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

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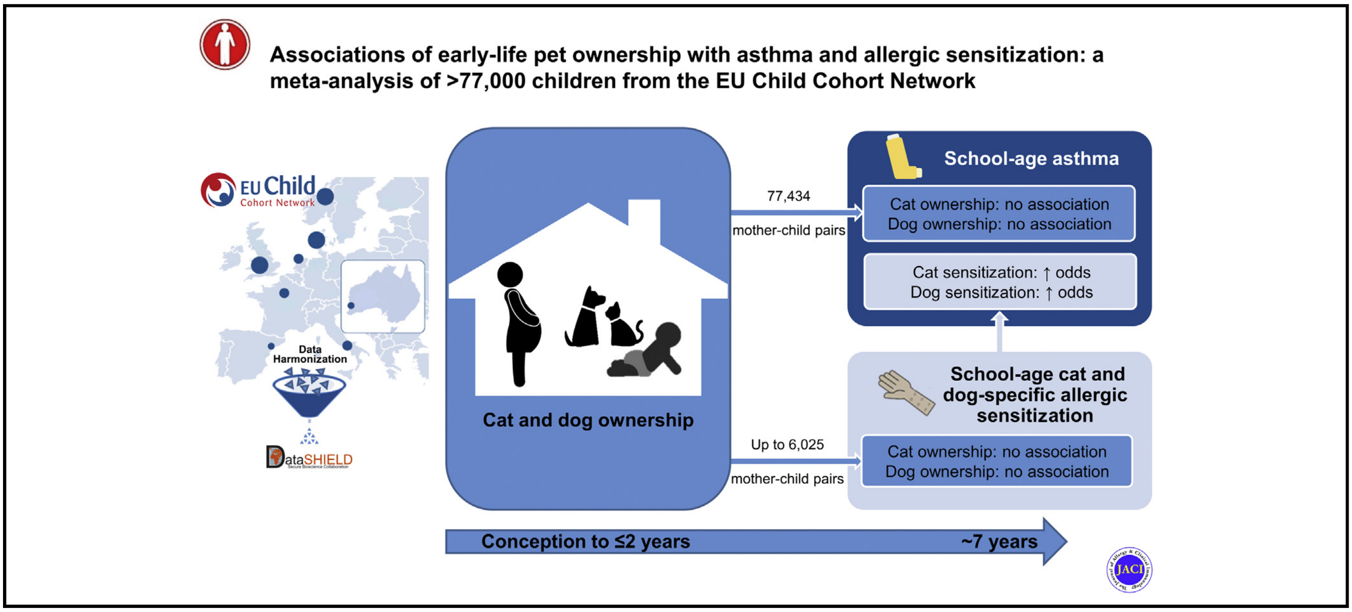
GRAPHICAL ABSTRACT



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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: Our aim was to study associations of early-life cat and dog ownership with asthma in school-aged children, including the role of type (cat vs dog), timing (never, prenatal, or early childhood), and degree of ownership (number of pets owned), and the role of allergic sensitization.

Methods: We used harmonized data from 77,434 mother-child dyads from 9 birth cohorts in the European Union Child Cohort Network when the child was 5 to 11 years old. Associations were examined through the DataSHIELD platform by using adjusted logistic regression models, which were fitted separately for each cohort and combined by using random effects meta-analysis.

Results: The prevalence of early-life cat and dog ownership ranged from 12% to 45% and 7% to 47%, respectively, and the prevalence of asthma ranged from 2% to 20%. There was no overall association between either cat or dog ownership and asthma (odds ratio [OR] = 0.97 [95% CI = 0.87-1.09] and 0.92 [95% CI = 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 sensitization (OR = 0.92 [95% CI = 0.75-1.13] and 0.93 [95% CI = 0.57-1.54], respectively). However, cat- and dog-specific allergic sensitization was strongly associated with school-age asthma (OR = 6.69 [95% CI = 4.91-9.10] and 5.98 [95% CI = 3.14-11.36], respectively). There was also some indication of an interaction between ownership and sensitization, suggesting that ownership may exacerbate the risks associated with pet-specific sensitization but offer some protection against asthma in the absence of sensitization.

Conclusion: Our findings do not support early-life cat and dog ownership in themselves increasing the risk of school-age asthma, but they do suggest that ownership may potentially exacerbate the risks associated with cat- and dog-specific allergic sensitization. (J Allergy Clin Immunol 2022;150:82-92.)

Key words: *Cat, dog, asthma, allergic sensitization, exposure, ownership, children, meta-analysis, birth cohort, life course epidemiology, FAIR (findable, accessible, interoperable, and reusable)*

Abbreviations used

ALSPAC:	Avon Longitudinal Study of Parents and Children
DNBC:	Danish National Birth Cohort
FVC:	Forced vital capacity
Gen R:	Generation R
INMA:	Infancia y Medio Ambiente (Environment and Childhood Project)
IPD:	Individual participant data
MoBa:	Norwegian Mother, Father and Child Cohort Study
NINFEA:	Nascita e INFanzia: gli Effetti dell'Ambiente (Birth and Childhood: Effects of the Environment)
OR:	Odds ratio
SWS:	Southampton Women's Survey

Asthma is the most prevalent noncommunicable disease of childhood,[1] and it represents a huge and growing burden for affected families, society, and health care systems.[2] Although its etiology is incompletely understood, evidence suggests that early-life environmental and lifestyle factors play a vital role in its development.

Allergic sensitization is a risk factor for asthma.[3,4] However, although allergen exposure has been consistently associated with more severe asthma[5-7] and increased frequency of asthma exacerbations[5,6,8-10] in children with asthma and sensitized to the corresponding allergen, the exact relationship between allergen exposure and the development of allergic sensitization 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 another[14] and are consequently ubiquitous in the environment.[15-18] There is evidence that exposure to high levels of pet allergens (more pets) may actually decrease a child's risk of sensitization by inducing immune tolerance, similar to allergen-specific immunotherapy. For instance, some studies have observed an inverse dose-response association between early-life pet exposure and risk of asthma and allergy,[19,20] and other studies have shown that children exposed to higher concentrations of cat allergen have higher IgG levels and decreased sensitivity to the major cat allergen *Felinus domesticus* 1.[21,22]

Timing of exposure may also be important, with the first year of life appearing to be a critical window for the development of tolerance.[23] Although fewer studies have examined the effect of prenatal pet exposure on later risk of allergic sensitization and asthma, there is evidence that these could also influence allergic disease development.[24-26] For example, offspring of mothers

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who underwent allergen-specific immunotherapy during pregnancy have been observed to have reduced risk of allergen-specific sensitization later in life.[27]

Finally, many studies have observed differences in effects depending on the type of pet owned,[28,29] suggesting that pet-specific differences in allergens, associated microbes,[30] and pet keeping practices[31] also influence whether pet exposure confers risk or protection against asthma and allergy.

The aim of this study was to examine the associations of early-life cat and dog ownership with the development of asthma in childhood. We specifically examined how these associations are influenced by type of pet (cat vs dog), timing of ownership (never, prenatal, or early-childhood) and number (0, 1, or >1) of cats or dogs owned. We also examined the role of cat- and dog-specific allergic sensitization. We hypothesized that cat- and dog-specific allergic sensitization is 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 European Union Child Cohort Network.[32] Details of how variables were harmonized for LifeCycle are provided at the EU Child Cohort Network Variable Catalogue (http://catalogue.lifecycle-project.eu) and elsewhere.[33]

Cohorts in the network were eligible for this study if they had the following data: (1) cat or dog ownership ascertained during pregnancy and/or when the child was aged 2 years or younger and (2) current asthma when the child was older than 5 years or cat- or dog-specific allergic sensitization in the child. The participating cohorts were as follows: the Avon Longitudinal Study of Parents and Children (ALSPAC United Kingdom),[34,35] the Danish National Birth Cohort (DNBC [Denmark]),[36] the Study on the Prenatal and Early Postnatal Determinants of Child Health and Development (Déterminants pré et post-natals du développement de la santé de l'enfant [EDEN] [France]),[37] Generation R (Gen R [The Netherlands]),[38] the Environment and Childhood Project (INMA [Spain]),[39] the Norwegian Mother, Father and Child Cohort Study (MoBa [Norway]),[40,41] the Birth and Childhood: Effects of the Environment (Nascita e INFanzia: gli Effetti dell'Ambiente [NINFEA] [Italy]),[42] the Raine Study [Australia],[43] and the Southampton Women's Survey (SWS [United Kingdom]).[44] Descriptions and characteristics of the participating cohorts are provided in Supplementary Information 1 and Tables E1 and E2 (all of which are available in the Online Repository at www.jacionline.org).

Cat and dog ownership

Our exposure measures were based on parental reports of having a cat or dog during pregnancy or early childhood (ie, ownership [see Table E3, which is available in the Online Repository at www.jacionline.org]), with the assumption that this equates to exposure. We harmonized data collected during pregnancy and the first 3 years of life to create 4 variables relating to (1) cat ownership at any time from conception to the age of 2 years (yes/no); (2) dog ownership at any time from conception to the age of 2 years (yes/no); (3) number of cats owned (0, 1, or >1); and (4) number of dogs owned (0, 1, or >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 the age of 2 years.

Two categoric variables were created to examine the influence of timing of cat and dog ownership (never, prenatal only, early childhood only, or 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 the age of 2 years.

Primary outcome: Current asthma at school age

Our primary outcome was current asthma at school age (median age 7 years, range 6-9 years), harmonized by using data obtained from parental questionnaires (see Table E4 in the Online Repository at www.jacionline.org) according to the MeDALL (Mechanisms of the Development of Allergy) definition,[45] whereby a child was classified as having current asthma when at least 2 of the following 3 criteria were reported: (1) doctor diagnosis of asthma ever, (2) use of asthma medication in the past 12 months, and (3) wheezing in the past 12 months according to the International Study of Asthma and Allergy in Childhood (ISAAC) parental core questionnaire.[46] Records with missing data on 2 of the 3 criteria were coded as missing. In 3 cohorts (ALSPAC, MoBa, and NINFEA), only partial harmonization was achieved (see Table E4). In cases in which data regarding current asthma were available at several ages, we analyzed current asthma at the age closest to the median "current asthma" age of the pooled study population (7 years).

Secondary outcomes: Allergic sensitization and lung function

Information on allergic sensitization to cat, dog, and other aeroallergens at school age (median age 7 years, range 5-11 years) was available in 8 cohorts; specifically, information on cat and other aeroallergens was available for 5 cohorts (ALSPAC, Gen R, INMA, the Raine Study, and SWS), and information on dog allergen was available for 3 cohorts (ALSPAC, Gen R, and SWS). Sensitization was defined as having a skin prick test response of at least 3 mm compared with the negative control in 2 cohorts (ALSPAC and SWS); as at least 40% of the positive histamine control in 1 cohort (Gen R); or as a serum allergen-specific IgE level higher than 0.35 allergen-specific kilounits per liter in 2 cohorts (INMA and the Raine Study) (see Table E4). In those cases in which allergic sensitization was measured at several ages, the measurements taken at the age closest to the median age of measurement (7 years) were analyzed.

Details of the lung function measurements (FEV_1, forced vital capacity [FVC], and FEV_1/FVC ratio) are given in Table E4 and Supplementary Information 2 (available in the Online Repository at www.jacionline.org).

Covariates

Potential confounders were identified on the basis of the literature and then selected by constructing directed acyclic graphs (see Figs E1 and E2 in the Online Repository at www.jacionline.org). The selected variables included (1) maternal asthma (yes/no), (2) maternal inhalant allergy (yes/no), (3) paternal asthma (yes/no), (4) maternal education level (low, medium, or high), (5) quartiles of predicted equivalized total disposable household income[47] or reported household income, (6) maternal ethnicity (white, Black, Asian, or minority ethnic/mixed), (7) sibling position (1, 2, or ≥3), (8) maternal smoking during pregnancy (yes/no), (9) maternal age at birth, (10) sex, and (11) number of children living in the household when the child was aged 2 years or younger (1, 2, or ≥3). For associations between allergic sensitization and asthma, confounders also included (12) gestational age (in days), (13) birth weight (in grams), (14) cesarean delivery (yes/no), (15) ever breast-fed (yes/no), (16) early-life cat ownership (yes/no), and (17) early-life dog ownership (yes/no). Information on covariates was obtained primarily from a questionnaire, interviews, or medical records (summarized in Table E5 in the Online Repository at www.jacionline.org).

Statistical analysis

All analyses were conducted in R software (version 3.5.2) by using the federated analysis platform DataSHIELD (version 6.0.1),[48,49] 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 (summarized in Fig 1).

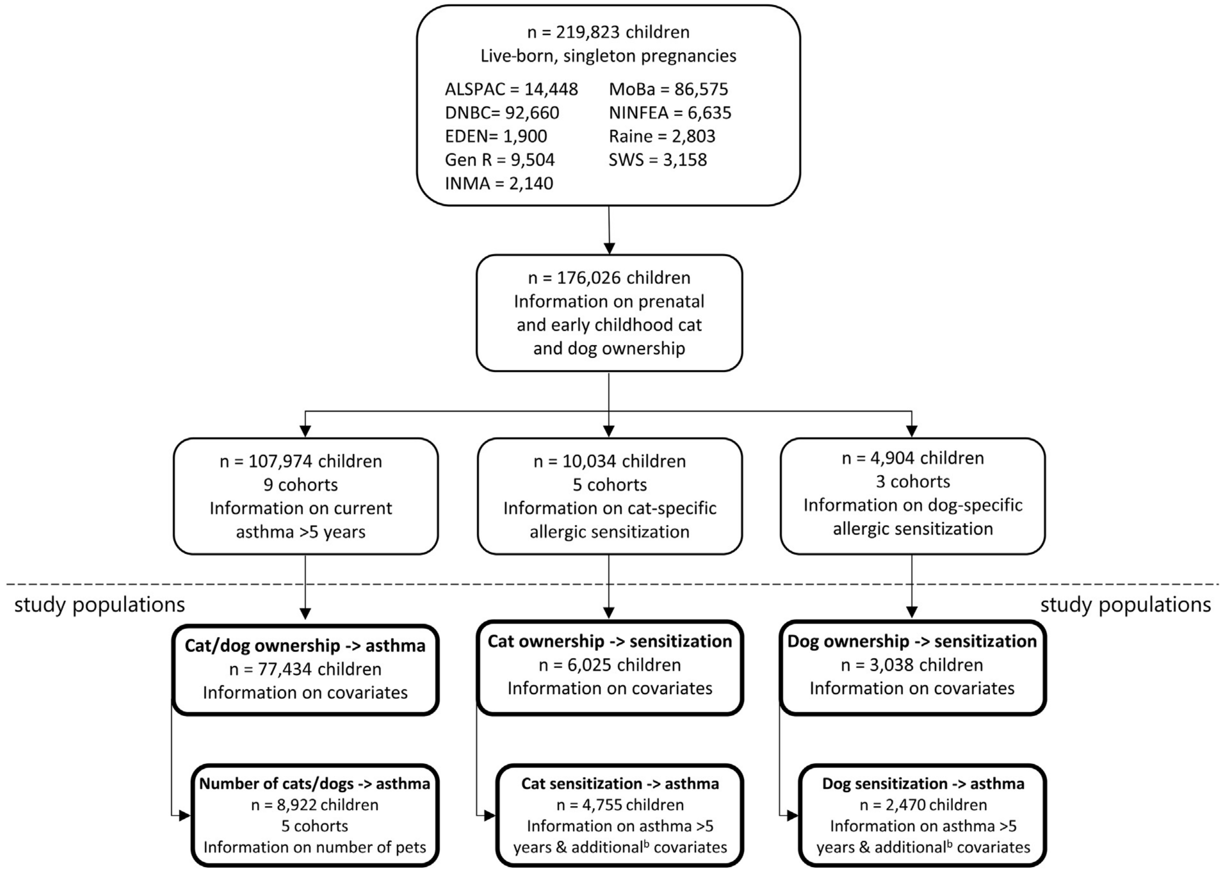

FIG 1. Flowchart illustrating participants included in the study.[a] [a]The same populations were used in both the crude and adjusted analyses. Descriptions of the individual cohorts participating in the study are given in Supplementary Information 1. [b]Analyses examining associations of cat- and dog-specific allergic sensitization with current asthma at school age included these additional covariates: gestational age (in days), birth weight (in grams), cesarean delivery (yes/no), and ever breast-fed (yes/no).

We examined associations of cat and dog ownership (yes/no, number, and timing) with school-age asthma by using logistic regression models. Logistic regression models were also used to examine associations of (1) cat and dog ownership with cat- and dog-specific allergic sensitization, respectively; (2) cat- and dog-specific allergic sensitization with asthma; and (3) cat and dog ownership with aeroallergens other than cat and dog. Associations of cat and dog ownership with lung function (FEV_1, FVC, and FEV_1/FVC ratio) were examined by using linear regression models (see 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 the "level 1" units and mothers as the "level 2" units. We performed analyses first without adjustment, then with adjustment for confounders, and finally with 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 up to age 2 years, respectively. To assess the joint effects of pet ownership and pet-specific allergic sensitization, we tested for multiplicative interaction and created 2 variables with the following categories: (1) no ownership and not sensitized, (2) ownership and not sensitized; (3) no ownership and sensitized; and (4) ownership and sensitized. 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 (βs) and SEs combined using random effects meta-analysis by using the restricted maximum likelihood estimator method. Between-cohort heterogeneity was evaluated by 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: (1) omitting covariates not available in all cohorts (maternal inhalant allergy, maternal ethnic background, and number of children in the home), (2) restricting the population to individuals with sensitization data, (3) excluding each cohort in turn, and (4) pooling data and including cohort as a fixed effect.

Ethical approval

Each participating cohort obtained ethical approval from its local ethics committee and consent from participants (see Supplementary Information 6 and 7 in the Online Repository at www.jacionline.org).

RESULTS

The prevalence of 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. Fig 2, *A* and *B* displays the respective timing of cat and dog ownership across cohorts. Ownership both prenatally and in early childhood was the most common timing of ownership, whereas ownership prenatally only was the least common timing of ownership. The characteristics of cat and dog owners were relatively consistent across cohorts (see Tables E1 and E2). Cat and dog owners tended to have a lower household income, lower maternal education, and higher prevalence of maternal smoking (see Tables E1 and E2). Prevalence of parental asthma was comparable between cat and dog owners and non–cat and dog owners, but prevalence of

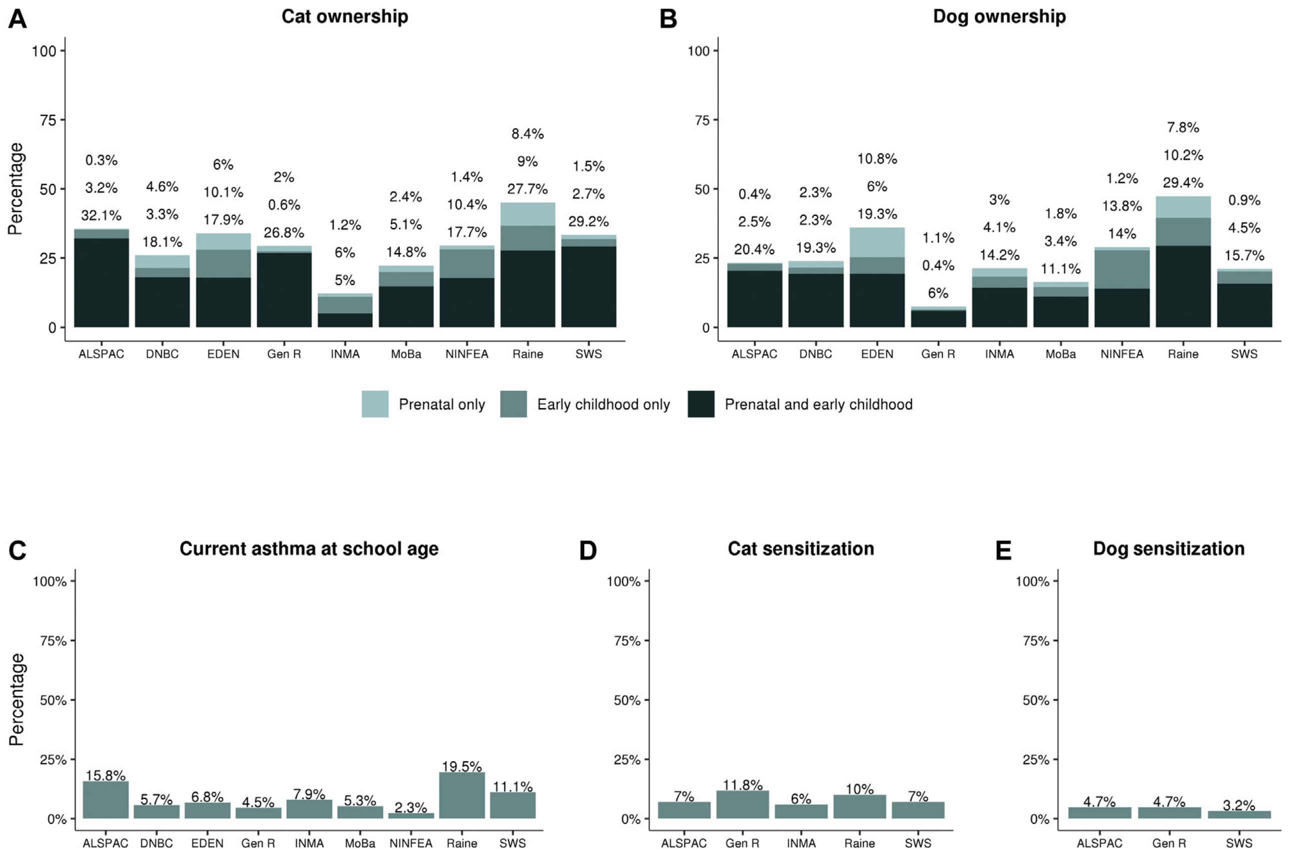

FIG 2. Distribution of exposures and outcomes in participating birth cohorts. **A,** Prevalence of cat ownership by timing. **B,** Prevalence of dog ownership by timing. **C,** Prevalence of current asthma at school age. **D,** Prevalence of cat-specific allergic sensitization. **E,** Prevalence of dog-specific allergic sensitization. **A** and **B,** values are for the following (*from top to bottom*): prenatal only, early childhood only, and prenatal and early childhood.

maternal inhalant allergy was slightly lower among cat and dog owners in some cohorts (see Table E2).

The prevalence of current asthma at school age ranged between 2.3% (NINFEA) and 19.5% (the Raine Study), whereas the prevalence of sensitization to cats and dogs ranged from 6% (INMA) to 12% (Gen R) and from 3% (SWS) to 5% (ALSPAC and Gen R), respectively (Figs 2, *C-E*).

Associations of cat and dog ownership with asthma and lung function

In total, 77,434 children from 9 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 see Fig E3 in the Online Repository at www.jacionline.org) or for wheezing in infancy or parental asthma modifying these associations (*Pinteraction* > .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 versus for boys (see Table E6 in the Online Repository at www.jacionline.org).

The results from the sensitivity analyses are summarized in Table E7 (available in the Online Repository at www.jacionline.org). When analyses were restricted to children with allergic sensitization data, slightly lower odds ratios (ORs) were observed for the effect of cat ownership on current asthma (see Table E7). Similarly, when the DNBC cohort was excluded, a slightly lower OR was observed for dog ownership (see Table E7). However, the differences in the ORs observed in the sensitivity analyses were not sufficient to alter conclusions.

In the 6 cohorts with relevant data (ALSPAC, INMA, EDEN, Gen R, the Raine Study, and 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 E8 and E9, all of which are available in the Online Repository at www.jacionline.org).

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, whereas both ownership in early childhood only and continuous ownership were associated with lower odds of school-age asthma than was no ownership (Table I). For all time windows, however, the ORs were close to the null.

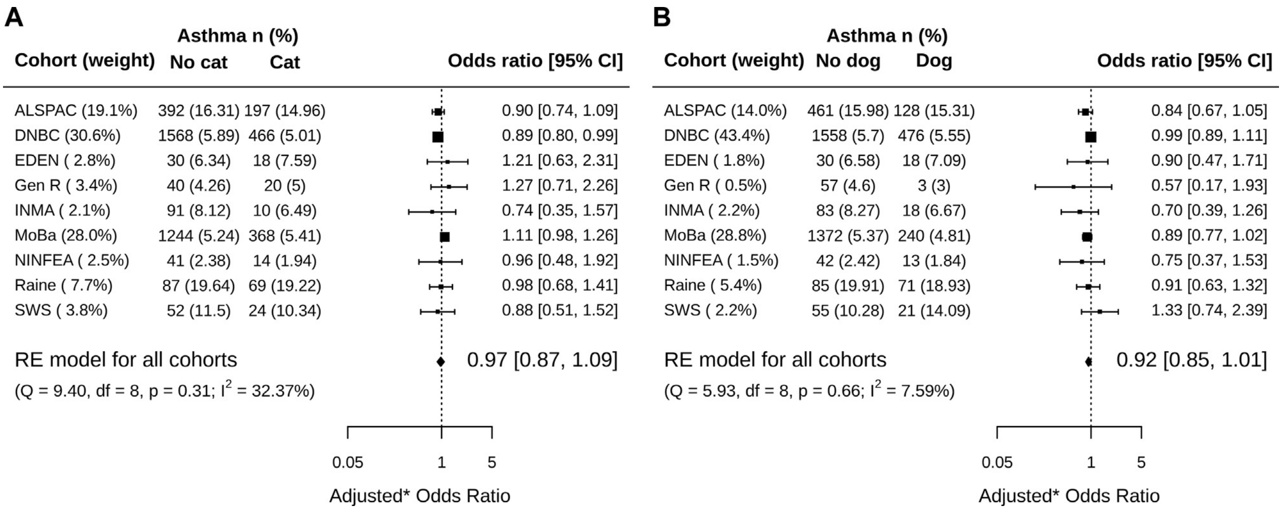

FIG 3. Forest plots for associations of family cat **(A)** and dog **(B)** ownership in pregnancy and early childhood with school-age asthma. *Adjusted for maternal and paternal asthma, maternal inhalant allergy, maternal education, household income, ethnic background, maternal age at birth, maternal smoking during pregnancy, birth order, number of children living in the home, and sex of the child; mutually adjusted for cat and dog ownership. *RE,* Random effects.

The odds of current asthma at school age were relatively constant for ownership of 1 versus multiple cats or dogs, suggesting either no or only a very weak association (Table II).

The role of cat- and dog-specific allergic sensitization

Cat and dog ownership were not associated with cat- and dog-specific allergic sensitization, respectively (Fig 4 and see Fig E4 in the Online Repository at www.jacionline.org). These results were not modified by parental asthma or infant wheeze ($P_{interaction} > .22$), and they were consistent for girls and boys (see Table E6). In contrast, both cat- and dog-specific allergic sensitization were associated with school-age asthma (Fig 5 and see Fig E5 in the Online Repository at www.jacionline.org), with stronger associations observed among girls than among boys (see Table E6).

There was also evidence for an interaction between dog ownership and dog-specific allergic sensitization, with the joint effect of early-life dog ownership and dog-specific allergic sensitization being greater than would be expected on either an additive or multiplicative scale (Table III). The small numbers and wide CIs should be noted, however. A similar, weaker tendency was observed for cat ownership and cat-specific allergic sensitization (Table III). Slightly lower odds of asthma were observed among children who had a cat or dog in early life but did not develop sensitization (Table III). In further analyses, cat and dog ownership were also associated with lower odds of allergic sensitization to aeroallergens other than cat and dog (see Fig E6 in the Online Repository at www.jacionline.org).

DISCUSSION

In this meta-analysis of 9 birth cohort studies including more than 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 FEV_1 and FEV_1/FVC ratio, both of which are objective markers of airflow obstruction. And similarly, no strong association was found 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 sensitization. There was some indication, however, of a possible interaction between ownership and sensitization. Cat-specific allergic sensitization and dog-specific allergic sensitization were both associated with school-age asthma, and this association was stronger among children who had a cat or dog in early-life, although it was based on small numbers. In contrast, early-life cat and dog ownership without sensitization was associated with slightly lower odds of asthma.

Strengths and limitations

This is the first study to use a federated approach to analyze harmonized individual participant data (IPD) from 9 birth cohorts from the European Union Child Cohort Network.[32,33] To date, all but 1 meta-analysis examining associations of early-life pet ownership with school-age asthma have been based on aggregate published data, and to our knowledge, this is the first meta-analysis using IPD to examine associations of cat and dog ownership with cat- and dog-specific allergic sensitization and lung function, as well as 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 harmonized data and consistent adjustment for confounding. Analyzing IPD also enabled us to investigate possible effect modification by parental asthma and infant wheeze, as well as interaction between ownership and sensitization. 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

TABLE I. Influence of timing of exposure on associations of cat and dog ownership with current asthma at school age

Timing of ownership	n	Odds of school-age asthma			
		Crude OR (95% CI)	I^2	Adjusted 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 I^2 values are from 2-stage random effects meta-analysis. All cohorts had relevant data and were included in analyses (ALSPAC, DNBC, EDEN, Gen R, INMA, MoBa, NINFEA, the Raine Study, and SWS).
*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.

TABLE II. Associations between number of cats and dogs owned and odds of current asthma at school age

Number of cats or dogs	n	Odds of current asthma at school-age			
		Crude OR (95% CI)	I^2	Adjusted OR* (95% CI)	I^2
Cats					
0	6449	Reference		Reference	
1	1504	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					
0	6957	Reference		Reference	
1	1575	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 I^2 values are from 2-stage random effects meta-analysis. Average number of cats and dogs across early-life (prenatally and early childhood). The cohorts with relevant data were ALSPAC, INMA, NINFEA, the Raine Study, and SWS. In SWS, data on number of cats and dogs were available only for the prenatal period.
*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.

asthma by using the International Study of Asthma and Allergy in Childhood questionnaires, or adaptions thereof, which have been extensively validated against bronchial hyperresponsiveness[50] and physician-diagnosed asthma.[51] In addition, our measure of school-age asthma was based on the Mechanisms of the Development of Allergy definition, which was developed by a panel of experts and considers symptoms of asthma, medication, and doctor diagnosis.[45] We were also able to explore associations with more objective measures of allergy and respiratory health by using skin prick test/IgE level 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[52,53]; 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 (eg, infant wheeze) may result in the removal of pets from the home; this may be less common than avoidance, however.[52] 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 because of allergies or asthma in the family. Unfortunately, these data were not available in the majority of cohorts.

All but 1 cohort (the Raine Study), lacked information on pet keeping practices (eg, whether the cat or dog was kept mainly or 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, families that include a member with allergy or asthma and own a pet could modify their pet keeping practices in an attempt to mitigate any associated detrimental health effects. Although there is very limited evidence that removing pets from main living areas or bedrooms is effective at reducing indoor allergen levels,[54] it could affect the exchange of microbiota,[55] 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.[56,57]

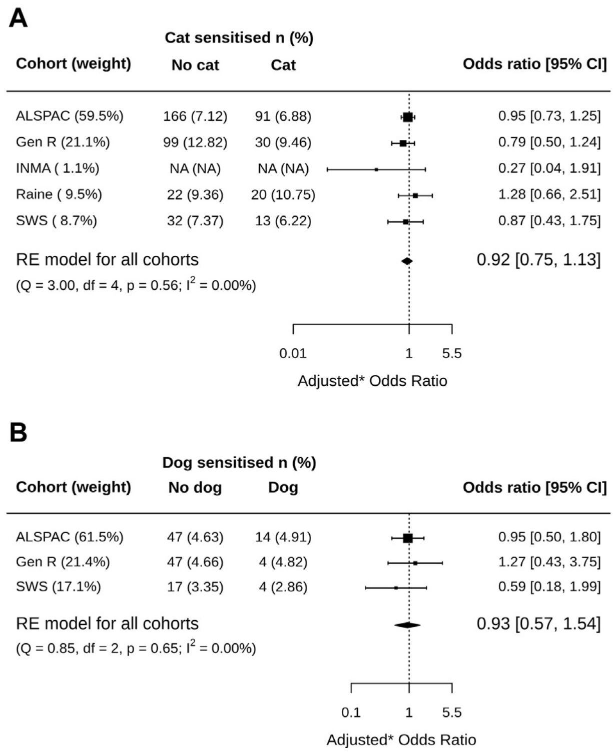

FIG 4. Forest plots for associations of cat ownership with cat-specific allergic sensitization **(A)** and dog ownership with dog-specific allergic sensitization **(B)**. *Adjusted for maternal and paternal asthma, maternal inhalant allergy, maternal education, household income, maternal ethnic background, 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. *NA,* Fewer than 3 for at least 1 summary statistic and not presented owing to risk of disclosure; *RE*, random effects.

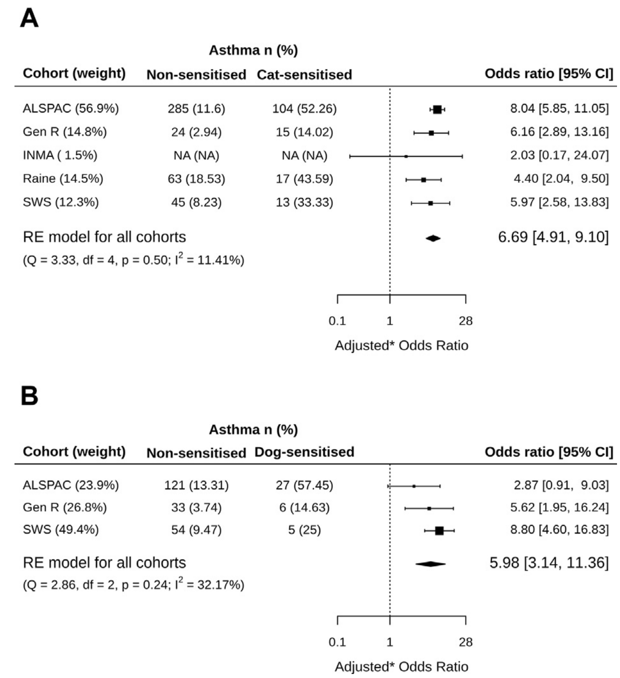

FIG 5. Forest plots for associations of cat-specific allergic sensitization **(A)** and dog-specific allergic sensitization **(B)** with current asthma at school age. *Adjusted for maternal and paternal asthma, maternal inhalant allergy, maternal education, household income, maternal ethnic background, maternal age at birth, maternal smoking during pregnancy, birth order, number of children living in the home, sex, gestational age, birth weight, cesarean delivery, ever breast-fed, early-life cat ownership, and early-life dog ownership. *NA,* Fewer than 3 for at least 1 summary statistic and not presented owing to risk of disclosure; *RE*, random effects.

A further limitation of the current study is our restricted measure of allergic sensitization and asthma. Although the large majority of epidemiologic studies investigating risk factors for allergic sensitization treat sensitization as an all or nothing (yes/no) phenomenon, evidence clearly demonstrates that degree of sensitization is an important determinant of clinical symptoms.[58-62] Moreover, the arbitrary cutoffs that are applied to determine allergic status have poor positive predictive value.[63] In light of this, examining associations of cat or dog ownership with quantitative measures of allergic sensitization may have provided more informative results; unfortunately, these data were available in only 2 of the participating cohorts.

Similarly, it is increasingly recognized that asthma and allergic sensitization are not single phenotypes and are instead umbrella terms for multiple phenotypes with different underlying etiologies.[64,65] Because 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 ownership of a furry or feathered pet in the first 2 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; such studies have reported null or weak and inconsistent associations, with substantial between-study heterogeneity.[29,66,67] 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 sensitization and harmful effect in the presence of sensitization.

We observed a suggestion of slightly higher 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 earlier in this article. 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.[68-71] 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 sensitization to the respective allergen, suggesting that ownership is unlikely to be the main determinant of cat- and dog-specific allergic sensitization; instead, other factors such as genetic susceptibility are likely decisive. Other cohort studies examining associations of pet ownership with allergic sensitization to associated allergens have

TABLE III. Associations of joint cat or dog ownership and cat or dog-specific allergic sensitization with current asthma at school age

		Odds of school-age asthma				
Ownership and sensitization status	**n**	**Crude OR (95% CI)**	**I^2**	**Adjusted OR* (95% CI)**	**I^2**	**$P_{interaction}$†**
Cat ownership						
No cat and not sensitized	2698	Reference		Reference		
Cat and not sensitized	1462	0.80 (0.64-0.99)	0%	0.80 (0.64-1.00)	0%	
No cat and sensitized	250	5.36 (3.71-7.73)	17%	5.94 (4.29-8.22)	0%	
Cat and sensitized	134	5.92 (3.04-11.50)	56%	6.55 (3.66-11.71)	32%	0.07
Dog ownership						
No dog and not sensitized	1983	Reference		Reference		
Dog and not sensitized	379	0.96 (0.66-1.39)	0%	0.78 (0.52-1.17)	0%	
No dog and sensitized	91	4.73 (2.32-9.66)	39%	4.32 (1.51-12.31)	63%	
Dog and sensitized	17	24.20 (6.58-89.03)	0%	23.36 (6.01-90.79)	0%	0.04

OR, 95% CI, and I^2 values are from 2-stage random effect meta-analysis. Cat or dog ownership in early life (from conception to age 2 years) and allergic sensitization at school age (median age 7 years, range 5-11 year). The cohorts with relevant data were ALSPAC, Gen R, the Raine Study and SWS; the INMA cohort was excluded from analyses owing to risk of disclosure.

*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, sex, gestational age, birth weight, cesarean delivery, and ever breast-fed; mutually adjusted for cat and dog ownership.

†$P_{interaction}$ on a multiplicative scale.

been conflicting, with some reporting a positive association[72,73] and others reporting either no[20,73-78] or an inverse association.[20,23,78-80] These inconsistencies could be related to differences in the timing of assessment of allergic sensitization, because trajectories of pet-specific allergic sensitization have been observed to differ in pet owners versus in non–pet owners.[81] In further analyses, cat and dog ownership were associated with slightly lower odds of allergic sensitization to aeroallergens other than cat and dog, suggesting that ownership may confer nonspecific effects. This could occur through alteration of the composition of the microbiome,[55,82-85] which is known to be important in immune development.[86,87]

Like those conducting other studies,[62,88] 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]; however, genome-wide association studies have observed little overlap between loci associated with asthma and those associated with IgE levels, favoring 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 sensitized children with asthma,[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 than for 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,[52] 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 sensitization. Ownership may even offer some protection against asthma among children who do not develop allergic sensitization. Our findings do, however, provide support for the idea of cat- and dog-specific allergic sensitization increasing the risk of school-age asthma and for this risk possibly being higher among children who own a cat or dog, respectively.

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

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