹⁰³ This link is represented by the fact that 40% of patients with allergic rhinitis have asthma, and that 30%–80% of patients with asthma also have allergic rhinitis.^{103–105} In addition, the presence of allergic rhinitis is associated with more severe asthma.¹⁰⁶ The pathophysiology of asthma and allergic rhinitis is based on an immune reaction to a foreign substance in both cases and based on IgE production in both cases and their attachment on mast cells in mucous membranes.¹⁰⁷ In addition, both diseases involve a variety of immune cells such as CD4+ T cells, B cells, macrophages, basophils, and neutrophils, leading to a similar local inflammatory reaction, albeit in different locations (nose vs. lower airways).^{102,108} Besides, the treatment of rhinitis can improve asthma and vice versa.^{109,110} The results from the meta-analysis of cohort studies on rhinitis were in agreement with those on asthma. Numerous pieces of evidence support the common epidemiology and shared pathophysiology of asthma and allergic rhinitis,⁴ suggesting a similar explanation for the protective effect of exposure to cats or dogs on the development of rhinitis.

Nevertheless, the exact mechanisms of the protective effect of allergen exposure on asthma and allergic rhinitis are still not completely understood.^{54,111–113} They could include a modified TH2 response leading to high levels of IgG/IgG4 without the production of IgE and to clinical tolerance despite the immune response.⁸⁸ A low level of IgE production but without high levels of IgG could also cause clinical tolerance.¹¹⁴ Some allergens such as Fel d 1 are able to stimulate IL-10 and IFN- γ production, decreasing the immune response.¹¹⁵ The presence of endotoxins in the environment with pets could lead to a downregulation of the immune response.¹¹⁶ Finally, microbes causing lower airway infections could affect the development of asthma and allergic rhinitis.¹¹⁷ Beyond the observation that some allergens can lead to immune tolerance, additional

studies are still necessary to understand the mechanisms involved.

This meta-analysis had some limitations. The included studies had design flaws, leading to marked heterogeneity. Although random-effect models were used as a conservative solution to decrease the potential impact of heterogeneity, random-effects meta-analyses are not always conservative.¹¹⁸ Thus, differences between the studies were explored to provide explanations for the heterogeneity of the effect measure. The characteristics of included studies, such as the type of study, study population, exposure, and cohort population, could only explain a portion of the heterogeneity. Other factors, including the number of animals, duration of exposure, and measurements on the true exposure to cats or dogs, might further increase the heterogeneity.^{36,119} Moreover, it is impossible to completely adjust the confounding effects of pet-keeping choices in allergic families. Some studies were outliers. This is a limitation inherent to any meta-analysis. Hopefully, the large number of studies in the present meta-analysis helped mitigate the influence of such outliers on the conclusions. Last, a risk of drawing a biased conclusion based on cohort studies still exists, although they are often perceived to be of stronger validity.

Conclusion

The findings of this study showed a potential protective effect of exposure to cats and dogs, especially ownership, on the development of asthma and allergic rhinitis.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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