

The effect of dog allergen exposure on asthma morbidity among inner-city children with asthma

To the Editor

Asthma impacts children, particularly in inner-city populations.¹ A recent US population-based study identified that dog allergen exposure was associated with worse asthma among sensitized children.² While this helped clarify prior inconsistent findings regarding the effect of dog allergen,³ their study population consisted of more affluent non-Hispanic white populations with more common dog ownership. The effect of dog allergen exposure on asthma morbidity among inner-city populations with existing disease remains unclear, as the few prior studies identified no effects.^{4,5}

Dog ownership contributes, not just to dog allergen, but also to other exposures (eg, endotoxin, microbes) and activities (eg, increased physical activity) that may impact asthma morbidity via different mechanisms.⁶ However, many studies use either measured dog allergen or pet ownership as a surrogate to assess associations with asthma morbidity, and the unmeasured dog-associated non-allergen exposures *en toto* may confound the association.⁷ We hypothesized that the dog allergen was just one constituent of animal exposures and that dog-associated non-allergen exposures could also be associated with respiratory outcomes among inner-city children with asthma (Figure S1).

To test this hypothesis, we performed a secondary data analysis from the DISCOVER longitudinal observational cohort study including both dog allergen and presence of dog as exposures. Inner-city children in Baltimore aged 5-12 years with physician-diagnosed asthma were recruited from January 2009 to February 2015 and assessed at baseline, and 3, 6, and 9 months. At each follow-up visit, respiratory outcomes, including pediatric asthma diary and FeNO concentration, and the home environment, including dog allergen concentrations and dog presence, were assessed. Generalized estimating equations were used to assess associations between dog presence and log-transformed dog allergen exposure on respiratory outcomes, including an interaction term for allergen exposure and sensitization. We used the terms "dog allergen" for Can f 1 concentrations measured in home dust, "dog presence" for evidence of dogs observed on home inspection, and "dog-associated non-allergen exposures" for the unmeasured non-allergen exposures introduced by the presence of dogs. Dog-associated non-allergen exposures were derived from residual effect of dog presence in the main model for the association between dog allergen exposure and asthma morbidity. Allergy testing was conducted at the baseline visit to determine sensitization status using percutaneous skin testing (PST) or specific

IgE testing (ImmunoCAP, Thermo Fisher). See the article's Online Repository for additional details on methods.

Among 162 participants, the majority were African American and 65.4% had persistent asthma. The baseline prevalence of observed dog presence was 36.0%. The baseline distribution [median, interquartile range (IQR)] and prevalence (Can f 1 ≥ 2 $\mu\text{g/g}$) of dog allergen exposures were as follows: 0.08 $\mu\text{g/g}$ [IQR: 0-0.21], 9.88% for bedroom; 0.04 $\mu\text{g/g}$ [IQR: 0-0.21], 8.13% for bedroom floor; and 0 $\mu\text{g/g}$ [IQR: 0-0.10], 11.88% for kitchen (Table S1). The allergen concentration, IgE antibody levels, and FeNO concentrations are summarized in Table S1.

To examine the effects of allergen exposures on respiratory outcomes and the interaction between allergen exposures and sensitization to specific allergens on outcomes, the population was stratified into four categories based on dichotomous allergen exposure status at different sites (eg, bed) and based on dog-specific sensitization status. Dog allergen exposure was highly associated with worse respiratory outcomes regardless of where dust was collected (Table 1, Table S2). However, the interaction between sensitization and exposure to dog allergen was not significant across all outcomes and locations.

The effects of dog presence and dog allergen exposure on asthma morbidity were stratified by specific sensitization status (Table 2). Dog presence was not significantly associated with worse respiratory outcomes regardless of allergic sensitization status in the models without the inclusion of allergen exposure. However, after accounting for dog allergen, dog-associated non-allergen exposures derived from the residual effect of dog presence became associated with lower odds of absence from school and nocturnal asthma symptoms among dog-sensitized children. Though other associations were not statistically significant, there were trends that suggested overall dog-associated non-allergen exposures may be associated with lower asthma morbidity. In comparison, dog allergen exposure was associated with worse asthma control regardless of sensitization status or model inclusion of dog presence. Dog presence was associated with less frequent detection of mouse allergen (Table S4).

Interaction between allergen exposure and sensitization was tested for other household animal exposures; worse asthma symptoms were observed in mouse sensitized-and-exposed children than children in other categories of sensitization and exposure (Table S2). Further, the effects of animal-associated non-allergen exposure derived from the presence of other animals and exposures to allergens

were tested and found not to be consistently associated with asthma morbidity, except for mouse allergen (Table S3).

This work is the first to target the independent effects of dog allergen and dog presence among inner-city children with existing asthma and identified that dog allergen exposure was independently associated with worse respiratory outcomes regardless of dog-specific sensitization status. Our finding of no interaction between sensitization status and allergen exposure on respiratory outcomes

TABLE 1 Asthma morbidity outcomes by dog allergen exposure and sensitization to dog allergen

Outcome	Kitchen (n = 144) ^d	
	OR ^a (95% CI)	Interaction p ^e
Breathing difficulty		
Not exposed/not sensitized ^c	Ref	0.71
Exposed/not sensitized	3.36 (1.41-8.01) (p<0.01)	
Not exposed/sensitized	0.76 (0.33-1.76)	
Exposed/sensitized	3.26 (1.25-8.49) (p=0.02)	
Bothered by asthma		
Not exposed/not sensitized	Ref	0.99
Exposed/not sensitized	3.19 (1.31-7.77) (p=0.01)	
Not exposed/sensitized	0.84 (0.36-1.95)	
Exposed/sensitized	2.71 (0.86-8.56)	
Activity limited by asthma		
Not exposed/not sensitized	Ref	0.29
Exposed/not sensitized	3.14 (1.24-7.93) (p=0.02)	
Not exposed/sensitized	0.75 (0.30-1.85)	
Exposed/sensitized	4.76 (1.77-12.75) (p<0.01)	
Evening inhaler use		
Not exposed/not sensitized	Ref	0.12
Exposed/not sensitized	5.25 (2.13-12.98) (p<0.01)	
Not exposed/sensitized	2.09 (0.73-5.98)	
Exposed/sensitized	3.24 (0.95-11.01)	
Morning inhaler use		
Not exposed/not sensitized	Ref	0.32
Exposed/not sensitized	4.15 (1.52-11.35) (p<0.01)	
Not exposed/sensitized	1.27 (0.44-3.65)	
Exposed/sensitized	1.77 (0.34-9.18)	
Nocturnal symptoms		
Not exposed/not sensitized	Ref	0.75
Exposed/not sensitized	1.77 (0.74-4.20)	
Not exposed/sensitized	0.50 (0.21-1.18)	
Exposed/sensitized	1.06 (0.43-2.59)	

(Continues)

TABLE 1 (Continued)

Outcome	Kitchen (n = 144) ^d	
	OR ^a (95% CI)	Interaction p ^e
Acute care visits		
Not exposed/not sensitized	Ref	0.17
Exposed/not sensitized	0.87 (0.21-3.70)	
Not exposed/sensitized	0.63 (0.19-2.12)	
Exposed/sensitized	1.90 (0.53-6.80)	
FeNO (ppb) ^b		
Not exposed/not sensitized	Ref	0.05
Exposed/not sensitized	-0.21 (-0.44-0.02)	
Not exposed/sensitized	0.16 (-0.18-0.50)	
Exposed/sensitized	0.50 (-0.11-1.11)	

Bold values indicate statistically significant value ($P < .05$).

^aBinomial regression model with generalized estimating equations method used; model was stratified on pests/pet allergen exposure and sensitization status. Adjusted for race/ethnicity, asthma severity, age, sex, insurance, smoking exposure, and number of allergic sensitizations.

^bFeNO: fractional exhaled nitric oxide; the higher value suggests poor response to medication, poor asthma control or airway inflammation; FeNO was log-transformed in the model.

^cEmpirical cutoff for dog allergen concentration (Can 2 µg/g) was used to dichotomize allergen exposure status.

^dNot exposed/not sensitized (n = 84); exposed/not sensitized (n = 16); not exposed/sensitized (n = 35); exposed/sensitized (n = 9)

^eSignificance level for interaction was defined as $P < .10$; OR: odds ratio.

differs from a recent US population-based study that identified higher asthma prevalence and asthma attacks among dog-sensitized individuals in affluent, non-Hispanic white populations.² However, this finding is compatible with Thorne et al's work showing endotoxin exposure was associated with worse asthma outcomes independent of sensitization status but were worsened among the poor.⁸ Our current study contributes to the small literature evaluating the relationship between dog allergen exposures and asthma morbidity among inner-city children with asthma,^{4,5} and supports that dog allergen—but not other aspects of dog presence—was associated with asthma morbidity.^{2,3,6}

It is interesting that the association between dog allergen exposure and respiratory outcomes was present regardless of sensitization status after adjustment for dog-associated non-allergen exposures and other animal allergen concentrations. This finding could result from our practice of using either specific IgE or PST to determine sensitization status, which might misclassify some sensitized individuals as non-sensitized. However, allergen exposure remained associated with respiratory outcomes in both the overall analysis using all participants and the stratified analyses, suggesting that this effect is independent of sensitization status. It is possible that dog allergen may induce airway inflammation via activation of the innate immune system, that is, Toll-like receptor (TLR) signaling.⁹ Alternatively, increased airway hypersensitivity may result from the

TABLE 2 Analysis of the independent effect of dog presence and dog allergen exposure on asthma morbidity

Outcome	Allergen or animal presence unadjusted			Allergen and animal presence adjusted		
		OR ^{b,c} (95% CI)	P-value		OR (95% CI)	P-value
Dog-sensitized patients (n = 44)						
Breathing difficulty	Animal presence	1.22 (0.56-2.69)	.62	Animal presence	0.65 (0.24-1.80)	.41
	Allergen	1.64 (1.20-2.24)	<.01	Allergen	1.85 (1.15-2.96)	.01
Bothered by asthma	Animal presence	0.99 (0.42-2.30)	.98	Animal presence	0.72 (0.28-1.86)	.49
	Allergen	1.28 (0.84-1.94)	.25	Allergen	1.40 (0.84-2.32)	.20
Activity limited by asthma	Animal presence	1.11 (0.50-2.48)	.80	Animal presence	0.48 (0.17-1.32)	.16
	Allergen	1.74 (1.36-2.24)	<.01	Allergen	2.15 (1.41-3.27)	<.01
Morning inhaler use	Animal presence	0.64 (0.22-1.90)	.42	Animal presence	0.53 (0.21-1.31)	.17
	Allergen	1.02 (0.38-2.73)	.97	Allergen	1.23 (0.45-3.35)	.69
Nocturnal symptoms	Animal presence	0.54 (0.25-1.16)	.11	Animal presence	0.36 (0.14-0.92)	.03
	Allergen	1.14 (0.80-1.61)	.46	Allergen	1.51 (0.96-2.38)	.07
School absent	Animal presence	0.31 (0.05-2.02)	.22	Animal presence	0.15 (0.02-1.00)	.05
	Allergen	1.26 (0.69-2.29)	.45	Allergen	1.94 (0.94-4.00)	.08
FeNO (β) ^a	Animal presence	0.14 (-0.23-0.51)	.46	Animal presence	0.13 (-0.24-0.50)	.49
	Allergen	0.05 (-0.20-0.31)	.69	Allergen	0.01 (-0.24-0.27)	.92
Dog non-sensitized patients (n = 100)						
Breathing difficulty	Animal presence	1.17 (0.61-2.24)	.63	Animal presence	0.86 (0.43-1.73)	.67
	Allergen	1.45 (1.06-1.99)	.02	Allergen	1.50 (1.06-2.13)	.02
Bothered by asthma	Animal presence	1.29 (0.66-2.49)	.46	Animal presence	0.98 (0.47-2.03)	.95
	Allergen	1.42 (1.04-1.95)	.03	Allergen	1.43 (1.01-2.02)	.04
Activity limited by asthma	Animal presence	1.09 (0.52-2.27)	.82	Animal presence	0.82 (0.38-1.79)	.63
	Allergen	1.39 (1.00-1.92)	.05	Allergen	1.45 (1.04-2.04)	.03
Morning inhaler use	Animal presence	1.03 (0.39-2.71)	.96	Animal presence	0.56 (0.21-1.47)	.24
	Allergen	1.67 (1.09-2.55)	.02	Allergen	1.92 (1.26-2.91)	<.01
Nocturnal symptoms	Animal presence	0.98 (0.51-1.87)	.95	Animal presence	0.82 (0.36-1.85)	.64
	Allergen	1.20 (0.86-1.68)	.27	Allergen	1.26 (0.83-1.92)	.28
School absent	Animal presence	0.76 (0.36-1.60)	.47	Animal presence	0.66 (0.28-1.58)	.35
	Allergen	1.07 (0.80-1.43)	.64	Allergen	1.18 (0.85-1.64)	.33
FeNO (β)	Animal presence	-0.05 (-0.23-0.14)	.61	Animal presence	-0.03 (-0.23-0.18)	.79
	Allergen	-0.04 (-0.12-0.05)	.40	Allergen	-0.03 (-0.12-0.06)	.52

Bold values indicate statistically significant value ($P < .05$).

^aFeNO: fractional exhaled nitric oxide; the higher value suggests poor response to medication, poor asthma control or airway inflammation; FeNO was log-transformed

^bBinomial regression model used; adjusted for race/ethnicity, asthma severity, age, sex, insurance, smoking exposure, and number of allergic sensitizations

^cLog-transformed dog allergen concentration settled on kitchen (n = 144) was used for mediation analysis; home inspection was used to ascertain dog presence

interaction between dog allergen and substances unmeasured in the current study (eg, endotoxin)¹⁰ (see Supplemental Discussion).

The intriguing finding that dog-associated non-allergen exposures may be associated with lower asthma morbidity after controlling for the deleterious effects from allergen exposure is biologically plausible. There is growing evidence that animal microbiota and endotoxin may exert immunomodulatory effects on the development of or progression of atopic diseases via associated cytokines and metabolites.⁶ Further, dog ownership is associated

with increased physical activity, which could benefit respiratory outcomes. Failure to partition joint deleterious and beneficial exposures related to dog ownership could contribute to mixed results from prior studies.

Several limitations temper study conclusions, including modest sample size, lack of documentation of direct child-dog contact, and lack of microbial or endotoxin assessment. Our study is strengthened by longitudinal measurement of outcomes and exposures. Even when exposure to other animal allergens was

included in the model, dog allergen exposure remained significantly associated with respiratory outcomes, which suggests that dog allergen is an independent risk factor for asthma morbidity. Future studies are needed to examine how dog allergen exposures impact asthma morbidity among non-sensitized patients.

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CONFLICT OF INTEREST

The authors declare that they have no relevant conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

1 Supplemental Method

2 Study Design

3 To understand the independent effects of both (1) allergen exposures and (2) dog-associated non-
4 allergen exposures, we conducted an analysis to evaluate the effect of dog allergen exposure on
5 asthma outcomes after controlling for dog-associated non-allergen exposures introduced by living with
6 a dog. This was performed via a secondary data analysis of longitudinal data collected from a
7 completed observational cohort (DISCOVER) of inner-city children with. A supplemental objective was
8 to determine if animal-associated non-allergen exposures, including cat, pest mouse, and pest
9 cockroach, were associated with asthma morbidity independent of the effect of animal allergen
10 exposure in the same population asthma (**Supplemental figure 1**). We used the terms “allergen
11 exposure” to mean exposure to animal allergen collected in the dust sample in the home, “animal
12 presence” to mean evidence of living with animal in the home, and “animal-associated non-allergen
13 exposures” to mean the unmeasured non-allergen effects introduced by living with an animal. The
14 DISCOVER (*Domestic Indoor Particulate Matter and Childhood Asthma Morbidity Study*) study was a
15 prospective observational cohort with a primary objective to evaluate the impact of air quality on asthma
16 morbidity in inner-city children with physician-diagnosed asthma.

17 Study Population and Setting

18 Inner-city children in Baltimore aged between 5-12 years who had physician-diagnosed asthma
19 were recruited from January 2009 to February 2015 and followed longitudinally at baseline and every 3
20 months for 9 months in the DISCOVER study (*Domestic Indoor Particulate Matter and Childhood
21 Asthma Morbidity Study*, n=194).^{1, 2}. At baseline, standardized questionnaires were given to evaluate
22 participants' demographics and asthma severity, and spirometry were performed to evaluate
23 participants' pulmonary function. At each follow-up point, evaluation of home environment by trained
24 personnel was conducted, and asthma morbidity for the past 8-day period was assessed through
25 caregiver report and objective measurement of FeNO (Fraction of exhaled nitric oxide, a biomarker of
26 lung inflammation). Individuals who did not have physician-diagnosed asthma and were enrolled in
27 DISCOVER as control participants; these control participants were excluded from the analyses (n=32).

28 Exposure Assessment

29 Animal presence for each home was determined by staff inspection of the home. At baseline and
30 each 3-month follow-up home visit (baseline, 3mo, 6mo, and 9mo visits), trained personnel inspected
31 the houses of participants for direct and indirect evidence of dogs or cats, and they also evaluated the

homes for evidence of cockroach and mouse infestation. Direct evidence included visualization of the presence of pets and pests, and indirect evidence included the presence of food dishes, litter boxes and/or the smell or hair of pets, or observation of cockroach and mouse droppings.

Animal allergen exposure for each home inspection was determined based on the measurement of allergen concentrations in the collected vacuum dust samples using ELISA Universal Allergen Standard (UAS) assay (Indoor Biotechnologies, Charlottesville, VA). Settled household dust samples were collected on an unwoven fabric collector inserted into the nozzle of a standard portable vacuum from the bed, bedroom floor and kitchen using standard methods.³ The fabric collector was removed from the vacuum and sealed in a plastic bag after sampling. An aqueous extract of 100 mg of the sieved dust (sieve size, 300 μ m) specimen was prepared in 2 mL borate-buffered saline. The extracts were stored at -30°C until they were assayed to quantify the concentration for Fel d 1, Can f 1, Bla g 1, and Mus m 1 using antibody-based ELISA.⁴⁻⁶ The limit of detection (LOD) for the assay was 0.98 ng/g for Mus m 1, 0.20 U/g for Bla g 1, 4.88 ng/g for Can f 1, and 3.9 ng/g for Fel d 1 after applying the dilution factor of 20 converting the unit from ng/ml to ng/g as every 100 mg of dust sample was extracted in 2 ml borate-buffered saline. Animal allergen concentrations were further treated in two ways: 1) as a continuous variable via log-transformation, and 2) as a binary variable (Can f 1, <2 or ≥ 2 $\mu\text{g/g}$). The allergen exposure status was considered positive using the following literature-based morbidity thresholds for cockroach, mouse, dog and cat (Bla g 1, 1 U/g; Mus m 1, 1 $\mu\text{g/g}$; Can f 1, 10 $\mu\text{g/g}$; and Fel d 1, 8 $\mu\text{g/g}$),⁷⁻¹⁰ which were comparable to the following thresholds using the UAS assay: Bla g 1, 1 U/g; Mus m 1, 1 $\mu\text{g/g}$; Can f 1, 2 $\mu\text{g/g}$; and Fel d 1, 3 $\mu\text{g/g}$.¹¹ By convention, dust sample with allergen concentrations below the limit of detection (LOD) were replaced by the LOD divided by the square root of 2.¹²⁻¹⁴

Clinical Assessment

Percutaneous skin testing (PST) or specific IgE testing (ImmunoCAP, ThermoFisher, Uppsala, Sweden) was conducted at the baseline visit to determine sensitization status using methods previously described.^{15, 16} Testing for sensitization to allergens included *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, mouse and rat, German cockroach, American cockroach, oak, *Alternaria tenuis*, *Aspergillus fumigatus*, common ragweed, and *Cladosporium herbarum* (Greer Laboratories, Lenoir, NC). A test was considered positive if the net orthogonal wheal diameter was equal to or larger than 3 mm on PST or IgE level was equal to or greater than 0.35kU/L on specific IgE testing. Participants were considered atopic with at least one positive test.

63 At baseline, the standardized questionnaires evaluating asthma severity was based on National
64 Asthma Education and Prevention Program (NAEPP) guidelines.¹⁷ Spirometry was performed using the
65 KoKo spirometer (nSpire Health, Inc., Longmont, CO) before and after albuterol administration, and the
66 spirometry curves were obtained based on American Thoracic Society guidelines.¹⁸ Predicted values of
67 forced expiratory volume (FEV₁) and forced vital capacity (FVC) were calculated using the formulae of
68 Hankinson et al.¹⁹

69 Participants and their caregivers were trained to complete daily activity questionnaire pediatric
70 asthma diary (PAD). These are closed-ended questions and scientifically-validated instruments that
71 evaluate the asthma symptom burden during each 8-day period.²⁰ Asthma symptoms include whether a
72 participant has daytime/evening inhaler use today, whether a participant was woken by asthma during
73 the night or in the morning today, whether a participant is absent from school due to asthma today,
74 whether a participant has an unscheduled acute care visit due to asthma today, whether a participant
75 has difficulty breathing today, whether asthma bothers the participant today, and whether a participant's
76 activity is limited by asthma today. On each 3-month follow-up visit, the questionnaire that evaluated
77 the asthma inhaler use, asthma symptom days and acute care visit over the 8-day period were
78 completed and collected by technicians. At each follow-visit, symptoms were quantified as the number
79 of symptomatic days in the prior 8-day period. At each follow-visit, FeNO levels were measured based
80 on the 2005 standardized procedure recommendations by the ATS/ERS joint committee.²¹

81 *Statistical Analyses*

82 Descriptive statistics were used to summarize the baseline characteristics of the participants
83 enrolled in DISCOVER study using proportions, means with standard deviations or medians with
84 interquartile ranges. Our primary outcome was asthma morbidity defined as the repeated measures of
85 the number days of asthma symptoms, inhaler use, days bothered or limited by asthma and acute care
86 visit in a week prior to the clinic visit.

87 Participants first were stratified by sensitization status given it is a known effect modifier on allergen
88 exposures.²² Binomial regression models were fit using generalized estimating equations with robust
89 variance estimation to assess the associations of asthma morbidity and animal presence as well as
90 animal allergen exposures, respectively. Linear regression models were fit using generalized estimating
91 equations with robust variance estimation to assess the associations of log-transformed FeNO and
92 animal presence as well as animal allergen exposures (log-transformed and binary), respectively. In
93 adjusted models, the number of allergic sensitizations was used in place of the binary variable for
94 atopic status. In the final model assessing the independent effect of animal allergen exposure collected

at kitchen on asthma morbidity, animal presence was added into the main model (association between allergen exposure and asthma morbidity) to prevent the potential confounding effect of animal-associated non-allergen exposures. Final models were adjusted for potential confounders, including age, sex, ethnicity, smoking exposure, asthma severity classification, type of insurance and number of specific allergic sensitizations. Covariates initially were determined based on potential relevance given the literature, and then were further refined using statistical backward selection approach. Additional sensitivity analyses were conducted that included all log-transformed allergen concentrations in the main model to prevent potential confounding effects on the association between animal allergen and asthma morbidity. Analysis of Covariance (ANCOVA) was conducted by introducing an interaction term for animal allergen sensitization and animal allergen exposure to the model using $p < 0.10$ as cutoff for statistical significance. Analyses were conducted using complete case approach, excluding the observations with missing dust specimen data in dust sample. All the analyses were performed with Stata statistical software, version 12.0 (Stata Corp, College Station, TX). Statistical significance was defined as $p < 0.05$.

Ethics

Johns Hopkins Medical Institutional Review Board approved the study and all participants provided written informed consent.

Supplemental Results

Participant characteristics

There were 162 out of 194 eligible participants enrolled in this study. Baseline characteristics, asthma severity, FeNO concentration, and dust sample data are detailed in **Supplemental Table 1**. Based on home inspection by trained staff, the baseline prevalences of observed animal exposures were as follows: pest mice: 72.0%, pest cockroaches: 69.8%, dogs: 36.0%, and cats: 33.5%. The baseline prevalences of animal allergen detection in the kitchen (clinically significant cutoff for concentrations of allergen in vacuum dust) were: pest cockroaches: 59.81%, pest mice: 58.72%, dogs: 11.88% and cats: 12.26%. Among all dust samples, there were 31.03%, 41.36% and 61.11% of dust sample with Can f 1 below the limit of detection in bedroom, bedroom floor, and kitchen, respectively. The IgE concentration using the RAST were: pest cockroaches (Bla g 1, kU/L): 0.1 (0.1, 1.1), pest mice (Mus m 1, kU/L): 0.1 (0.1, 0.5), dogs (Can f 1, kU/L): 0.1 (0.1, 3.0), and cats (Fel d 1, kU/L): 0.1 (0.1, 7.2).

Effect of animal allergen exposures and effect modification of specific sensitization on asthma morbidity

126 For the dog categories, the association with asthma morbidity was highly associated with dog
127 allergen exposure for almost every respiratory outcome regardless of where in the house the dust
128 sample was collected. To identify if these findings were specific to dog or common to all household
129 animals identified (whether pet or pest), we additionally explored the same associations with cat, pest
130 mouse, and pest cockroach exposures. However, the pattern observed for dogs was not observed
131 among those exposed or sensitized to cats (**Supplemental Table 2b**). For pest cockroaches and mice,
132 the exposures were not consistently associated with better or worse asthma control on the adjusted
133 models. On the Analysis of Covariance (ANCOVA), the result of stratified multivariable analyses
134 showed significant interactions between mouse allergen exposure and sensitization to mouse on
135 multiple outcomes regardless of sites (**Supplemental Table 2a**). As compared to being sensitized or
136 exposed to allergen alone, mouse allergen exposure and sensitization were associated with higher
137 odds of increased days with breathing difficulty, days bothered by asthma, days with activity limited by
138 asthma, days with morning and evening inhaler use and increased FeNO. However, the interaction
139 between sensitization and exposure to allergen was not observed for dogs, cats, or pest cockroaches.

140 *Effect of animal exposures on asthma morbidity*

141 The effect of animal exposures on asthma morbidity was stratified on specific sensitization status
142 and presented in **Supplemental Tables 3a** and **3b**. After accounting for animal allergen exposure, no
143 animal presence was associated with worse asthma control regardless of sensitization in the adjusted
144 models.

145 *Independent effects of allergen and non-allergen exposures on asthma morbidity*

146 On the analyses that controlled for dog allergen exposure, we partitioned the effect of dog exposure
147 into allergen exposure and dog-associated non-allergen exposure. Among those sensitized to dog
148 allergen, dog-associated non-allergen exposures were associated with lower odds of absence from
149 school and having nocturnal asthma symptoms, while dog allergen exposure was associated with
150 higher odds of absence from school and having nocturnal symptoms. The lower risk effect from animal-
151 associated non-allergen exposures was not observed in individuals sensitized and exposed to pest
152 cockroaches, pest mice or cats (**Supplemental Table 3b**). The results of sensitivity analyses
153 substituting self-reported (rather than observed) animal exposure for home inspection were also
154 performed and demonstrated that the associations between asthma morbidity and pest-associated non-
155 allergen exposures (e.g. cockroach, mouse) were generally attenuated, while the associations between
156 asthma morbidity and pet-associated non-allergen exposures (e.g. dog, cat) remained comparable to
157 the results using home inspection.

Supplemental Discussion

It is interesting that the association between dog allergen exposure and respiratory outcomes was present regardless of allergic sensitization status after adjustment for dog-associated non-allergen exposures and other animal allergen concentrations. Our study used either specific IgE or PST to determine allergic sensitization status, and it is possible that some sensitized individuals may have been incorrectly categorized as non-sensitized. This could also partially explain the insignificant difference in asthma symptoms severity between participants who were both sensitized AND exposed to dog allergen than those who were either sensitized OR exposed to dog allergen. However, allergen exposure remained associated with respiratory outcomes in both the overall analysis using all study participants as well as the stratified analyses, which suggests that this effect is independent of sensitization status. A similar phenomenon was observed in dog-non-sensitized asthmatic subjects in another study of 248 participants with physician-diagnosed asthma in UK.²³ It is possible that airway inflammation may be caused by a direct irritant effect from exposure to Can f 1 allergen, an lipocalin allergen belonging to a family that also includes Can f 6 and Fel d 1, via activation of the innate immune system, *i.e.* Toll-like receptor (TLR) signaling.^{24, 25} Another hypothesis is that asthma morbidity could be caused by the interaction between dog allergen and the substances or effects unmeasured in current study (e.g. endotoxin) that enhanced the interplay between lipopolysaccharides and Toll-like receptors in macrophages.^{26, 27}

The results of this study should be interpreted given its strength and limitations. To our knowledge, this is among the first study that attempts to evaluate the effect of dog allergen exposure on respiratory outcomes among inner-city children with asthma while adjusting for the confounding effect of dog-associated non-allergen exposures. Our findings suggest that dog allergen exposure is independently associated with respiratory outcomes regardless of specific sensitization status. However, this study has several limitations. First, the population consisted mainly of African American children with asthma in Baltimore, and the findings may not be generalizable to other populations. Second, because this is a secondary data analysis of a prospective study, we could not conduct power calculation *a priori*. As a result, the lack of significant interaction between exposure and sensitization to dog allergen on asthma morbidity could be due to inadequate statistical power as there were limited numbers of children in the exposed and sensitized stratum ($n < 10$). Future studies with sufficient statistical power will be needed to address this issue. Third, two allergy testing methods were used to ascertain allergic sensitization status which could partially explain the association between dog allergen exposures and asthma morbidity among non-sensitized participants. However, the associations between dog allergen exposures and asthma morbidity regardless of sensitization status remain on the stratified analyses

using only one allergy testing (e.g. specific IgE or PST) or on non-stratified analyses using the entire cohort of study participants. This suggests that dog allergen could be associated with airway hypersensitivity via mechanisms other than allergenicity. Fourth, we did not include the effect of asthma medication that might reduce the impact of dog allergen exposure, as we aim to evaluate the overall impact of dog allergen exposure on asthma among inner-city asthmatics. Furthermore, the fact that the association between dog allergen exposure and asthma morbidity remains significant while unadjusted for medication (which could be expected to attenuate the association between allergen exposure and asthma morbidity) suggests dog allergen exposure has a public health impact on asthma morbidity among inner-city children with asthma. Fifth, there are potential misclassification biases for animal presence using home inspection which might fail to capture the effect from outdoor exposures and prior animal exposure. However, given that most Americans spend 90% of their time indoors,²⁸ and given that the use of home inspection by trained staff to ascertain animal exposures is less prone to recall biases and stigmatization associated with self-report, this study likely captures an important and dominant route of exposure. Another source of misclassification bias could result from a moderate proportion (44.63%) of dust samples with Can f 1 below limit of detection requiring empirical imputation using LOD divided by the square root of 2. Finally, animal-associated non-allergen exposures were not measured in this study directly. It is impossible to differentiate the effect of each factor on asthma morbidity without measurement of each of the constituents, *i.e.* microbiome, endotoxin, effect of animal ownership on physical activity, *etc.* That endotoxin was found associated with worse respiratory outcomes among children exposed to dog allergen in a populational study where both endotoxin and allergen were measured supports our hypothesis that animal-associated non-allergen exposures exists and has an impact on respiratory outcomes independent from allergen.²⁶

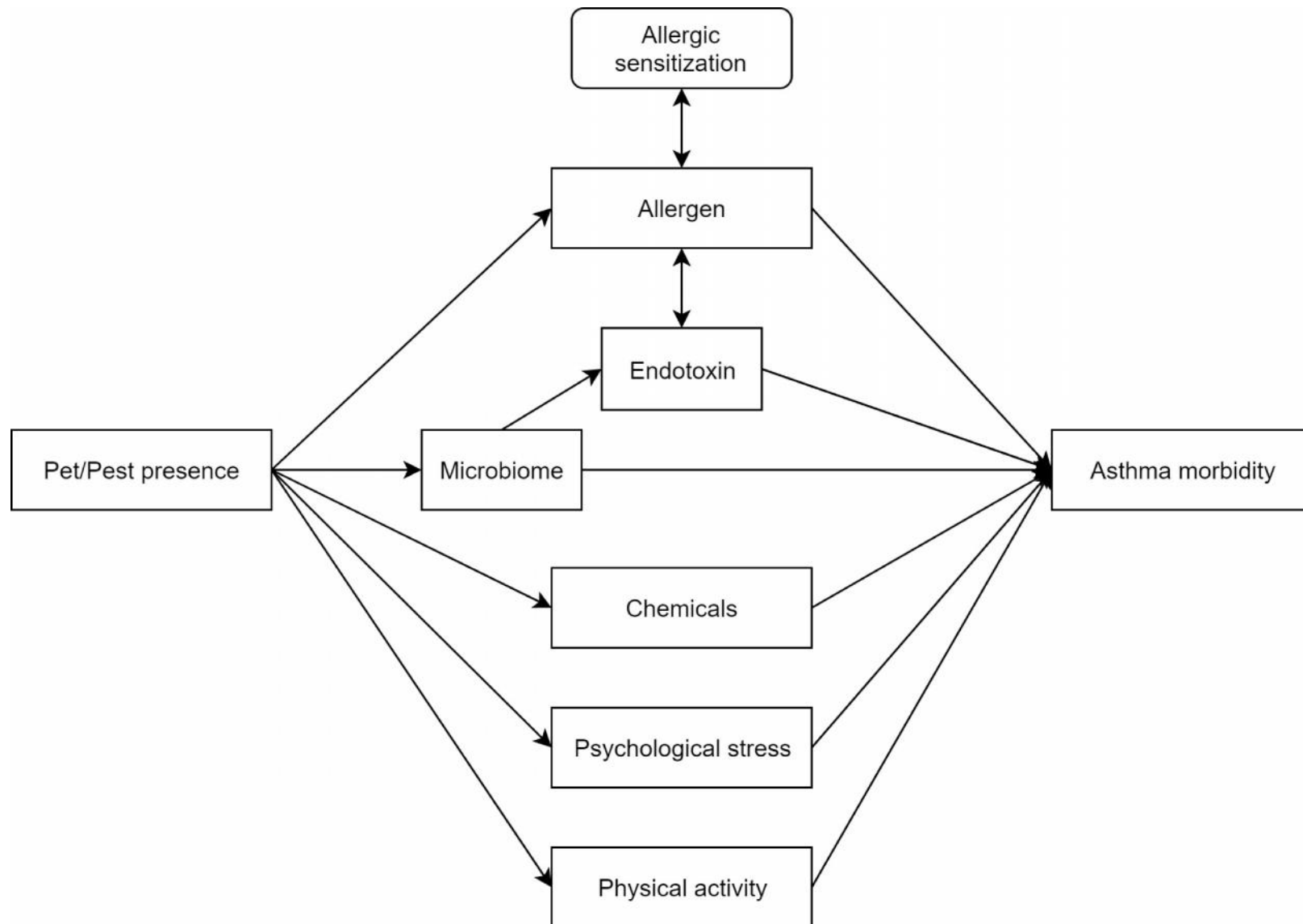
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Figure S1. Directed acyclic graph of the association between pet/pest presence and asthma morbidity



Supplemental Table 1. Baseline Summary Statistics of Study Population

Demographic characteristics		DISCOVER (n=162)
Age, median (IQR)		9.6 (7.9, 11.4)
Male, n (%)		88 (54.3%)
African American, n (%)		152 (93.8%)
BMI, median (IQR)		18.8 (16.3, 24.0)
Underweight, n (%)		10 (6.3%)
Normal, n (%)		75 (47.2%)
Overweight, n (%)		22 (13.8%)
Obese, n (%)		52 (32.7%)
Insurance, n (%)		
Public		142 (87.75%)
Primary caregiver, n (%)		
Birth mother		138 (85.2%)
Grandmother		10 (6.2%)
Birth father		9 (5.6%)
Other		5 (3.1%)
Education, n (%)		
less than 8th grade		1 (0.7%)
Not high school graduate		41 (28.7%)
High school graduate		74 (51.7%)
At least some college		27 (18.9%)
Exposure to smoking, n (%)		84 (51.9%)
Household income (annual), n (%)		
< \$25,000		67 (41.4%)
\$25,000–\$50,000		24 (14.8%)
> \$50,000		8 (4.9%)
Not reported		63 (38.9%)
Clinical characteristics, n (%)		
Asthma severity (based on symptoms)		
Mild intermittent		56 (34.6%)
Mild persistent		31 (19.1%)
Moderate persistent		46 (28.4%)
Severe persistent		29 (17.9%)
Asthma severity (based on symptoms and PFT)		
Mild intermittent		41 (25.3%)
Mild persistent		18 (11.1%)
Moderate persistent		53 (32.7%)

Severe persistent	50 (30.9%)
FeNO (ppb)	17.5 (9.0, 35.5)
Allergen sensitization, n (%)	
Atopic ^a	106 (67.5%)
Cockroach	69 (44.2%)
Mouse	56 (35.4%)
Dog	47 (29.7%)
Cat	65 (41.1%)
IgE concentrations (RAST), median (IQR)	
Cockroach (Bla g 1, kU/L)	0.1 (0.1, 1.1)
Mouse (Mus m 1, kU/L)	0.1 (0.1, 0.5)
Dog (Can f 1, kU/L)	0.1 (0.1, 3.0)
Cat (Fel d 1, kU/L)	0.1 (0.1, 7.2)
Animal presence based on home inspection, n (%)	
Cockroach	113 (69.8%)
Mouse	116 (72.0%)
Dog	58 (36.0%)
Cat	54 (33.5%)
Allergen exposure, median (IQR)	
Bed	
Bla g 1 (U/g)	0.00 (0.00, 1.30)
Mus m 1 (µg/g)	0.63 (0.18, 5.42)
Can f 1 (µg/g) ^b	0.08 (0.00, 447.48)
Feld d 1 (µg/g)	0.33 (0.10, 1.44)
Bedroom floor	
Bla g 1 (U/g)	1.30 (0.00, 5.20)
Mus m 1 (µg/g)	1.63 (0.43, 9.23)
Can f 1 (µg/g) ^b	0.04 (0.00, 57.82)
Feld d 1 (µg/g)	0.14 (0.01, 0.71)
Kitchen	
Bla g 1 (U/g)	3.50 (0.00, 27.00)
Mus m 1 (µg/g)	3.13 (0.27, 25.77)
Can f 1 (µg/g) ^b	0.00 (0.00, 59.04)
Feld d 1 (µg/g)	0.01 (0.00, 0.40)

- Participants were considered atopic if the net orthogonal wheal diameter was equal to or larger than 3 mm on PST or IgE level was equal to or greater than 0.35kU/L on specific IgE testing.
- Range was used instead of IQR given the skewed distribution of the dog allergen.
- Abbreviation: FeNO, fractional exhaled nitric oxide; RAST, radioallergosorbent test; IQR, interquartile range

Table S2a. Asthma morbidity outcomes by exposure and sensitization to specific allergens (cockroach and mouse) over time

Outcome	Cockroach (Bed) OR (95% CI)	<i>p</i> ^a	Cockroach (Bedroom) OR (95% CI)	<i>p</i>	Cockroach (Kitchen) OR (95% CI)	<i>p</i>	Mouse (Bed) OR (95% CI)	<i>p</i>	Mouse (Bedroom) OR (95% CI)	<i>p</i>	Mouse (Kitchen) OR (95% CI)	<i>p</i>
Breathing difficulty												
Not exposed/not sensitized	Ref	0.60	Ref	0.46	Ref	0.90	Ref	<0.01	Ref	0.01	Ref	0.04
Exposed/not sensitized	0.53 (0.21 - 1.38)		0.54 (0.31 - 0.95)		0.80 (0.39 - 1.64)		0.31 (0.14 - 0.70)		0.62 (0.34 - 1.11)		0.50 (0.26 - 0.95)	
Not exposed/sensitized	0.64 (0.28 - 1.49)		1.11 (0.57 - 2.15)		1.09 (0.46 - 2.62)		0.57 (0.22 - 1.44)		0.69 (0.27 - 1.75)		0.92 (0.31 - 2.70)	
Exposed/sensitized	0.47 (0.16 - 1.40)		0.82 (0.39 - 1.72)		0.83 (0.35 - 1.98)		1.83 (0.75 - 4.50)		1.35 (0.56 - 3.24)		1.33 (0.50 - 3.52)	
Bothered by asthma												
Not exposed/not sensitized	Ref	0.17	Ref	0.31	Ref	0.71	Ref	<0.01	Ref	0.01	Ref	0.05
Exposed/not sensitized	0.33 (0.12 - 0.86)		0.56 (0.31 - 1.01)		0.78 (0.37 - 1.62)		0.31 (0.13 - 0.73)		0.71 (0.37 - 1.35)		0.56 (0.29 - 1.10)	
Not exposed/sensitized	0.61 (0.28 - 1.31)		0.93 (0.49 - 1.78)		1.26 (0.55 - 2.89)		0.69 (0.27 - 1.76)		0.64 (0.25 - 1.68)		1.11 (0.37 - 3.29)	
Exposed/sensitized	0.45 (0.16 - 1.30)		0.79 (0.38 - 1.66)		0.83 (0.34 - 1.98)		2.03 (0.82 - 5.02)		1.58 (0.64 - 3.91)		1.73 (0.68 - 4.43)	
Activity limited by asthma												
Not exposed/not sensitized	Ref	0.06	Ref	0.47	Ref	0.68	Ref	<0.01	Ref	0.01	Ref	0.08
Exposed/not sensitized	0.24 (0.09 - 0.61)		0.63 (0.34 - 1.15)		0.74 (0.32 - 1.68)		0.40 (0.17 - 0.92)		0.71 (0.36 - 1.43)		0.69 (0.34 - 1.40)	
Not exposed/sensitized	0.70 (0.32 - 1.55)		1.07 (0.53 - 2.15)		1.36 (0.55 - 3.32)		0.77 (0.29 - 2.05)		0.59 (0.19 - 1.83)		1.31 (0.39 - 4.40)	
Exposed/sensitized	0.53 (0.17 - 1.59)		0.92 (0.42 - 2.03)		0.81 (0.30 - 2.17)		2.76 (1.14 - 6.70)		1.57 (0.53 - 4.61)		2.36 (0.80 - 6.93)	
Evening inhaler use												
Not exposed/not sensitized	Ref	0.85	Ref	0.17	Ref	0.17	Ref	0.14	Ref	0.12	Ref	<0.01
Exposed/not sensitized	1.39 (0.53 - 3.62)		0.53 (0.24 - 1.18)		1.08 (0.48 - 2.40)		0.68 (0.34 - 1.36)		0.51 (0.26 - 0.98)		0.30 (0.14 - 0.61)	
Not exposed/sensitized	0.70 (0.22 - 2.26)		0.73 (0.29 - 1.83)		1.58 (0.58 - 4.31)		1.50 (0.55 - 4.08)		0.93 (0.28 - 3.06)		0.61 (0.20 - 1.88)	
Exposed/sensitized	1.09 (0.34 - 3.51)		0.75 (0.27 - 2.09)		0.76 (0.29 - 2.02)		2.33 (0.97 - 5.62)		1.03 (0.36 - 2.91)		0.91 (0.31 - 2.64)	
Morning inhaler use												
Not exposed/not sensitized	Ref	0.75	Ref	0.18	Ref	0.83	Ref	0.34	Ref	0.20	Ref	0.01
Exposed/not sensitized	2.27 (0.78 - 6.66)		0.69 (0.30 - 1.57)		0.82 (0.34 - 1.99)		0.80 (0.34 - 1.93)		0.59 (0.26 - 1.31)		0.33 (0.14 - 0.78)	
Not exposed/sensitized	1.05 (0.34 - 3.22)		0.86 (0.35 - 2.11)		1.46 (0.50 - 4.27)		1.60 (0.53 - 4.90)		0.99 (0.26 - 3.80)		1.08 (0.33 - 3.58)	
Exposed/sensitized	1.96 (0.61 - 6.29)		1.20 (0.48 - 2.97)		1.36 (0.50 - 3.73)		2.44 (0.77 - 7.74)		1.19 (0.37 - 3.82)		1.59 (0.47 - 5.38)	
Nocturnal symptoms												
Not exposed/not sensitized	Ref	0.38	Ref	0.09	Ref	0.05	Ref	<0.01	Ref	0.11	Ref	0.03
Exposed/not sensitized	0.51 (0.15 - 1.76)		0.55 (0.29 - 1.07)		0.48 (0.23 - 1.00)		0.48 (0.17 - 1.30)		1.00 (0.43 - 2.30)		0.50 (0.23 - 1.10)	
Not exposed/sensitized	1.29 (0.54 - 3.13)		0.79 (0.33 - 1.87)		0.65 (0.23 - 1.83)		0.77 (0.26 - 2.21)		0.60 (0.16 - 2.24)		1.02 (0.33 - 3.16)	
Exposed/sensitized	1.21 (0.39 - 3.76)		1.07 (0.46 - 2.52)		0.95 (0.35 - 2.58)		2.46 (0.99 - 6.07)		1.45 (0.42 - 5.05)		1.69 (0.53 - 5.37)	
Acute care visits												
Not exposed/not sensitized	Ref	0.75	Ref	0.05	Ref	0.22	Ref	0.43	Ref	0.84	Ref	0.75
Exposed/not sensitized	1.04 (0.23 - 4.62)		0.36 (0.11 - 1.22)		0.62 (0.18 - 2.20)		2.58 (0.55 - 11.98)		1.65 (0.56 - 4.91)		0.79 (0.27 - 2.30)	
Not exposed/sensitized	1.30 (0.33 - 5.12)		0.49 (0.09 - 2.54)		0.89 (0.20 - 4.01)		2.40 (0.42 - 13.82)		1.25 (0.22 - 7.25)		1.60 (0.42 - 6.17)	
Exposed/sensitized	1.89 (0.56 - 6.42)		1.31 (0.47 - 3.69)		1.81 (0.50 - 6.47)		2.77 (0.70 - 11.02)		2.51 (0.68 - 9.25)		1.63 (0.43 - 6.08)	
FeNO (ppb)^{c,d}												
Not exposed/not sensitized	Ref	0.19	Ref	0.01	Ref	0.92	Ref	0.13	Ref	0.30	Ref	0.06
Exposed/not sensitized	-0.23 (-0.52 - 0.06)		-0.28 (-0.52 - -0.05)		-0.08 (-0.37 - 0.20)		-0.00 (-0.21 - 0.21)		-0.10 (-0.29 - 0.10)		-0.14 (-0.34 - 0.06)	
Not exposed/sensitized	0.08 (-0.23 - 0.38)		-0.14 (-0.42 - 0.15)		0.06 (-0.26 - 0.37)		0.29 (-0.10 - 0.69)		0.42 (0.01 - 0.83)		0.38 (-0.01 - 0.76)	
Exposed/sensitized	0.11 (-0.22 - 0.44)		0.02 (-0.27 - 0.31)		-0.05 (-0.36 - 0.26)		0.59 (0.26 - 0.93)		0.51 (0.18 - 0.83)		0.59 (0.24 - 0.94)	

a. Binomial regression model with GEE was used; model was stratified on animal allergen exposure and sensitization to specific allergen, and adjusted for race/ethnicity, asthma severity, age, sex, insurance type, smoking exposure and sensitization to other allergens; Generalized linear model with GEE was used for log-transformed FeNO

b. Following thresholds were used to dichotomize each allergen: Bla g 1, 1 U/g; Mus m 1, 1 µg/g; Fel d 1, 3 µg/g; Can f1, 2 µg/g

- c. Numbers of children in each exposure and sensitization stratum in the cockroach group: Not exposed/not sensitized (n=40 for bedroom, n=27 for bedroom floor and n=21 for kitchen), Exposed/not sensitized (n=23 for bedroom, n=54 for bedroom floor and n=56 for kitchen); Not exposed/sensitized (n=28 for bedroom, n=21 for bedroom floor and n=15 for kitchen); Exposed/sensitized (n=29 for bedroom, n=46 for bedroom floor and n=50 for kitchen)
- d. Numbers of children in each exposure and sensitization stratum in the mouse group: Not exposed/not sensitized (n=40 for bedroom, n=30 for bedroom floor and n=31 for kitchen), Exposed/not sensitized (n=35 for bedroom, n=65 for bedroom floor and n=60 for kitchen); Not exposed/sensitized (n=18 for bedroom, n=11 for bedroom floor and n=16 for kitchen); Exposed/sensitized (n=29 for bedroom, n=44 for bedroom floor and n=37 for kitchen)

Table S2b. Asthma morbidity outcomes by exposure and sensitization to specific allergens (dog and cat) over time

Outcome	Dog (Bed) OR (95% CI)	<i>p</i> ^a	Dog (Bedroom) OR (95% CI)	<i>p</i>	Dog (Kitchen) OR (95% CI)	<i>p</i>	Cat (Bed) OR (95% CI)	<i>p</i>	Cat (Bedroom) OR (95% CI)	<i>p</i>	Cat (Kitchen) OR (95% CI)	<i>P</i>
Breathing difficulty												
Not exposed/not sensitized	Ref	0.31	Ref	0.28	Ref	0.71	Ref	0.99	Ref	0.05	Ref	0.27
Exposed/not sensitized	1.09 (0.40 - 2.95)		3.13 (1.70 - 5.76)		3.36 (1.41 - 8.01)		0.55 (0.27 - 1.13)		0.96 (0.53 - 1.73)		1.27 (0.55 - 2.98)	
Not exposed/sensitized	0.60 (0.24 - 1.45)		0.84 (0.42 - 1.69)		0.76 (0.33 - 1.76)		1.20 (0.49 - 2.93)		1.31 (0.61 - 2.83)		1.89 (0.79 - 4.50)	
Exposed/sensitized	1.40 (0.43 - 4.54)		1.20 (0.30 - 4.84)		3.26 (1.25 - 8.49)		0.67 (0.28 - 1.59)		0.41 (0.13 - 1.26)		1.16 (0.33 - 4.11)	
Bothered by asthma												
Not exposed/not sensitized	Ref	0.59	Ref	0.44	Ref	0.99	Ref	0.67	Ref	0.04	Ref	0.10
Exposed/not sensitized	0.98 (0.34 - 2.84)		3.05 (1.60 - 5.81)		3.19 (1.31 - 7.77)		0.74 (0.35 - 1.57)		1.21 (0.60 - 2.43)		1.85 (0.77 - 4.40)	
Not exposed/sensitized	0.67 (0.27 - 1.67)		0.91 (0.45 - 1.84)		0.84 (0.36 - 1.95)		1.32 (0.52 - 3.35)		1.23 (0.56 - 2.71)		2.00 (0.83 - 4.79)	
Exposed/sensitized	1.08 (0.22 - 5.21)		1.58 (0.39 - 6.40)		2.71 (0.86 - 8.56)		0.78 (0.31 - 1.95)		0.43 (0.13 - 1.39)		1.27 (0.38 - 4.26)	
Activity limited by asthma												
Not exposed/not sensitized	Ref	0.30	Ref	0.57	Ref	0.29	Ref	0.52	Ref	0.05	Ref	0.06
Exposed/not sensitized	1.00 (0.34 - 2.88)		2.72 (1.34 - 5.55)		3.14 (1.24 - 7.93)		0.76 (0.37 - 1.56)		0.91 (0.40 - 2.06)		1.25 (0.54 - 2.88)	
Not exposed/sensitized	0.61 (0.23 - 1.62)		0.89 (0.42 - 1.88)		0.75 (0.30 - 1.85)		1.18 (0.45 - 3.13)		1.27 (0.53 - 3.06)		1.99 (0.77 - 5.13)	
Exposed/sensitized	1.55 (0.36 - 6.78)		1.57 (0.36 - 6.85)		4.76 (1.77 - 12.75)		0.61 (0.22 - 1.71)		0.32 (0.09 - 1.13)		0.75 (0.23 - 2.42)	
Evening inhaler use												
Not exposed/not sensitized	Ref	0.47	Ref	0.92	Ref	0.12	Ref	0.23	Ref	0.94	Ref	0.33
Exposed/not sensitized	3.14 (1.14 - 8.68)		2.70 (1.42 - 5.13)		5.25 (2.13 - 12.98)		0.41 (0.16 - 1.10)		0.75 (0.38 - 1.49)		1.13 (0.35 - 3.70)	
Not exposed/sensitized	1.34 (0.48 - 3.77)		1.39 (0.57 - 3.38)		2.09 (0.73 - 5.98)		0.68 (0.27 - 1.75)		0.92 (0.42 - 2.00)		1.51 (0.62 - 3.67)	
Exposed/sensitized	2.28 (0.59 - 8.77)		3.51 (1.00 - 12.33)		3.24 (0.95 - 11.01)		0.88 (0.19 - 4.17)		0.64 (0.11 - 3.83)		0.68 (0.13 - 3.56)	
Morning inhaler use												
Not exposed/not sensitized	Ref	0.26	Ref	0.88	Ref	0.32	Ref	0.34	Ref	0.69	Ref	0.35
Exposed/not sensitized	4.45 (1.50 - 13.26)		2.04 (0.85 - 4.90)		4.15 (1.52 - 11.35)		0.40 (0.14 - 1.16)		0.95 (0.40 - 2.25)		1.26 (0.37 - 4.30)	
Not exposed/sensitized	1.07 (0.43 - 2.68)		1.02 (0.41 - 2.54)		1.27 (0.44 - 3.65)		0.54 (0.19 - 1.56)		0.52 (0.21 - 1.28)		0.51 (0.17 - 1.52)	
Exposed/sensitized	1.55 (0.28 - 8.72)		1.82 (0.42 - 7.92)		1.77 (0.34 - 9.18)		0.51 (0.11 - 2.33)		0.35 (0.07 - 1.74)		0.27 (0.05 - 1.42)	
Nocturnal symptoms												
Not exposed/not sensitized	Ref	0.19	Ref	0.24	Ref	0.75	Ref	0.20	Ref	0.03	Ref	0.20
Exposed/not sensitized	2.50 (1.13 - 5.55)		2.00 (0.99 - 4.06)		1.77 (0.74 - 4.20)		0.80 (0.36 - 1.79)		0.87 (0.37 - 2.06)		1.27 (0.53 - 3.03)	
Not exposed/sensitized	0.53 (0.21 - 1.31)		0.52 (0.24 - 1.12)		0.50 (0.21 - 1.18)		0.92 (0.30 - 2.76)		0.89 (0.31 - 2.53)		1.26 (0.37 - 4.32)	
Exposed/sensitized	0.40 (0.08 - 2.01)		0.42 (0.09 - 2.00)		1.06 (0.43 - 2.59)		0.35 (0.11 - 1.06)		0.19 (0.05 - 0.69)		0.75 (0.15 - 3.64)	
Acute care visits												
Not exposed/not sensitized	Ref	0.78	Ref	0.64	Ref	0.17	Ref	0.56	Ref	<0.01	Ref	0.65
Exposed/not sensitized	3.56 (1.14 - 11.10)		1.32 (0.35 - 4.98)		0.87 (0.21 - 3.70)		0.77 (0.11 - 5.50)		0.00 (0.00 - 0.00)		0.85 (0.13 - 5.37)	
Not exposed/sensitized	0.65 (0.13 - 3.23)		0.43 (0.11 - 1.71)		0.63 (0.19 - 2.12)		0.98 (0.32 - 3.02)		0.65 (0.19 - 2.32)		0.90 (0.25 - 3.27)	
Exposed/sensitized	3.13 (0.66 - 14.71)		0.96 (0.16 - 5.89)		1.90 (0.53 - 6.80)		1.81 (0.30 - 11.00)		0.35 (0.04 - 3.37)		1.36 (0.23 - 8.14)	
FeNO (β)^{c,d}												
Not exposed/not sensitized	Ref	0.84	Ref	0.39	Ref	0.05	Ref	0.78	Ref	0.59	Ref	0.43
Exposed/not sensitized	0.01 (-0.34 - 0.35)		-0.02 (-0.26 - 0.22)		-0.21 (-0.44 - 0.02)		-0.00 (-0.26 - 0.25)		-0.03 (-0.25 - 0.19)		-0.09 (-0.38 - 0.19)	
Not exposed/sensitized	0.14 (-0.25 - 0.52)		0.20 (-0.18 - 0.57)		0.16 (-0.18 - 0.50)		0.10 (-0.21 - 0.41)		0.09 (-0.19 - 0.37)		0.27 (0.00 - 0.53)	
Exposed/sensitized	0.23 (-0.53 - 0.99)		0.43 (-0.14 - 1.01)		0.50 (-0.11 - 1.11)		0.18 (-0.33 - 0.68)		0.20 (-0.32 - 0.72)		0.37 (-0.06 - 0.79)	

a. Binomial regression model with GEE was used; model was stratified on animal allergen exposure and sensitization to specific allergen, and adjusted for race/ethnicity, asthma severity, age, sex, insurance type, smoking exposure and sensitization to other allergens; Generalized linear model with GEE was used for log-transformed FeNO

b. Following thresholds were used to dichotomize each allergen: Bla g 1, 1 U/g; Mus m 1, 1 µg/g; Fel d 1, 3 µg/g; Can f1, 2 µg/g

- c. Numbers of children in each exposure and sensitization stratum in the dog group: Not exposed/not sensitized (n=66 for bedroom, n=87 for bedroom floor and n=84 for kitchen), Exposed/not sensitized (n=16 for bedroom, n=19 for bedroom floor and n=16 for kitchen); Not exposed/sensitized (n=31 for bedroom, n=34 for bedroom floor and n=35 for kitchen); Exposed/sensitized (n=9 for bedroom, n=10 for bedroom floor and n=9 for kitchen)
- d. Numbers of children in each exposure and sensitization stratum in the cat group: Not exposed/not sensitized (n=48 for bedroom, n=63 for bedroom floor and n=68 for kitchen), Exposed/not sensitized (n=22 for bedroom, n=26 for bedroom floor and n=14 for kitchen); Not exposed/sensitized (n=41 for bedroom, n=50 for bedroom floor and n=50 for kitchen); Exposed/sensitized (n=11 for bedroom, n=11 for bedroom floor and n=12 for kitchen)

Table S3a Analysis of the independent effect of animal exposure (cockroach and mouse) and allergen exposure on asthma morbidity

Sensitized participants		Cockroach				Mouse			
Outcome		Allergen or AP ^d unadjusted		Allergen and AP adjusted		Allergen or AP unadjusted		Allergen and AP adjusted	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Breathing difficulty	AP	1.32 (0.73 - 2.37)	0.36	AP	1.38 (0.75 - 2.54)	0.29	AP	1.15 (0.56 - 2.37)	0.71
	Allergen	0.93 (0.80 - 1.09)	0.37	Allergen	0.92 (0.79 - 1.08)	0.31	Allergen	1.11 (0.92 - 1.34)	0.30
Bothered by asthma	AP	1.34 (0.73 - 2.46)	0.35	AP	1.44 (0.78 - 2.67)	0.25	AP	1.01 (0.47 - 2.19)	0.98
	Allergen	0.90 (0.77 - 1.04)	0.16	Allergen	0.89 (0.76 - 1.03)	0.12	Allergen	1.10 (0.91 - 1.33)	0.34
Activity limited by asthma	AP	1.16 (0.60 - 2.25)	0.66	AP	1.27 (0.64 - 2.49)	0.50	AP	1.03 (0.45 - 2.35)	0.95
	Allergen	0.88 (0.76 - 1.02)	0.09	Allergen	0.87 (0.75 - 1.01)	0.08	Allergen	1.19 (0.99 - 1.43)	0.06
Morning inhaler use	AP	1.70 (0.73 - 3.97)	0.22	AP	1.77 (0.75 - 4.17)	0.19	AP	1.31 (0.49 - 3.51)	0.60
	Allergen	0.95 (0.77 - 1.16)	0.58	Allergen	0.93 (0.76 - 1.14)	0.48	Allergen	1.19 (0.93 - 1.53)	0.17
Nocturnal symptoms	AP	1.00 (0.46 - 2.19)	0.99	AP	0.99 (0.45 - 2.20)	0.99	AP	1.26 (0.54 - 2.96)	0.59
	Allergen	1.02 (0.86 - 1.21)	0.80	Allergen	1.02 (0.86 - 1.21)	0.80	Allergen	1.17 (0.95 - 1.44)	0.14
School absent	AP	0.37 (0.14 - 0.97)	0.04	AP	0.34 (0.12 - 0.95)	0.04	AP	0.54 (0.20 - 1.47)	0.23
	Allergen	1.18 (0.96 - 1.46)	0.12	Allergen	1.20 (0.96 - 1.51)	0.11	Allergen	1.26 (1.01 - 1.56)	0.04
FeNO ^a (β)	AP	0.29 (0.02 - 0.57)	0.03	AP	0.31 (0.03 - 0.58)	0.03	AP	0.13 (-0.19 - 0.45)	0.44
	Allergen	-0.02 (-0.10 - 0.07)	0.69	Allergen	-0.02 (-0.11 - 0.06)	0.56	Allergen	0.05 (-0.04 - 0.14)	0.24
Non-sensitized participants		Cockroach				Mouse			
Outcome		Allergen or AP ^d unadjusted		Allergen and AP adjusted		Allergen or AP unadjusted		Allergen and AP adjusted	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Breathing difficulty	AP	1.02 (0.51 - 2.04)	0.95	AP	1.02 (0.51 - 2.03)	0.95	AP	1.25 (0.70 - 2.26)	0.45
	Allergen	1.00 (0.83 - 1.20)	0.97	Allergen	1.00 (0.83 - 1.20)	0.97	Allergen	0.72 (0.57 - 0.92)	0.01
Bothered by asthma	AP	0.91 (0.43 - 1.95)	0.82	AP	0.91 (0.43 - 1.95)	0.81	AP	1.35 (0.73 - 2.51)	0.34
	Allergen	1.02 (0.82 - 1.28)	0.86	Allergen	1.02 (0.82 - 1.28)	0.85	Allergen	0.74 (0.59 - 0.93)	0.01
Activity limited by asthma	AP	0.94 (0.41 - 2.18)	0.89	AP	0.94 (0.41 - 2.18)	0.89	AP	1.38 (0.68 - 2.82)	0.37
	Allergen	0.99 (0.77 - 1.27)	0.92	Allergen	0.99 (0.77 - 1.27)	0.92	Allergen	0.80 (0.62 - 1.05)	0.10
Morning inhaler use	AP	0.67 (0.28 - 1.57)	0.35	AP	0.67 (0.29 - 1.57)	0.36	AP	1.12 (0.46 - 2.69)	0.81
	Allergen	0.96 (0.75 - 1.22)	0.72	Allergen	0.97 (0.76 - 1.22)	0.77	Allergen	0.74 (0.54 - 1.03)	0.07
Nocturnal symptoms	AP	0.79 (0.30 - 2.04)	0.62	AP	0.83 (0.33 - 2.12)	0.70	AP	1.06 (0.42 - 2.69)	0.90
	Allergen	0.88 (0.69 - 1.11)	0.27	Allergen	0.88 (0.70 - 1.11)	0.28	Allergen	0.69 (0.54 - 0.89)	<0.01
School absent	AP	5.06 (0.61 - 41.72)	0.13	AP	5.47 (0.62 - 48.22)	0.13	AP	3.11 (0.79 - 12.21)	0.10
	Allergen	1.10 (0.73 - 1.66)	0.65	Allergen	1.14 (0.78 - 1.66)	0.51	Allergen	1.04 (0.71 - 1.52)	0.84
FeNO (β)	AP	0.05 (-0.20 - 0.30)	0.71	AP	0.06 (-0.19 - 0.31)	0.64	AP	-0.03 (-0.23 - 0.18)	0.79
	Allergen	-0.03 (-0.10 - 0.04)	0.43	Allergen	-0.03 (-0.11 - 0.04)	0.40	Allergen	-0.07 (-0.13 - -0.01)	0.02

- a. FENO: Fractional exhaled nitric oxide, the higher value suggests poor response to medication, poor asthma control or airway inflammation; FeNO was log-transformed
- b. Binomial regression model used; Adjusted for race/ethnicity, asthma severity, age, sex, insurance, smoking, numbers of positive atopic status
- c. Log-transformed cockroach and mouse allergen concentration settled on kitchen was used for mediation analysis; home inspection was used to ascertain animal presence
- d. Abbreviation: Animal presence=AP

Table S3b Analysis of the independent effect of animal exposure (dog and cat) and allergen exposure on asthma morbidity

Sensitized participants		Dog				Cat			
		Allergen or AP ^d unadjusted		Allergen and AP adjusted		Allergen or AP unadjusted		Allergen and AP adjusted	
Outcome		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Breathing difficulty	AP	1.22 (0.56 - 2.69)	0.62	AP	0.65 (0.24 - 1.80)	0.41	AP	0.67 (0.35 - 1.29)	0.23
	Allergen	1.64 (1.20 - 2.24)	<0.01	Allergen	1.85 (1.16 - 2.96)	0.01	Allergen	0.84 (0.53 - 1.33)	0.45
Bothered by asthma	AP	0.99 (0.42 - 2.30)	0.98	AP	0.72 (0.28 - 1.86)	0.49	AP	0.60 (0.31 - 1.17)	0.13
	Allergen	1.28 (0.84 - 1.94)	0.25	Allergen	1.40 (0.84 - 2.33)	0.20	Allergen	0.83 (0.53 - 1.29)	0.40
Activity limited by asthma	AP	1.11 (0.50 - 2.48)	0.80	AP	0.48 (0.17 - 1.32)	0.16	AP	0.57 (0.29 - 1.11)	0.10
	Allergen	1.74 (1.36 - 2.24)	<0.01	Allergen	2.15 (1.41 - 3.27)	<0.01	Allergen	0.67 (0.40 - 1.10)	0.11
Morning inhaler use	AP	0.64 (0.22 - 1.90)	0.42	AP	0.53 (0.21 - 1.31)	0.17	AP	0.39 (0.17 - 0.86)	0.02
	Allergen	1.02 (0.38 - 2.73)	0.97	Allergen	1.23 (0.45 - 3.35)	0.69	Allergen	0.68 (0.33 - 1.41)	0.30
Nocturnal symptoms	AP	0.54 (0.25 - 1.16)	0.11	AP	0.36 (0.14 - 0.92)	0.03	AP	0.80 (0.31 - 2.05)	0.64
	Allergen	1.14 (0.80 - 1.61)	0.46	Allergen	1.51 (0.96 - 2.38)	0.07	Allergen	0.80 (0.51 - 1.24)	0.31
School absent	AP	0.31 (0.05 - 2.02)	0.22	AP	0.15 (0.02 - 1.00)	0.05	AP	0.29 (0.10 - 0.83)	0.02
	Allergen	1.26 (0.69 - 2.29)	0.45	Allergen	1.94 (0.94 - 4.01)	0.08	Allergen	0.54 (0.20 - 1.50)	0.24
FeNO (β)	AP	0.14 (-0.23 - 0.51)	0.46	AP	0.13 (-0.24 - 0.50)	0.49	AP	0.06 (-0.25 - 0.38)	0.70
	Allergen	0.05 (-0.20 - 0.31)	0.69	Allergen	0.01 (-0.24 - 0.27)	0.92	Allergen	0.02 (-0.12 - 0.17)	0.74
Non-sensitized participants		Dog				Cat			
		OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)	
Outcome			p		p		p		p
Breathing difficulty	AP	1.17 (0.61 - 2.24)	0.63	AP	0.86 (0.43 - 1.73)	0.67	AP	1.70 (0.83 - 3.47)	0.15
	Allergen	1.45 (1.06 - 1.99)	0.02	Allergen	1.50 (1.06 - 2.13)	0.02	Allergen	1.10 (0.83 - 1.48)	0.50
Bothered by asthma	AP	1.29 (0.66 - 2.49)	0.46	AP	0.98 (0.47 - 2.03)	0.95	AP	1.88 (0.90 - 3.95)	0.09
	Allergen	1.42 (1.04 - 1.95)	0.03	Allergen	1.43 (1.01 - 2.02)	0.04	Allergen	1.27 (0.93 - 1.73)	0.14
Activity limited by asthma	AP	1.09 (0.52 - 2.27)	0.82	AP	0.82 (0.38 - 1.79)	0.63	AP	1.49 (0.68 - 3.30)	0.32
	Allergen	1.39 (1.00 - 1.92)	0.05	Allergen	1.45 (1.04 - 2.04)	0.03	Allergen	1.17 (0.86 - 1.58)	0.32
Morning inhaler use	AP	1.03 (0.39 - 2.71)	0.96	AP	0.56 (0.21 - 1.47)	0.24	AP	1.26 (0.50 - 3.15)	0.63
	Allergen	1.67 (1.09 - 2.55)	0.02	Allergen	1.92 (1.26 - 2.91)	<0.01	Allergen	1.29 (0.79 - 2.10)	0.31
Nocturnal symptoms	AP	0.98 (0.51 - 1.87)	0.95	AP	0.82 (0.36 - 1.85)	0.64	AP	0.80 (0.35 - 1.79)	0.58
	Allergen	1.20 (0.86 - 1.68)	0.27	Allergen	1.26 (0.83 - 1.92)	0.28	Allergen	1.15 (0.86 - 1.53)	0.35
School absent	AP	0.76 (0.36 - 1.60)	0.47	AP	0.66 (0.28 - 1.58)	0.35	AP	0.68 (0.20 - 2.36)	0.54
	Allergen	1.07 (0.80 - 1.43)	0.64	Allergen	1.18 (0.85 - 1.64)	0.33	Allergen	1.05 (0.79 - 1.39)	0.75
FeNO (β)	AP	-0.05 (-0.23 - 0.14)	0.61	AP	-0.03 (-0.23 - 0.18)	0.79	AP	-0.03 (-0.23 - 0.18)	0.81
	Allergen	-0.04 (-0.12 - 0.05)	0.40	Allergen	-0.03 (-0.12 - 0.06)	0.52	Allergen	0.01 (-0.09 - 0.11)	0.87

a. FeNO: Fractional exhaled nitric oxide, the higher value suggests poor response to medication, poor asthma control or airway inflammation; FeNO was log-transformed

b. Binomial regression model used; Adjusted for race/ethnicity, asthma severity, age, sex, insurance, smoking, numbers of positive atopic status

c. Log-transformed dog and cat allergen concentration settled on kitchen was used for mediation analysis; home inspection was used to ascertain animal presence

d. Abbreviation: Animal presence=AP

Table S4. Correlation between the results of home inspection and allergen presence

	HI (Co)	Dust (Co)	HI (M)	Dust (M)	HI (D)	Dust (D)	HI (Ca)	Dust (Ca)
HI (Co)	1.00							
Dust (Co)	0.12	1.00						
HI (M)	0.90	0.08	1.00					
Dust (M)	-0.05	0.12	-0.08	1.00				
HI (D)	0.25	0.16	0.21	-0.12	1.00			
Dust (D)	0.13	0.05	0.09	0.01	0.42	1.00		
HI (Ca)	0.27	0.14	0.23	-0.16	0.94	0.37	1.00	
Dust (Ca)	0.02	0.03	0.02	-0.16	0.40	0.01	0.42	1.00

a. Following thresholds were used to dichotomize each allergen: Bla g 1, 1 U/g; Mus m 1, 1 µg/g; Fel d 1, 3 µg/g; Can f1, 2 µg/g

b. HI: home inspection; Dust: allergen from dust sample; Co: cockroach; M: mouse; D: dog; Ca: cat