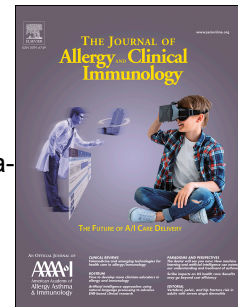


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Associations of early-life pet ownership with asthma and allergic sensitization: a meta-analysis of >77,000 children from the EU Child Cohort Network

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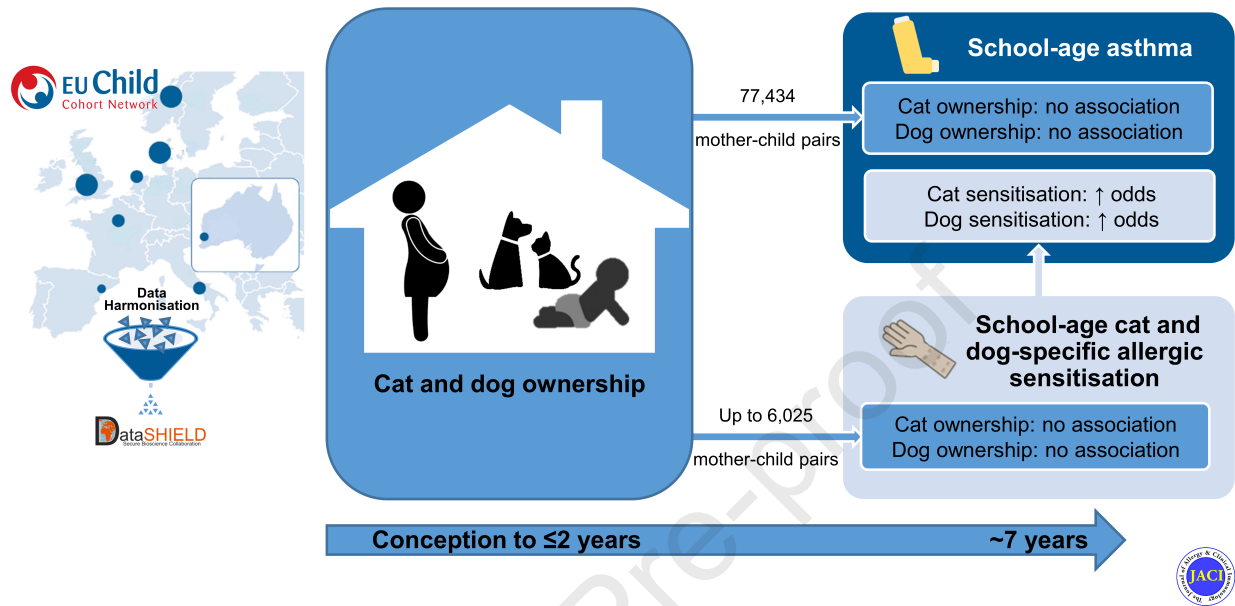
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Declarations

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Conflicts of interest/Competing interests

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Ethics approval

Study-specific ethics approval statements are available in the supplementary material.

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Abstract

Background: Studies examining associations of early-life cat and dog ownership with childhood asthma have reported inconsistent results. Several factors could explain these inconsistencies, including type of pet, timing and degree of exposure.

Objective: To study associations of early-life cat and dog ownership with school-age asthma, including the role of type (cat versus dog), timing (never, prenatal or early childhood) and degree (number) of ownership, and the role of allergic sensitisation.

Methods: We used harmonised data from 77,434 mother-child dyads aged 5-11 years from nine birth cohorts in the EU Child Cohort Network. Associations were examined through the DataSHIELD platform using adjusted logistic regression models, fitted separately for each cohort and combined using random-effects meta-analysis.

Results: Early-life cat and dog ownership ranged between 12-45% and 7-47% respectively, and prevalence of asthma between 2-20%. There was no overall association between either cat or dog ownership and asthma (OR: 0.97 (95% CI: 0.87-1.09) and 0.92 (0.85-1.01), respectively). Timing and degree of ownership did not strongly influence associations.

Cat and dog ownership were also not associated with cat- and dog-specific allergic sensitisation (OR: 0.92 (0.75-1.13) and 0.93 (0.57-1.54), respectively). However, cat- and dog-specific allergic sensitisation were strongly associated with school-age asthma (OR: 6.69 (4.91-9.10) and 5.98 (3.14-11.36), respectively). There was also some indication of an interaction between ownership and sensitisation, suggesting that ownership may exacerbate the risks associated with pet-specific sensitisation, but offer some protection against asthma in the absence of sensitisation.

Conclusion: Our findings do not support early-life cat and dog ownership in themselves increasing the risk of school-age asthma, but suggest that ownership may potentially exacerbate the risks associated with cat- and dog-specific allergic sensitisation.

Clinical Implications

Cat and dog ownership in themselves are unlikely to increase the risk of school-age asthma and cat- and dog-specific allergic sensitisation, but may exacerbate the risks associated with cat- and dog-specific allergic sensitization.

Capsule Summary

Our meta-analysis found no overall association between early-life cat or dog ownership and school-age asthma or pet-specific allergic sensitisation. Pet-specific allergic sensitisation was associated with increased odds of asthma, however, which was strengthened by pet ownership.

82 **Keywords**

83 Cat, dog, asthma, allergic sensitisation, exposure, ownership, children, meta-analysis, birth cohort, lifecourse
84 epidemiology, FAIR (findable, accessible, interoperable and reusable).

85

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Abbreviations

ALSPAC - Avon Longitudinal Study of Parents and Children; *ASIT* – allergen-specific immunotherapy; *CI* – confidence interval; *DNBC* - Danish National Birth Cohort; *EDEN* - Study on the pre- & early postnatal determinants of child health & development; *FAIR* - findable, accessible, interoperable and reusable; *FEV1* – forced expiratory volume in the first second; *FVC* – forced vital capacity; *Gen R* - Generation R; *Ig* – immunoglobulin; *INMA* - Environment and Childhood Project; *IPD* - individual participant data; *ISAAC* - International Study of Asthma and Allergy in Childhood; *MeDALL* - Mechanisms of the Development of ALLergy; *MoBa* - Norwegian Mother, Father and Child Cohort Study; *NINFEA* - Nascita e INFanzia: gli Effetti dell'Ambiente; *OR* – odds ratio; *RE* - random-effects; *REML* - restricted maximum-likelihood estimator; *SE* - standard errors; *SPT* - skin prick test; *SWS* - Southampton Women's Survey.

Introduction

Asthma is the most prevalent non-communicable disease of childhood¹ and represents a huge and growing burden for affected families, society and healthcare systems.² Although its aetiology is incompletely understood, evidence suggests that early-life environmental and lifestyle factors play a vital role in its development.

Allergic sensitisation is a risk factor for asthma.^{3,4} However, while allergen exposure has been consistently associated with more severe asthma⁵⁻⁷ and increased frequency of asthma exacerbations^{5,6,8-10} in asthmatic children sensitised to the corresponding allergen, the exact relationship between allergen exposure and the development of allergic sensitisation and symptomatic allergic diseases such as asthma remains controversial. This is illustrated by studies examining associations between early-life pet exposure and later risk of childhood asthma, which have produced conflicting results.¹¹⁻¹³

Several factors could explain these differences in findings, including degree of allergen exposure both inside and outside the home. The aerodynamic nature of pet allergens means that they are easily transferred from one environment to another¹⁴ and are consequently ubiquitous in the environment.¹⁵⁻¹⁷ There is evidence that exposure to high levels of pet allergens (more pets) may actually decrease a child's risk of sensitisation by inducing immune tolerance, similar to allergen-specific immunotherapy (ASIT). For instance, some studies have observed an inverse dose-response association between early-life pet exposure and risk of asthma and allergy,^{18,19} and other studies have shown that children exposed to higher concentrations of cat allergen have higher immunoglobulin G (IgG) levels and decreased sensitivity to the major cat allergen Fel d 1.^{20,21}

Timing of exposure may also be important, with the first year of life appearing to be a critical window for the development of tolerance.²² Although fewer studies have examined the effect of prenatal pet exposure on later risk of allergic sensitisation and asthma, there is evidence that these could also influence allergic disease development.²³⁻²⁵ For example, offspring of mothers who underwent ASIT during pregnancy have been observed to have reduced risk of allergen-specific sensitisation later in life.²⁶

Finally, many studies have observed differences in effects depending on the type of pet owned,^{27,28} suggesting that pet-specific differences in allergens, associated microbes²⁹ and pet-keeping practices³⁰ also influence whether pet exposure confers risk or protection against asthma and allergy.

The aim of this study is to examine the associations of early-life cat and dog ownership with the development of asthma in childhood. We specifically examine how these associations are influenced by type of pet (cat vs. dog), timing of ownership (never, prenatal or early childhood) and number (none, one or >one) of cats or dogs owned. We also examine the role of cat and dog-specific allergic sensitisation. We hypothesise that cat- and dog-specific allergic sensitisation are on the causal pathway between cat and dog ownership and childhood asthma, and that this mechanism is likely to be influenced by type of pet, timing of ownership and number of pets.

Methods

Study design and participating cohorts

This study is part of the LifeCycle Project, a collaboration between Australian and European birth cohort studies, which has established a FAIR (findable, accessible, interoperable and reusable) data resource known as the EU Child Cohort Network.³¹ Details of how variables were harmonised for LifeCycle are provided in <http://catalogue.lifecycle-project.eu> and elsewhere.³²

Cohorts in the network were eligible for this study if they had the following data: i) cat or dog ownership ascertained during pregnancy and/or ≤ 2 years; ii) current asthma at >5 years, or cat- or dog-specific allergic sensitisation in the child. The participating cohorts were: Avon Longitudinal Study of Parents and Children (ALSPAC (UK)),^{33, 34} Danish National Birth Cohort (DNBC (Denmark)),³⁵ Study on the pre- & early postnatal determinants of child health & development (EDEN (France)),³⁶ Generation R (Gen R (The Netherlands)),³⁷ Environment and Childhood Project (INMA (Spain)),³⁸ Norwegian Mother, Father and Child Cohort Study (MoBa (Norway)),^{39, 40} Nascita e INFanzia: gli Effetti dell'Ambiente (NINFEA (Italy)),⁴¹ the Raine Study (Australia),⁴² and Southampton Women's Survey (SWS (UK)).⁴³ Descriptions and characteristics of the participating cohorts are provided in Supplementary Information 1 and Tables S1-S2.

Cat and dog ownership

Our exposure measures were based on parental reports of having a cat or dog during pregnancy or early childhood (i.e. ownership; detailed in Table S3), with the assumption that this equates to exposure. We harmonised data collected during pregnancy and the first three years of life to create four variables relating to: i) cat ownership ever from conception to ≤ 2 years (yes/no); ii) dog ownership ever from conception to ≤ 2 years (yes/no); iii) number of cats owned (none/1/ >1); iv) number of dogs owned (none/1/ >1). For variables relating to number of cats and dogs owned, averages were calculated if data were available at several time points from conception to ≤ 2 years.

Two categorical variables were created to examine the influence of timing of cat and dog ownership (never/prenatal only/early childhood only/prenatal and early childhood). For ownership in early childhood, children were classified as exposed if a cat or dog was reported at any data collection from birth to ≤ 2 years.

Primary outcome: current asthma at school age

Our primary outcome was current asthma at school age (median age 7y, range 6-9y), harmonised using data obtained from parental questionnaires (detailed in Table S4) according to the MeDALL (Mechanisms of the Development of ALLergy) criterion,⁴⁴ whereby a child was classified as having current asthma when at least two of three criteria were reported: i) doctor diagnosis of asthma ever; (ii) use of asthma medication in the past 12 months; iii) wheezing in the past 12 months according to the ISAAC (International Study of Asthma and Allergy in Childhood) parental core questionnaire.⁴⁵ Records with missing data on two of the three criteria were coded as missing. In three cohorts (ALSPAC, MoBa and NINFEA), only partial harmonization was achieved (detailed in Table S4). Where current asthma was available at several ages, we analysed current asthma at the age closest to the median “current asthma” age of the pooled study population (7y).

Secondary outcomes: allergic sensitisation and lung function

Information on allergic sensitisation to cat, dog and other aeroallergens at school age (median age 7y, range 5-11y) was available in five cohorts (cat and other aeroallergens; ALSPAC, Gen R, INMA, the Raine Study and SWS) and three cohorts (dog allergen; ALSPAC, Gen R and SWS). Sensitisation was defined as having a skin prick test response ≥ 3 mm compared with the negative control in two cohorts (ALSPAC and SWS); as $\geq 40\%$ of the positive histamine control in one cohort (Gen R); as serum allergen-specific-IgE levels >0.35 allergen-specific kilounits per litre in two cohorts (INMA and the Raine Study), Table S4. Where allergic sensitisation was measured at several ages, measurements taken at the age closest to the median age of measurement (7y) were analysed.

Details of lung function measurements (FEV1, FVC, FEV1/FVC) are given in Table S4 and Supplementary Information 2.

Covariates

Potential confounders were identified based on the literature and then selected by constructing directed acyclic graphs (Fig S1-S2). The selected variables included: i) maternal asthma (yes/no); ii) maternal inhalant allergy (yes/no); iii) paternal asthma (yes/no); iv) maternal education level (low/medium/high); v) quartiles of predicted equivalised total disposable household income⁴⁶ or reported household income; vi) maternal

ethnicity (white/Black, Asian or minority ethnic/mixed); vii) sibling position (1/2/ ≥ 3); viii) maternal smoking during pregnancy (yes/no); ix) maternal age at birth; x) sex; xi) number of children living in the household when the child was ≤ 2 years (1/2/ ≥ 3). For associations between allergic sensitisation and asthma, confounders also included: xii) gestational age (days); xiii) birth weight (g); xiv) caesarean delivery (yes/no); xv) ever breastfed (yes/no); xvi) early-life cat ownership (yes/no); xvi) early-life dog ownership (yes/no). Information on covariates were primarily obtained by questionnaire, interviews, or from medical records (summarized in Table S5).

Statistical analysis

All analyses were conducted in R (version 3.5.2) using the federated analysis platform DataSHIELD (version 6.0.1),^{47, 48} via a central analysis server using RStudio (<https://rstudio.com/products/rstudio/#rstudio-server>) and DataSHIELD-specific libraries (<https://github.com/datashield>).

Analyses were restricted to singleton pregnancies resulting in a live-born child. The number of children and covariates included in each analysis varied depending on data availability (summarised in Fig 1).

We examined associations of cat and dog ownership (yes/no, number and timing) with school-age asthma using logistic regression models. Logistic regression models were also used to examine associations of: i) cat and dog ownership with cat- and dog-specific allergic sensitisation, respectively; ii) cat- and dog-specific allergic sensitisation with asthma; iii) cat and dog ownership with other aeroallergens than cat and dog. Associations of cat and dog ownership with lung function (FEV1, FVC, FEV1/FVC) were examined using linear regression models (detailed in Supplementary Information 2).

To allow for between-sibling correlation in cohorts (ALSPAC, DNBC, Gen R, MoBa and NINFEA), we applied 2-level regression models, with children as “level 1” and mothers as “level 2” units. We performed analyses first without adjustment, then with adjustment for confounders, and mutual adjustment for cat/dog ownership.

Confounding by indication and reverse causation were investigated by assessing the presence of effect modification by parental asthma and wheeze ≤ 2 years, respectively. To assess the joint effects of pet ownership and pet-specific allergic sensitisation, we tested for multiplicative interaction and created two variables with the following categories: i) no ownership and not sensitised; ii) ownership and not sensitised; iii) no ownership and sensitised; iv) ownership and sensitised. Finally, to explore differences in associations between girls and boys, we also stratified analyses by sex.

Regression models were fitted separately for each cohort and regression coefficients (β s) and standard errors (SEs) combined using random-effects meta-analysis using the restricted maximum-likelihood estimator method (REML). Between-cohort heterogeneity was evaluated using I^2 and the chi-squared Q-statistic.

For the main analysis examining associations of cat and dog ownership with asthma, the following sensitivity analyses were conducted: i) omitting covariates not available in all cohorts (maternal inhalant allergy, maternal ethnic background and number of children in the home); ii) restricting the population to individuals with sensitisation data; iii) excluding each cohort in turn; iv) pooling data and including cohort as a fixed effect.

Ethical approval

Each participating cohort obtained ethical approval from their local ethics committee, detailed in Supplementary Information S6.

Results

Cat and dog ownership ranged from 12.2% (INMA) to 45.1% (the Raine Study) and from 7.4% (Gen R) to 47.4% (the Raine Study), respectively. Figs 2a-b display the respective timing of cat and dog ownership across cohorts. Ownership both prenatally and in early childhood was the most common timing of ownership, whilst ownership prenatally only was the least common timing of ownership. The characteristics of cat and dog owners were relatively consistent across cohorts (Tables S1-S2). Cat and dog owners tended to have a lower household income, lower maternal education, and higher prevalence of maternal smoking (Tables S1-S2). Prevalence of parental asthma was comparable between cat/dog owners and non-cat/dog owners, but prevalence of maternal inhalant allergy was slightly lower among cat/dog owners in some cohorts (Table S2). Prevalence of current asthma at school age ranged between 2.3% (NINFEA) and 19.5% (the Raine Study), while sensitisation to cats and dogs ranged between 6% (INMA) and 12% (Gen R), and 3% (SWS) and 5% (ALSPAC and Gen R), respectively (Figs 2c-e).

Associations of cat and dog ownership with asthma and lung function

In total, 77,434 children from nine cohorts were included in analyses examining associations of early-life cat and dog ownership with current asthma at school age (Fig 1). Overall, there was no strong evidence for an association between early-life cat or dog ownership and school-age asthma (Fig 3 and S3), nor for wheezing in infancy or parental asthma modifying these associations ($P_{interaction} > 0.26$). Heterogeneity across studies was moderate for cat ownership ($I^2 = 32.4\%$) and low for dog ownership ($I^2 = 7.6\%$) in the adjusted models, Fig 3. Results were consistent for girls vs. boys (Table S6).

Results from sensitivity analyses are summarised in Table S7. When analyses were restricted to children with allergic sensitisation data, slightly lower ORs were observed for the effect of cat ownership on current asthma (Table S7). Similarly, when the DNBC cohort was excluded, a slightly lower OR was observed for dog ownership (Table S7). However, the differences in ORs observed in sensitivity analyses were not sufficient to alter conclusions.

In the six cohorts with relevant data (ALSPAC, INMA, EDEN, Gen R, the Raine Study, SWS), we also examined associations of cat and dog ownership with lung function. Here, there was no evidence for an overall

association between cat or dog ownership and lung function (described in full in Supplementary Information 3 and Tables S8-S9).

Influence of timing, and number of cats and dogs owned

For both cat and dog ownership, ownership prenatally only was associated with greater odds of school-age asthma, whilst both ownership in early childhood only and continuous ownership, were associated with lower odds of school-age asthma compared with no ownership (Table 1). For all time windows, however, ORs were close to the null.

Odds of current asthma at school age were relatively constant for one versus multiple cats or dogs, and were consistent with no or only a very weak association (Table 2).

The role of cat- and dog-specific allergic sensitisation

Cat and dog ownership were not associated with cat- and dog-specific allergic sensitisation, respectively (Fig 4 and Fig S4). These results were not modified by parental asthma or infant wheeze ($P_{\text{interaction}} > 0.22$), and were consistent for girls and boys (Table S6). In contrast, both cat- and dog-specific allergic sensitisation were associated with school-age asthma (Fig 5 and Fig S5), with stronger associations observed among girls compared with boys (Table S6).

There was also evidence for an interaction between dog ownership and dog-specific allergic sensitisation, where the joint effect of early-life dog ownership and dog-specific allergic sensitisation was greater than would be expected on either an additive or multiplicative scale (Table 3). The small numbers and wide confidence intervals should be noted, however. A similar, weaker, tendency was observed for cat ownership and cat-specific allergic sensitisation (Table 3). Slightly lower odds of asthma were observed among children who had a cat or dog in early life but did not develop sensitisation (Table 3). In further analyses, cat and dog ownership were also associated with lower odds of allergic sensitisation to other aeroallergens than cat and dog (Fig S6).

Discussion

In this meta-analysis of nine birth cohort studies including >77,000 children, we found no strong overall association between early-life cat or dog ownership and current asthma at school age. We also found no overall association of early-life cat or dog ownership with FEV1 and FEV1/FVC, objective markers of airflow obstruction. And similarly no strong association between timing or number of cats or dogs owned and current asthma at school-age. Consistent with these findings, cat and dog ownership were also not associated with cat- and dog-specific allergic sensitisation. There was some indication, however, of a possible interaction between ownership and sensitisation. Cat- and dog-specific allergic sensitisation were both associated with school-age asthma, and this association was stronger among children who had a cat or dog in early-life, although based on small numbers. In contrast, early-life cat and dog ownership without sensitisation were associated with slightly lower odds of asthma.

Strengths and limitations

This is the first study to use a federated approach to analyse harmonised individual participant data (IPD) from nine birth cohorts from the EU Child Cohort Network.^{31, 32} To date, all but one meta-analysis examining associations of early-life pet ownership with school-age asthma have been based on aggregate, published data, and this is the first meta-analysis using IPD, to our knowledge, to examine associations of cat and dog ownership with cat- and dog-specific allergic sensitisation and lung function, and to examine associations of number of cats or dogs owned with school-age asthma. Meta-analysis of IPD has a number of advantages over meta-analysis of published, aggregate data; most notably, the lack of publication bias and ability to reduce between-study heterogeneity by using harmonised data and consistent adjustment for confounding. Analysing IPD also enabled us to investigate possible effect modification by parental asthma and infant wheeze, and interaction between ownership and sensitisation. We were also able to conduct a number of sensitivity analyses to assess the robustness of results.

Another key strength of the current study is the fact that the majority of participating studies ascertained symptoms of asthma using ISAAC questionnaires, or adaptations thereof, which have been extensively validated against bronchial hyper-responsiveness⁴⁹ and doctor-diagnosed asthma.⁵⁰ In addition, our measure of school-age asthma was based on the MeDALL criterion, which was developed by a panel of experts and considers symptoms of asthma, medication and doctor diagnosis in its definition.⁴⁴ We were also able to explore

associations with more objective measures of allergy and respiratory health, using SPT/IgE and spirometry data. Finally, despite the considerable variation in the prevalence of cat and dog ownership and asthma between the birth cohorts, and the varied social and cultural environments of the cohorts, heterogeneity between study estimates, particularly for dogs, was small.

There are, however, also some limitations that should be considered when interpreting our findings, in particular the possibility of confounding by indication and reverse causation. Studies have demonstrated selective avoidance of pets, especially cats, among families with asthma or allergies;^{51, 52} thus it is likely that children at highest risk of developing allergies or asthma are also less likely to live with cats or dogs. Similarly, it is also possible that the development of early respiratory symptoms in the child, for example infant wheeze, may result in the removal of pets from the home; this may be less common than avoidance however.⁵¹ Although we have tried to assess these possibilities by investigating whether parental asthma and infant wheeze modified results, a preferred approach would be to exclude children whose parents reported avoidance of pets due to allergies or asthma in the family. Unfortunately, these data were not available in the majority of cohorts.

All but one cohort (the Raine Study), lacked information on pet keeping practices, for example whether the cat or dog was kept mainly/only outside and whether the pet was allowed into the child's bedroom. These practices may vary from cohort to cohort, introducing between-study heterogeneity in exposure measures. In addition, allergic or asthmatic families who own a pet could modify their pet keeping practices in an attempt to mitigate any associated detrimental health effects. While there is very limited evidence that removing pets from main living areas or bedrooms is effective at reducing indoor allergen levels,⁵³ it could affect the exchange of microbiota⁵⁴, which could be important for immune development and homeostasis. However, studies suggest that people with asthma frequently choose to ignore medical advice to avoid or modify their pet keeping practices.^{55, 56}

A further limitation of the current study is our restricted measure of allergic sensitisation and asthma. Although the large majority of epidemiological studies investigating risk factors for allergic sensitisation treat sensitisation as an all or nothing (yes/no) phenomenon, evidence clearly demonstrates that degree of sensitisation is an important determinant of clinical symptoms.⁵⁷⁻⁶¹ Moreover, the arbitrary cut-offs that are applied to determine allergic status have poor positive predictive value.⁶² In light of this, examining associations of cat or dog ownership with quantitative measures of allergic sensitisation may have provided more informative results; unfortunately, these data were only available in two of the participating cohorts.

Similarly, it is increasingly recognized that asthma and allergic sensitisation are not single phenotypes, but instead umbrella terms for multiple phenotypes with different underlying aetiologies.^{63, 64} Since different phenotypes are likely to have different environmental associations, the real picture is likely to be more complex than what is presented here.

Comparison with the literature and interpretation of results

Our findings of no overall association between cat and dog ownership and school-age asthma mirror those of a similar meta-analysis using data from approximately 11,000 children across 11 European birth cohort studies.¹² In that meta-analysis, no association was observed between furry and feathered pet ownership in the first two years of life and school-age asthma. The picture from systematic reviews and meta-analyses of published, aggregate, cohort data examining associations of pet ownership with asthma is less clear; these have reported null or weak and inconsistent associations, with substantial between-study heterogeneity.^{28, 65, 66} The current meta-analysis adds to the current body of knowledge by demonstrating a lack of association regardless of number of pets owned and with lung function, but potentially a small protective effect in the absence of sensitisation and harmful effect in the presence of sensitisation.

We observed a suggestion of slightly greater odds of school-age asthma among children who owned a cat or dog prenatally only, but slightly lower odds among children who owned a cat or dog continuously or in early childhood only. This would be consistent with reverse causation, namely the removal of cats or dogs from the homes of children with early manifestations of allergy or asthma, as discussed above. Alternatively, it could suggest that sustained exposure is required to maintain any protection conferred by early-life dog or cat ownership, as has been suggested by farm studies.⁶⁷⁻⁷⁰ Given the small effect sizes, however, these patterns could also be due to chance alone.

We found no strong evidence for an association between cat or dog ownership and allergic sensitisation to the respective allergen, suggesting that ownership is unlikely to be the main determinant of cat- and dog-specific allergic sensitisation; instead, other factors such as genetic susceptibility are likely decisive. Other cohort studies examining associations of pet ownership with allergic sensitisation to associated allergens have been conflicting, with some reporting a positive association,^{71, 72} and others either no^{19, 72-77} or an inverse association.^{19, 22, 77-79} These inconsistencies could be related to differences in the timing of allergic sensitisation assessment, since trajectories of pet-specific allergic sensitisation have been observed to differ in pet owners

versus non-pet owners.⁸⁰ In further analyses, cat and dog ownership were associated with slightly lower odds of allergic sensitisation to other aeroallergens than cat and dog, suggesting that ownership may confer non-specific effects. This could be through altering the composition of the microbiome,^{54, 81-84} which is known to be important in immune development.^{85, 86}

Similar to other studies,^{61, 88} we observed an association between cat- and dog-specific allergic sensitization and childhood asthma. There is some controversy as to whether this association is causal or an epiphenomenon.^{89, 9} Genome-wide association studies have observed little overlap between loci associated with asthma and those associated with IgE levels, however, favouring the latter explanation.⁹⁰ Although we observed evidence for an interaction between cat or dog ownership and allergic sensitization, given that allergen exposure is known to increase asthma symptoms in sensitised, asthmatic children,⁵⁻¹⁰ this could also be explained by joint exposure increasing the likelihood of diagnosis or reporting of symptoms rather than asthma development *per se*. The stronger interaction observed for dog ownership compared with cat ownership may reflect changes in cat keeping practices or a reduced likelihood of continued cat ownership among children who develop cat-specific allergic sensitization,⁵¹ which would suggest that sustained pet exposure is required for the observed joint effect.

In summary, our findings do not support early-life cat and dog ownership in themselves increasing the risk of school-age asthma or pet-specific allergic sensitisation. Ownership may even offer some protection against asthma among children who do not develop allergic sensitisation. Our findings do, however, support cat- and dog-specific allergic sensitisation increasing the risk of school-age asthma, and for this risk possibly being greater among children who own a cat or dog, respectively.

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Tables

Table 1. Influence of timing of exposure on associations of cat and dog ownership with current asthma at school age^a

Odds of school-age asthma					
	N	Crude OR (95% CI)	I ²	Adjusted ^b OR (95% CI)	I ²
Cat ownership					
Never	57,910	reference		reference	
Prenatal only	2,575	1.13 (0.95, 1.36)	4%	1.17 (0.96, 1.42)	7%
Early childhood only	3,337	0.90 (0.74, 1.09)	10%	0.91 (0.77, 1.07)	0%
Prenatal and early childhood	13,612	0.94 (0.83, 1.07)	38%	0.99 (0.85, 1.14)	44%
Dog ownership					
Never	61,183	reference		reference	
Prenatal only	1,610	1.16 (0.95, 1.41)	0%	1.08 (0.88, 1.33)	0%
Early childhood only	2,517	1.00 (0.77, 1.30)	36%	0.92 (0.77, 1.11)	0%
Prenatal and early childhood	12,124	0.93 (0.85, 1.01)	0%	0.90 (0.81, 1.01)	15%

OR, 95% CI and I² from 2-stage random-effects meta-analysis.

^aAll cohorts had relevant data and were included in analyses (ALSPAC, DNBC, EDEN, Gen R, INMA, MoBa, NINFEA, the Raine Study and SWS)

^bAdjusted for maternal and paternal asthma, maternal inhalant allergy, maternal education, household income, maternal ethnic background, maternal age at birth, maternal smoking during pregnancy, birth order, number of children living in the home and sex; mutually adjusted for cat and dog ownership.

Table 2. Associations between number^a of cats and dogs owned and odds of current asthma at school age

Odds of current asthma at school-age					
	N	Crude OR (95% CI)	I ²	Adjusted ^b OR (95% CI)	I ²
Cats					
None	6,449	reference		reference	
1	1,504	0.95 (0.79, 1.13)	0%	0.95 (0.79, 1.14)	0%
>1	969	1.09 (0.71, 1.67)	58%	1.11 (0.70, 1.76)	60%
Dogs					
None	6,957	reference		reference	
1	1,575	0.92 (0.77, 1.10)	0%	0.84 (0.70, 1.02)	0%
>1	390	1.06 (0.77, 1.45)	0%	0.87 (0.63, 1.21)	0%

OR, 95% CI and I² from 2-stage random-effects meta-analysis.

^a Average number of cats and dogs across early-life (prenatally and early childhood). Cohorts with relevant data were: ALSPAC, INMA, NINFEA, the Raine Study and SWS. In SWS, data on number of cats and dogs were only available for the prenatal period.

^b Adjusted for maternal and paternal asthma, maternal inhalant allergy, maternal education, household income, ethnic background, maternal age at birth, maternal smoking during pregnancy, birth order, number of children living in the home and sex of the child; mutually adjusted for number of cats or dogs owned

Table 3. Associations of joint cat or dog ownership and cat or dog-specific allergic sensitisation^a with current asthma at school age^b

	Odds of school-age asthma					
	N	Crude OR (95% CI)	I ²	Adjusted ^c OR (95% CI)	I ²	P _{interaction} ^d
<i>Cat ownership</i>						
No cat and not sensitised	2698	reference		reference		
Cat and not sensitised	1462	0.80 (0.64, 0.99)	0%	0.80 (0.64, 1.00)	0%	
No cat and sensitised	250	5.36 (3.71, 7.73)	17%	5.94 (4.29, 8.22)	0%	
Cat and sensitised	134	5.92 (3.04, 11.50)	56%	6.55 (3.66, 11.71)	32%	0.07
<i>Dog ownership</i>						
No dog and not sensitised	1983	reference		reference		
Dog and not sensitised	379	0.96 (0.66, 1.39)	0%	0.78 (0.52, 1.17)	0%	
No dog and sensitised	91	4.73 (2.32, 9.66)	39%	4.32 (1.51, 12.31)	63%	
Dog and sensitised	17	24.20 (6.58, 89.03)	0%	23.36 (6.01, 90.79)	0%	0.04

OR, 95% CI and I² from 2-stage random-effect meta-analysis.

^aCat or dog ownership in early-life (from conception to ≤2 years) and allergic sensitisation at school age (median age 7y, range 5-11y)

^bCohorts with relevant data were: ALSPAC, Gen R, the Raine Study and SWS; INMA was excluded from analyses due to risk of disclosure

^cAdjusted for maternal and paternal asthma, maternal inhalant allergy, maternal education, household income, maternal ethnic background, maternal age at birth, maternal smoking during pregnancy, birth order, number of children living in the home and sex, gestational age, birth weight, caesarean delivery, ever breastfed; mutually adjusted for cat and dog ownership.

^dP_{interaction} on a multiplicative scale

Figure legends

Fig 1. Flow chart illustrating participants included in the study^a

^aThe same populations were used in both crude and adjusted analyses. Descriptions of the individual cohorts participating in the study are given in Supplementary Information S1.

^bAnalyses examining associations of cat- and dog-specific allergic sensitisation with current asthma at school age included these additional covariates: gestational age (days), birth weight (g), caesarean delivery (yes/no), ever breastfed (yes/no).

Fig 2. Distribution of exposures and outcomes in participating birth cohorts

A, Percentage of cat ownership by timing. B, Percentage of dog ownership by timing. C, Prevalence of current asthma at school age. D, Prevalence of cat-specific allergic sensitisation. E, Prevalence of dog-specific allergic sensitization. For plots A and B, values are for (from top to bottom): prenatal only, early childhood only and prenatal and early childhood.

Fig 3. Forest plots for associations of (A) cat and (B) dog ownership in pregnancy and infancy with school-age asthma.

RE – random-effects

* Adjusted for maternal and paternal asthma, maternal inhalant allergy, maternal education, household income, ethnic background, maternal age at birth, maternal smoking during pregnancy, birth order, number of children living in the home and sex of the child; mutually adjusted for cat and dog ownership.

Fig 4. Forest plots for associations of (A) cat ownership with cat-specific allergic sensitisation, (B) dog ownership with dog-specific allergic sensitisation.

NA – $n < 3$ for at least one summary statistic and not presented due to risk of disclosure

RE – random-effects

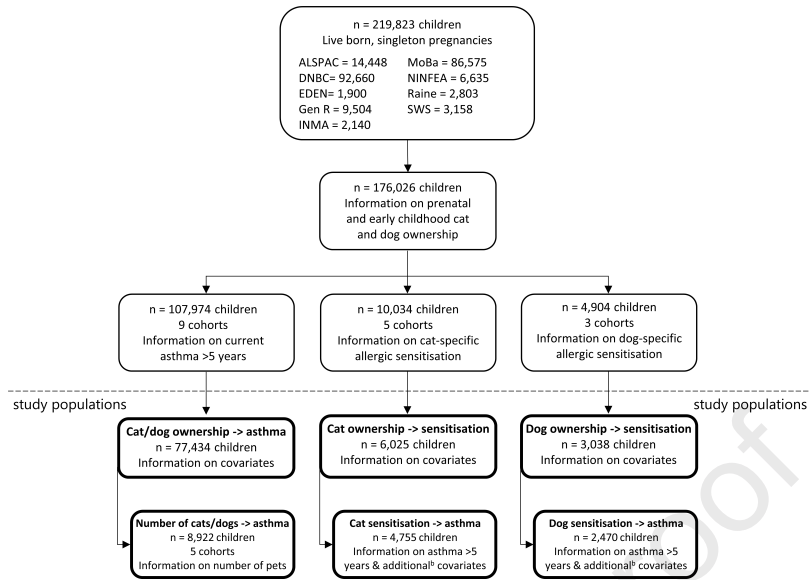
* Adjusted for maternal and paternal asthma, maternal inhalant allergy, maternal education, household income, maternal ethnic background, maternal age at birth, maternal smoking during pregnancy, birth order, number of children living in the home and sex; mutually adjusted for cat and dog ownership.

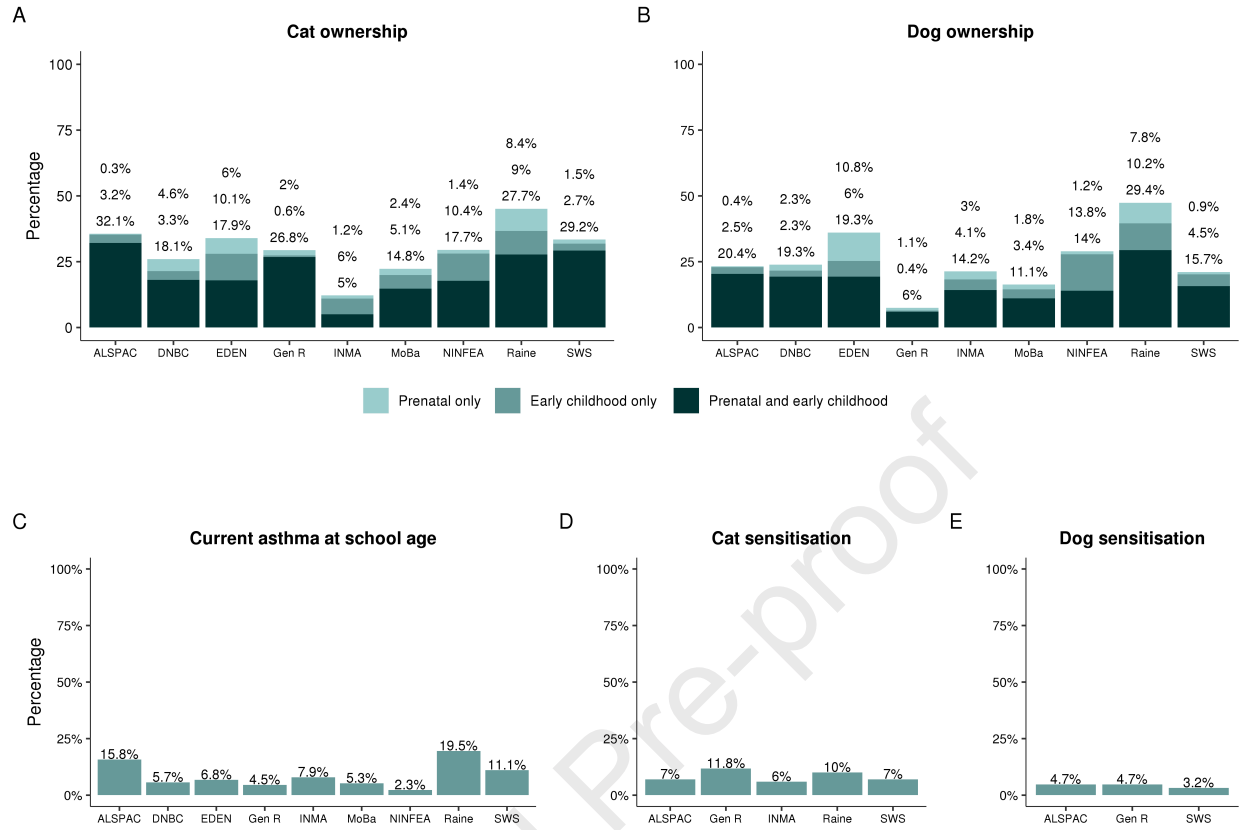
Fig 5. Forest plots for associations of (A) cat-specific allergic sensitisation and (B) dog-specific allergic sensitisation with current asthma at school age.

NA – $n < 3$ for at least one summary statistic and not presented due to risk of disclosure

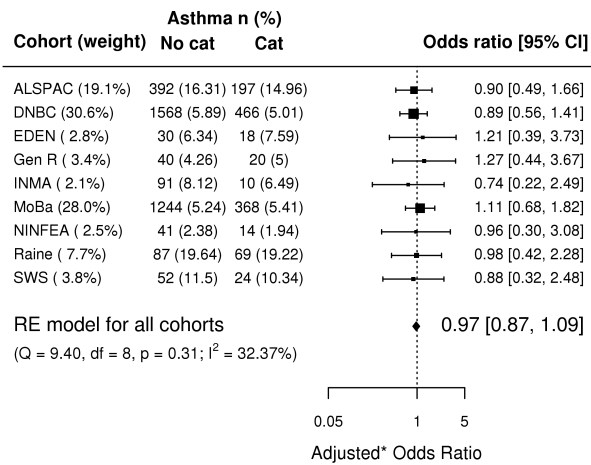
RE – random-effects

* Adjusted for maternal and paternal asthma, maternal inhalant allergy, maternal education, household income, maternal ethnic background, maternal age at birth, maternal smoking during pregnancy, birth order, number of children living in the home and sex, gestational age, birth weight, caesarean delivery, ever breastfed, early-life cat ownership, early-life dog ownership.

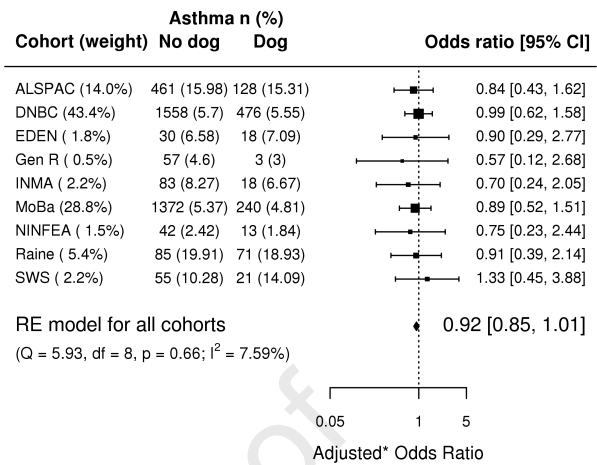




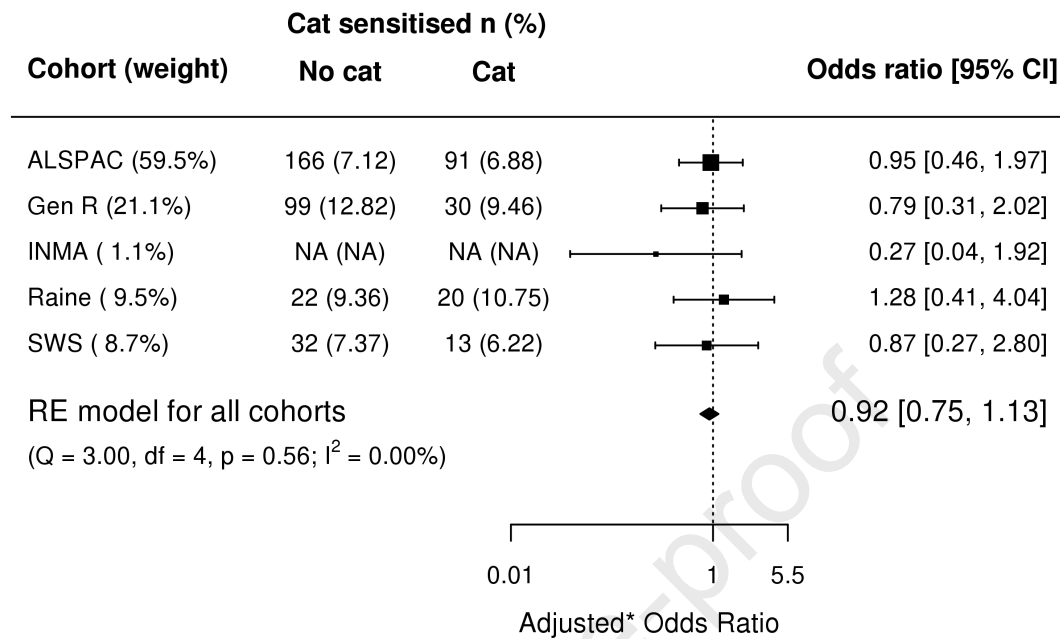
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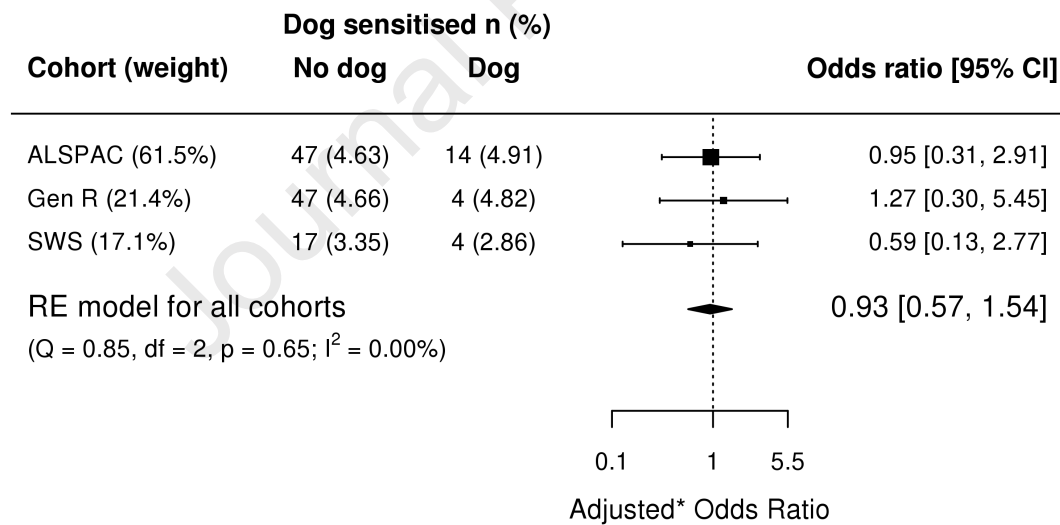
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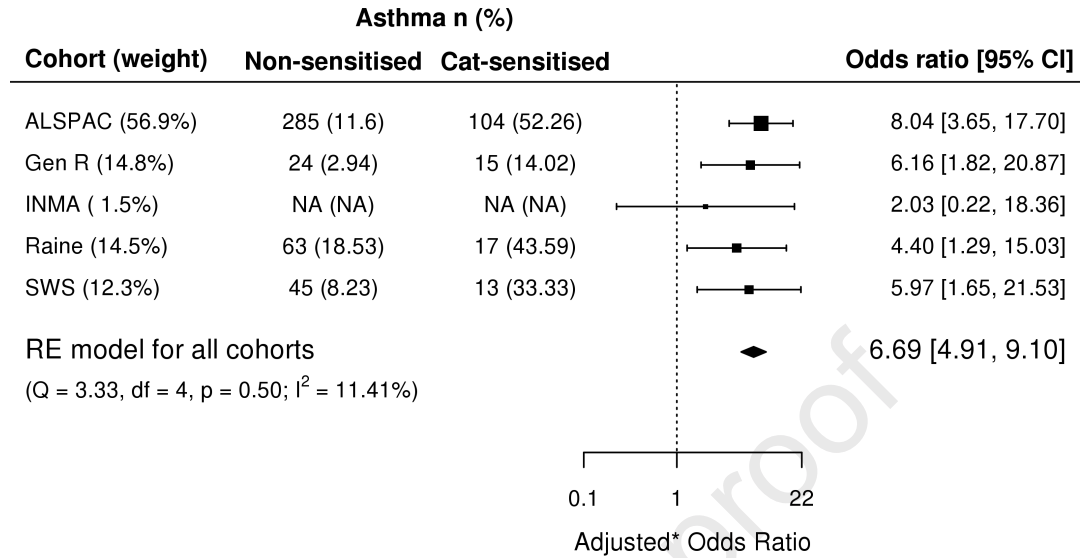
A



B



A



B

