Dog ownership in infancy is protective for persistent wheeze in 17q21 asthma-risk carriers

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Background: Asthma-associated single nucleotide polymorphisms from large genome-wide association studies only explain a fraction of genetic heritability. Likely causes of the missing heritability include broad phenotype definitions and gene-environment interactions (GxE). The mechanisms underlying GxE in asthma are poorly understood. Previous GxE studies on pet ownership showed discordant results.
Objectives: We sought to study the GxE between the 17q12-21 locus and pet ownership in infancy in relation to wheeze.
Methods: Wheezing classes derived from 5 UK-based birth cohorts (latent class analysis) were used to study GxE between the 17q12-21 asthma-risk variant rs2305480 and dog and cat ownership in infancy, using multinomial logistic regression. A total of 9149 children had both pet ownership and genotype data available. Summary statistics from individual analyses were meta-analyzed.
Results: rs2305480 G allele was associated with increased risk of persistent wheeze (additive model odds ratio, 1.37; 95% CI, 1.25-1.51). There was no evidence of an association between dog or cat ownership and wheeze. We found significant evidence of a GxE interaction between rs2305480 and dog ownership ($P = 8.3 \times 10^{-4}$) on persistent wheeze; among dog owners, the G allele was no longer associated with an increased risk of persistent wheeze (additive model odds ratio, 0.95; 95% CI, 0.73-1.24). For those without pets, G allele was associated with increased risk of persistent wheeze (odds ratio, 1.61; 95% CI, 1.40-1.86). Among cat owners, no such dampening of the genetic effect was observed.
Conclusions: Among dog owners, rs2305480 G was no longer associated with an increased risk of persistent wheeze (or asthma). Early-life environmental exposures may therefore attenuate likelihood of asthma in those carrying 17q12-21 risk alleles. (J Allergy Clin Immunol 2022;■■■:■■■-■■■.)

Key words: *Gene-environment interaction, asthma, wheeze, meta-analysis, birth cohort, longitudinal, LCA, dog, cat, ownership, 17q, ALSPAC, STELAR, UNICORN*

Asthma is an umbrella term used to define a heterogeneous collection of conditions that show similar clinical features of cough, wheeze, breathlessness, and chest tightness, usually associated with variable lung function and airway inflammation. Large twin studies estimated the asthma heritability to be between 60% and 90%.[1,2] Conversely, the heritability explained by the genetic variants identified in recent, very large, genome-wide association studies (eg, UK biobank cohort 64,538 cases and 329,321 controls) has been estimated to be only approximately 9%.[3] Gene-environment interactions (GxE) and the usage of broad asthma definitions are thought to likely contribute significantly to the observed "missing" heritability in genome-wide association studies.[4]

When studying GxE, the assumption is that the environmental exposures must precede the clinical manifestations. This makes GxE particularly difficult to study, because asthma usually starts early in life and timing of environmental exposure may be critical for the maturing immune system. For childhood asthma, where many children show clinical signs of the disease at a very young age, relevant exposures likely occur in the first years of life. The ideal population for the study of GxE in childhood asthma is population-based birth cohorts; environmental exposures can be

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Abbreviations used
AE16: Asthma ever at age 16 years
ALSPAC: Avon Longitudinal Study of Parents and Children
GxE: Gene-environment interactions
IOW: Isle of Wight
LCA: Latent class analysis
GSDMB: Gasdermin-B
MAAS: Manchester Asthma and Allergy Study
OR: Odds ratio
OR_{int}: Multiplicative interaction OR, eg, $OR_{DogOwners}/OR_{NoPetOwners}$
RE: Random effect
SEATON: Study of Eczema and Asthma to Observe the Effects of Nutrition
SNP: Single nucleotide polymorphism
STELAR: Study Team for Early Life Asthma Research

recorded prospectively from birth and phenotypes can be precisely defined. Because such studies are labor intensive and costly, they tend to be relatively small with hundreds rather than thousands of participants, and may be underpowered for standalone GxE analysis. To overcome this challenge, 5 unselected UK birth cohorts created The Study Team for Early Life Asthma Research (STELAR) consortium (Avon Longitudinal Study of Parents and Children [ALSPAC], Ashford [ASHFORD], Isle of Wight [IOW], Manchester Asthma and Allergy Study [MAAS], and the Aberdeen Study of Eczema and Asthma to Observe the Effects of Nutrition [SEATON]). Using latent class analysis (LCA) on harmonized longitudinal data collected from birth to adolescence on more than 15,000 well-characterized participants, we have recently described more homogeneous groups of longitudinal wheezing patterns.[5]

Variants in the 17q12-21 locus (commonly called 17q21) are the most frequently replicated genetic associations for asthma. Seventeen single nucleotide polymorphisms (SNPs) in multiple genes (including *GSDMA*, *ORMDL3*, Gasdermin-B [*GSDMB*], *ZPBP2*, *IKZF3*, *ERBB2*, and *PGAP3*) within the 17q12-q21 region have been shown to be associated with asthma,[6] but the causal variant(s) has not been confirmed. However, the *GSDMB* missense variant rs2305480 (892G>A, Pro298Ser) has been widely replicated in association studies of asthma, and was the lead SNP identified in the GABRIEL study and a study of asthma exacerbations.[7,8] More recently, in a transethnic meta-analysis study (where reduced linkage disequilibrium was seen in this region in populations of African ancestry), rs2305480 was identified as the likely causative variant.[9] Previous studies on rs2305480 interaction with environmental exposures already identified maternal smoking and tobacco smoke exposure in early life as an asthma risk factor.[10,11]

Because sensitization to cats and dogs is a common feature of childhood asthma, environmental exposure to pets in early life in relation to asthma development has been widely investigated, but epidemiologic studies showed inconsistent results,[12-14] possibly reflecting different effects of cats and dogs, and differing genetic susceptibilities of study subjects. Four studies have focused on the interaction between 17q12-q21 SNPs and pet ownership, but the study designs and the findings were heterogeneous,[15-18] summarized in Table E1 in this article's Online Repository at www.jacionline.org.

The aim of this study was to evaluate the gene-environment interaction between the missense variant rs2305480 from 17q12-q21 locus and cat and dog ownership in infancy (separately) in relation to the novel wheeze classes in the STELAR cohorts and to a more commonly used asthma definition.

METHODS

Study design, setting, and participants

Information was collected through validated questionnaires at multiple time points from birth to adolescence in 5 population-based birth cohorts brought together in the STELAR consortium (ALSPAC,[18,19] ASHFORD,[20] IOW,[21] MAAS,[22] and SEATON[23]; see Table E2 in this article's Online Repository at www.jacionline.org). A detailed description of each cohort is available in this article's Online Repository at www.jacionline.org.

Definition of exposures: Dog and cat ownership

We focused on individual dog and cat ownership during the first year of life by restricting the analysis to the groups of dog owners only (do not own a cat), cat owners only (do not own a dog), and people who own neither a dog nor a cat. As a comparison, the group of owners of dogs and cats was also used. If siblings were members of the same cohort, only 1 sibling was chosen randomly to be included in the study. Ownership of other pets was not taken into account but, for the scope of this study, we will refer to the group with no dogs or cats as non–pet owners. The variables used to define pet ownership in each cohort can be found in Table E3 in this article's Online Repository at www.jacionline.org.

Definition of outcomes

We used wheezing classes derived from LCA on longitudinal wheezing data collected from birth up to 18 years.[7] To obtain consistent classes between cohorts, children from all 5 cohorts with data collected in at least 2 (of 5) time points were pooled together (n = 15,941). As previously reported, a 5-class solution was selected as the optimal model and, based on wheezing patterns, the classes were labeled as (1) never/infrequent wheeze (52.4%); (2) early-onset preschool remitting wheeze (18.6%); (3) early-onset middle-childhood remitting wheeze (9.8%); (4) persistent wheeze (10.4%); and (5) late-onset wheeze (8.8%). A more detailed description on how the classes were derived is provided in this article's Online Repository at www.jacionline.org together with their frequency within each cohort (see Table E5 in this article's Online Repository at www.jacionline.org). We also used the broad binary asthma definition asthma ever at age 16 years (AE16). The variables used for each individual cohort to derive the phenotypes are reported in Table E3.

rs2305480 genotype

GSDMB missense variant rs2305480 was genotyped and passed quality control in all 5 cohorts (call rate of >95% and Hardy-Weinberg equilibrium *P* value $>3 \times^{-8}$). MAAS children were genotyped using the Illumina 610 quad genome-wide SNP genotyping platform (Illumina, Inc, San Diego, Calif). IOW, SEATON, and ASHFORD were genotyped using the Illumina Infinium Omni2.5-8 v1.3 BeadChip genotyping platform (Illumina, Inc). ALSPAC children were genotyped using the Illumina HumanHap550 quad genome-wide SNP genotyping platform (Illumina, Inc) by the Wellcome Trust Sanger Institute (Cambridge, UK) and the Laboratory Corporation of America (Burlington, NC), using support from 23andMe.

The genotype was coded as dosage of the alternative, asthma risk (G) allele (0 = AA, 1 = AG, 2 = GG).

Statistical analysis

MAAS, IOW, SEATON, and ASHFORD cohorts were jointly analyzed (hereafter referred to as Joint cohort), whereas ALSPAC was analyzed separately. The robustness of pooling the participants as opposed to pooling

TABLE I. Number of study participants available for each analysis

	MAAS	IOW	SEATON	ASHFORD	Joint total	ALSPAC	Joint + ALSPAC
With pet ownership and genotype data*	653	983	553	398	2587	6562	9149
Female	317 (48.5)	503 (51.2)	295 (53.3)	197 (49.4)	1312 (50.7)	3222 (49.1)	4534 (49.6)
Own cat and dog	9 (1.4)	80 (8.1)	20 (3.6)	0 (0)	109 (4.2)	413 (6.3)	522 (5.7)
Own only dog	79 (12.1)	184 (18.7)	66 (11.9)	15 (3.8)	344 (13.3)	1133 (17.3)	1477 (16.1)
Own only cat	102 (15.6)	212 (21.6)	112 (20.2)	12 (3)	438 (16.9)	1719 (26.2)	2157 (23.6)
LCA	643 (98.5)	902 (91.8)	532 (96.2)	398 (100)	2475 (95.7)	5850 (89.1)	8325 (90.1)
AE16	527 (80.7)	902 (91.8)	527 (95.3)	398 (100)	2354 (90.1)	2991 (45.6)	5345 (58.4)

Values are n (%). Percentage denominator is the group with pet ownership and genotype data.
*Siblings of an index case excluded.

the estimates (meta-analysis of the 4 individual cohorts) and power of the analysis were evaluated and presented in Table E6, Table E7, and Table E15 in this article's Online Repository at www.jacionline.org. The summary statistics from the analysis of the Joint and ALSPAC cohorts were meta-analyzed. Dog and cat ownership and rs2305480 genotype (additive model), and their interaction, were tested for association with AE16 using logistic regression. Multinomial logistic regression was used to test for association of dog and cat ownership and rs2305480, and their interaction, with LCA wheezing classes using never-infrequent wheeze (hereafter simply referred to as never wheeze) as the reference phenotype. Sex was used as a covariate in all regression models. For the Joint cohort, the cohort IDs were also included as covariate to control for differences in the frequencies of LCA clusters between cohorts. Statistical analysis of the Joint cohort was performed with R version 3.6.0 with glm and mlogit functions from the R packages stats and mlogit (https://cran.r-project.org/package=mlogit). Statistical analysis for ALSPAC was performed in STATA (https://www.stata.com/). Summary statistics from the independent analyses of Joint and ALSPAC cohorts are presented in Tables E8 to E13 and Fig E2 in this article's Online Repository at www.jacionline.org. Finally, the estimates from the 2 individual analyses (Joint and ALSPAC cohorts) were meta-analyzed using both fixed-effect and random-effect (RE) models with metafor v2.4 R package, and presented in the main results.

Environmental exposures

For the MAAS cohort, at age 5 years (N = 1024), floor dust was collected from the living room by vacuuming 2 areas of 1 m^2 for 2 minutes.[24] A kinetic limulus assay was used to measure the endotoxin levels.[25] Pet ownership data at age 5 years were also collected. Endotoxin levels (log normal transformed) were tested for association with pet ownership and LCA wheezing classes with Wilcoxon test and multinomial logistic regression, respectively.

RESULTS

Participants flow

Joint cohorts' population. Of the 3031 children with genotype data, 32 were excluded because they were siblings of an index case, 412 were excluded because data on pet ownership in early life were not available, leaving 2587 subjects with genotype and pet ownership data available for analysis (G allele frequency: overall Joint cohorts, 52%; ASHFORD, 55%; IOW, 53%; MAAS, 52%; SEATON, 51%) (Table I; Table E4). Of these, 438 and 344 children exclusively owned a cat or a dog, respectively, whereas 109 owned both pets. Of 2587 available subjects, 2475 and 2354 subjects also had LCA and AE16 data available, respectively (Table I).

ALSPAC. For the ALSPAC cohort, of 8952 children with genotype data, 81 siblings and 2309 children with no pet information were excluded, leaving 6149 children with both genotype and pet ownership information (G allele frequency 52%). Of these, 5850 and 2991 also had LCA and AE16 phenotype, respectively (Table I; Table E4).

Relationship between LCA classes and asthma

Depending on the asthma definition or the age of the participants used for the study, the composition of the case and control groups can change dramatically. Of 2587 participants from the Joint cohort, with both pet ownership and genotype data (which are used in all subsequent analyses), 2475 also had data available for LCA class and AE16. Fig 1, *A*, shows the relationship between asthma and the wheezing classes. When comparing AE16 with LCA wheezing classes, derived from wheezing data from birth up to 18 years, both the asthmatic and nonasthmatic groups are composed by a mix of all 5 LCA wheezing classes. Conversely, 90% of participants who are classified as without asthma based on the AE16 definition are in the never-wheeze LCA class. The same is true as the persistent wheeze LCA class, where 89% of participants are classified as asthmatic patients (Fig 1, *B*).

Meta-analysis of rs2305480, dog, and cat ownership association with asthma and wheeze

The summary statistics of the individual associations (main effects) of rs2305480 (additive model), cat, and dog ownership with asthma and LCA wheezing classes in the Joint and ALSPAC cohorts were meta-analyzed.

The meta-analysis of the summary statistics for rs2305480 association with asthma showed that the SNP was associated with AE16 (RE model $P = 5.4 \times 10^{-7}$). The SNP was also associated with persistent wheeze (RE $P = 8.4 \times 10^{-11}$) and late-onset (RE $P = .03$) wheeze LCA classes (Fig 2, *A*). The meta-analysis of summary statistics for pet ownership in the first year of life showed no association for either pet with asthma or with any wheezing classes (Fig 2, *B-D*).

Meta-analysis of stratified results

To investigate the effect of pet ownership in the context of genotype on the clinical outcomes, we first meta-analyzed the genetic associations of rs2305480 with asthma and wheezing classes stratified by pet ownership. In the non–pet owners, the *GSDMB* missense variant (G allele) of rs2305480 was associated with increased risk of AE16 and the LCA classes late-onset and persistent wheeze (Fig 3, *A*). Similar results were seen for cat owners (Fig 3, *B*), where the G allele of rs2305480 was associated with increased risk of the asthma phenotype AE16 and the LCA class persistent wheeze (RE odds ratio [OR], 1.2; $P = .04$). In

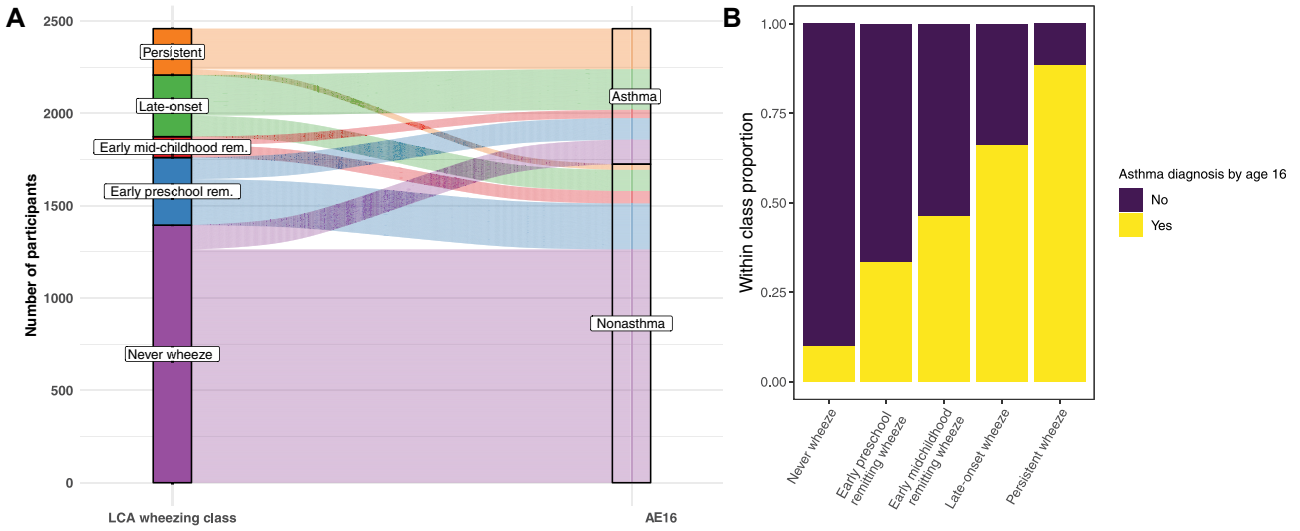

FIG 1. Relationship between the LCA wheezing classes and asthma diagnosis at age 16 years. **A,** Alluvial plot (Joint cohort only) showing how the asthma group is made by a mix of LCA wheezing classes. LCA wheezing classes: persistent wheeze, late-onset wheeze, early midchildhood remittent wheeze, early preschool remitting wheeze, never wheeze. **B,** Frequency of asthma diagnosis at age 16 years within each LCA class. *Rem.*, Remitting.

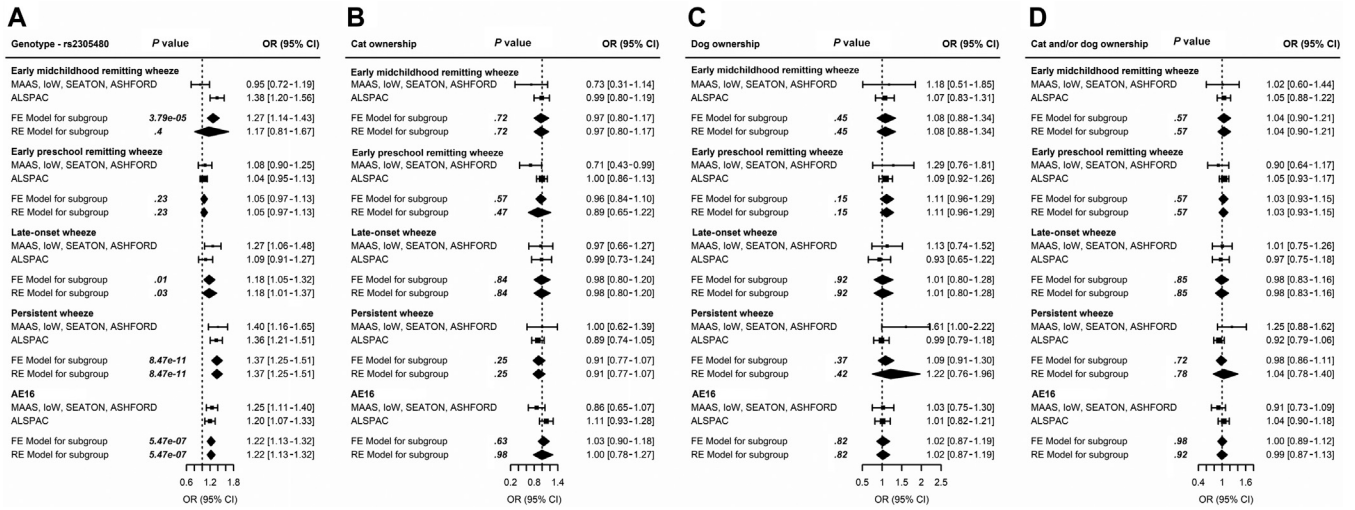

FIG 2. Association of rs2305480, cat, and dog ownership with asthma and wheezing classes—main effects (additive model). Meta-analysis (fixed-effect model = FE, RE model = RE) of main effects associations of rs2305480 (G allele; **A**), strict cat (**B**), strict dog (**C**), and cat and/or dog ownership (**D**) with binary asthma phenotype and LCA wheezing classes.

contrast, for dog owners, there was no association between rs2305480 genotype and AE16 or any wheezing class (persistent wheeze RE OR, 0.95; $P = .71$; Fig 3, *C*).

Meta-analysis of rs2305480 interaction with pet ownership in asthma and wheeze

To formally investigate the interaction between rs2305480 genotype and dog or cat ownership, we meta-analyzed the summary statistics of the logistic models interaction terms (Fig 4). Evidence of a significant multiplicative interaction OR (OR_{int}, interpretable as the ratio of the adjusted stratum-specific ORs, eg, $OR_{DogOwners}/OR_{NoPetOwners}$) was identified between dog ownership and rs2305480 genotype in relation to the LCA class of persistent wheeze, with dog ownership significantly attenuating the risk due to carrying the rs2305480 asthma-risk allele (RE OR_{int}, 0.59; $P = 8.3 \times 10^{-4}$). This is consistent with the stratified results where rs2305480 G allele was associated with an increased risk of persistent wheeze only in the non–pet owners group (while it had null effect for dog owners). Cat ownership, although showing a trend in the same direction as dog ownership, did not show a significant interaction with

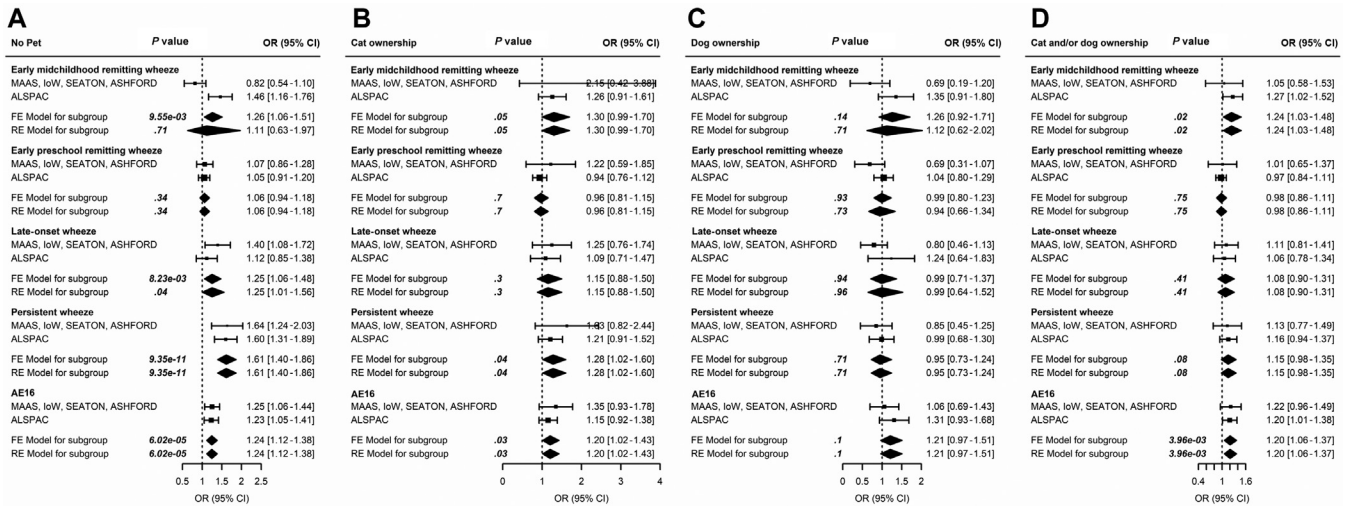

FIG 3. Association of rs2305480 with asthma and wheezing classes stratified by pets' ownership (additive model). Forest plots of meta-analyses (fixed-effect model = FE, RE model = RE) of associations of rs2305480 with binary asthma phenotype and LCA wheezing classes stratified by pet ownership. The forest plots show the results for (**A**) no-pet, (**B**) strict cat, (**C**) strict dog, and (**D**) cat and/or dog owners.

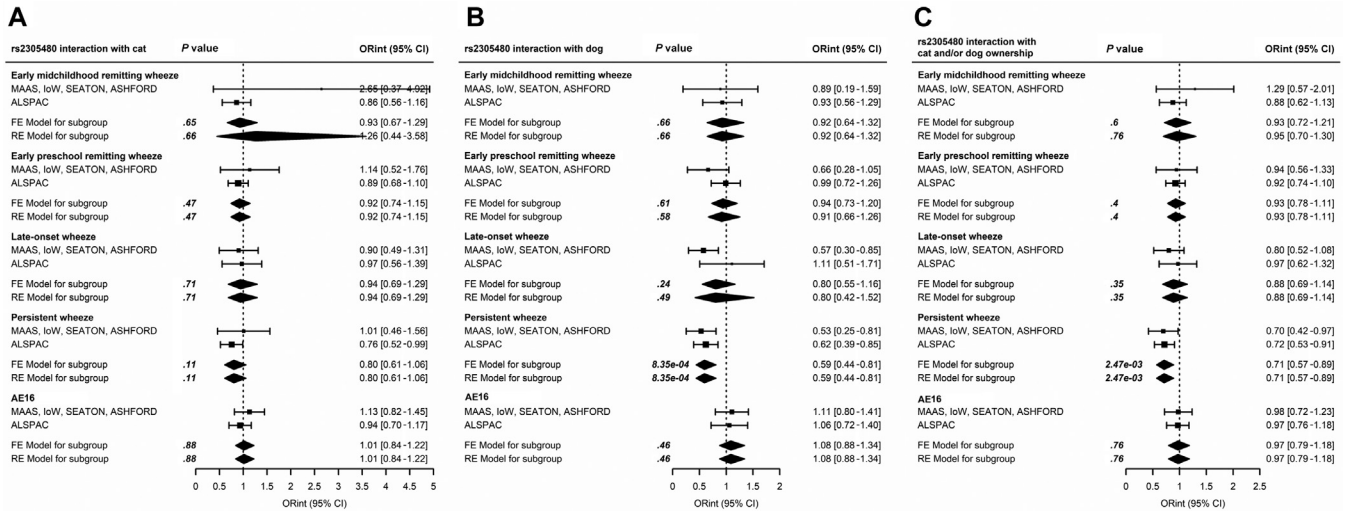

FIG 4. rs2305480 interaction with cat and dog ownership. Meta-analysis of interaction terms of (**A**) cat, (**B**) dog, and (**C**) both pets ownership from logistic regression on AE16 and multinomial logistic regression on LCA classes. Results of the model fit of the interaction term are also available in Table E14.

rs2305480 genotype for the asthma or wheeze outcomes (persistent wheeze RE OR_{int}, 0.8; $P = .1$). Dog and cat ownership (owners of either a cat or a dog were excluded from this analysis) showed the same attenuation of risk of persistent wheeze as dog ownership (Table E16)

To better interpret the interaction between dog ownership and genotype for persistent wheeze, the frequency of participants (from Joint and ALSPAC together) stratified by pet ownership and genotype was visualized (as additive model in Fig 5 and recessive model in Fig E1). Among those without pets (Fig 5 purple line), those carrying the GG (risk) genotype showed an increased prevalence of persistent wheeze. Among cat owners (Fig 5 green line), the risk of persistent wheeze is significantly higher in those carrying the GG genotype, as it was for those without pets (Fig 5). In contrast, dog owners who were homozygous for the rs2305480 asthma-risk allele (GG) showed no increased prevalence of persistent wheeze compared with the other genotype groups (Fig 5 orange line; Fig E3). In this group only, there was no effect of genotype on risk of persistent wheeze.

To help the interpretability of the results and identify possible biological mechanisms, house dust endotoxin levels from the MAAS cohort (no endotoxin level measurement was available for the other cohorts) at age 5 years were tested for association with pet ownership (at age 5 years) and LCA wheezing classes. Endotoxin levels were significantly higher in the houses of pet owners compared with those of non–pet owners (see Table E18 and Fig E4 in this article's Online Repository at www.jacionline.org), with levels higher in the homes of dog owners

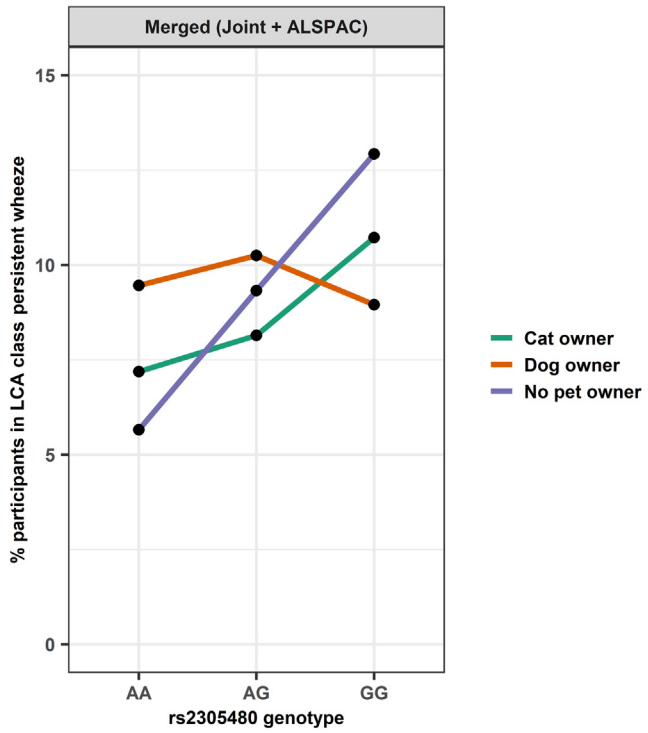

FIG 5. Persistent wheeze stratified frequency. Frequency of participants (Joint + ALSPAC) in the persistent wheeze class by pet ownership and genotype.

than in those of cat owners (Fig E4). Higher endotoxin levels were also found to be specifically associated with a reduced risk of persistent wheeze (OR, 0.89, $P = .04$; Table E18).

DISCUSSION

We present the results of the largest study to date of the GxE between 17q21 locus and cat and dog ownership in infancy, for asthma and wheeze in young adults. As expected, for the whole population, we replicated the finding that rs2305480 risk allele (G) was associated with increased risk of asthma. We also found that the rs2305480 asthma-risk allele increased the risk of late-onset and persistent wheeze. Consistent with the recently reported results of a very large meta-analysis on European children,[14] we found no association between dog and cat ownership in the first year of life and asthma or any wheeze outcome when studied in the whole population. When the interaction between genotype and pet ownership was investigated, our most striking finding was that among dog owners, this most replicated asthma risk allele (rs2305480_G) was no longer associated with an increased risk of asthma or any wheeze phenotype. Among cat owners we saw no such dampening of the genetic effect.

GSDMB missense variant rs2305480 showed a stronger association with persistent wheeze than with asthma

Although the *GSDMB* missense variant rs2305480 was significantly associated with the asthma phenotype, AE16 (OR_{AE16}, 1.22), the largest effect size was seen with persistent wheeze ($OR_{Persistent}$, 1.37), supporting our hypothesis that using a more precise phenotype increases power in genetic association studies (although it has to be noted that the 95% CIs partially overlapped). We also showed that rs2305480 was associated with late-onset wheeze and not with either of the early remitting classes.

The interaction between dog ownership and rs2305480 and wheeze

The meta-analysis of rs2305480 association with asthma and LCA wheezing classes stratified by pets' ownership and the meta-analysis of the interaction terms between pets and genotype showed consistent findings.

Among children who had dogs in the home in the first year of life, carrying the risk allele of the SNP was not associated with an increased risk of asthma or any of the wheeze phenotypes investigated. In contrast, among those children not exposed to pets or exposed to cats only, the risk allele was consistently associated with an increased risk of asthma and wheeze. The effect of this variant, which has been consistently shown to increase asthma risk in numerous studies (and is present in 56% of the European population), appeared to be mitigated by the presence of a dog. Children living with a dog in infancy and with the asthma risk variant were at no increased risk of asthma or wheeze compared with those homozygous for the nonrisk "A" allele.

Comparison with other studies

There are currently only 4 studies (in European ancestry populations) that report on the interaction between 17q21 variants and pet ownership in early life (Table E1). Only 1 looked specifically at rs2305480.[16] This pediatric case-control study found no association between rs2305480 (or rs7216389) and asthma, nor did they find any interaction between these SNPs and pet ownership in relation to asthma. They did however report an interaction between cat and dog ownership in the first year of life and an SNP in *GSDMA* and childhood asthma. The 3 other studies investigated SNPs in high linkage disequlibrium with rs2305480. One study of a rural birth cohort found no interaction between their SNP, dog ownership, and wheeze at age 1 year.[26] Another study of a nested case-control study within a national birth cohort found mild evidence that, for risk allele homozygotes, the presence of current furred pets decreased the risk of wheeze at 18 months.[17] The third study, a high-risk birth cohort, reported a strong trend for cat and/or dog exposure from birth to be associated with a lower risk of asthma at age 12 years ($P = .05$). Further analysis revealed that this was statistically significant only among those homozygous for the risk allele ($P = .02$); this was also seen for household cat (but not dog) allergen levels, causing the authors to conclude that the association was driven by cat exposure.[15] The heterogeneity of study designs (in relation to asthma definitions, age of subjects, and classification of pet exposure) makes it challenging to summarize these findings to draw any conclusions.

Interpretation of results

The attenuating effect of dog ownership on persistent wheeze for those with the asthma-risk allele observed in the current study is likely due to an environmental exposure for which dogs are a

proxy (ie, microbiota, endotoxin levels). Consistent with this observation, we found that higher house endotoxin levels at age 5 years were associated with a reduced risk of persistent wheeze (Table E18). Also, although there was no significant difference in endotoxin levels between the houses of cat and dog owners (Table E17), the levels for both pets were significantly higher than in houses with no pets. It is also possible that not only the quantity but also the type of microbial exposure contributes to a protective effect (for which endotoxin level is a proxy) and that the observed effect for dog in the current study is the same as the one previously reported for growing up in animal farms.[27] In fact, the dust collected from animal farm's houses was previously reported to have a more diverse microbiota than that of houses in urban areas and this diversity (including both bacterial and fungi) was significantly associated with a reduced risk of doctor-diagnosed asthma at age 6 to 13 years.[28] Both dog and cat ownership were shown, in independent studies, to increase the skin and/or gut microbial diversity of their adult owners, with a stronger effect in females.[29,30] Dog ownership was also shown to increase the microbial diversity inside the house, with a particularly strong effect on pillowcases.[31]

Two studies on a Canadian cohort focused on the effect of pet exposure on the gut microbiota of infants (3-5-month-old). Both studies reported that exposure to furry pets in infancy (both prenatal and postnatal exposure) was associated with increased diversity of the infants' gut microbiome.[32,33]

Limitations

The persistent and never-wheeze LCA classes were highly homogeneous, whereas the other wheezing classes showed some degree of variability. The larger heterogeneity of these "intermediate" classes, possibly coupled with smaller effect sizes in these groups, might have driven the observed lack of association. Future longitudinal wheezing classification strategies[34] will help elucidate whether a GxE exists for these classes. It is also to be noted that, because of the nature of the STELAR cohorts, which are restricted to participants with British ancestry, the generalizability of the results in other ethnicities will have to be investigated in future studies. Finally, rs2305480 was used as proxy for the 17q locus, but more studies are needed to identify the causal variant associated with the observed GxE.

Conclusions

Despite the aforementioned limitations, we reported the results from the largest study to date on 17q interaction with pet ownership—because of the collaboration of 5 UK birth cohorts in the STELAR consortium, our study is more than 4 times the size of the previous largest study of 17q21 and pet ownership. Moreover, thanks to the precise phenotype definitions (derived from LCA on longitudinal data to age 18 years), we identified a strong interaction of dog ownership in the first year of life and the 17q asthma-risk variant, which removed the genetic influence of the locus on asthma and wheeze, which would have been missed by using broad asthma definitions commonly used in genetic studies. Future studies will be required to confirm the generalizability of the results in non-European populations with precise phenotyping. Furthermore, polygenic risk score approaches could be used to investigate the role of common environmental exposures (such as pet ownership) on the development of asthma.

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Key messages

- **17q12-21 locus SNP rs2305480 G allele has been extensively associated with increased risk of wheeze and asthma.**
- **Children with the G risk allele for rs2305480 who also had a dog in infancy did not show an increase in the risk of persistent wheeze.**
- **Cat ownership in infancy did not show such dampening of the genetic effect.**

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