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The Effect of Dog Allergen Exposure on Asthma Morbidity among Inner-city Children with Asthma

Po-Yang Tsou¹, Meredith C. McCormack², Elizabeth C. Matsui², Roger D. Peng³, Gregory B. Diette², Nadia N. Hansel², Meghan F. Davis⁴

¹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

²Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

³Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

⁴Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

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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 (*e.g.* endotoxin, microbes) and activities (*e.g.* 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

Corresponding author: Po-Yang Tsou, MD MPH, ptsou1@jhmi.edu, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street E7612 Baltimore, Maryland 21205. Alternate corresponding author: Meghan F. Davis, PhD, mdavis65@jhu.edu, Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street E7612 Baltimore, Maryland 21205., TEL: (1) 410-614-8283.

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

exposures, and that dog-associated non-allergen exposures could also be associated with respiratory outcomes among inner-city children with asthma (Supplemental Figure 1).

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 ages 5–12 years with physician-diagnosed asthma were recruited from January 2009 to February 2015 and assessed at baseline, 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, ThermoFisher, Uppsala, Sweden). 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 was: 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 (Supplemental Table 1). The allergen concentration, IgE antibody levels and FeNO concentrations are summarized in Supplemental Table 1.

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 (e.g. 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, Supplemental Table 2). 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 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 (Supplemental Table 4).

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 (Supplemental Table 2). Further, the effects of animal-associated non-allergen exposure derived from presence of other animals and exposures to allergens were tested and found to not to be consistently associated with asthma morbidity, except for mouse allergen (Supplemental Table 3).

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 differs from a recent U.S. 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 in 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, *i.e.* Toll-like receptor (TLR) signaling.⁹ Alternatively, increased airway hypersensitivity may result from the interaction between dog allergen and substances unmeasured in current study (*e.g.* 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation

FeNO	fractional exhaled nitric oxide
DISCOVER study	Domestic Indoor Particulate Matter and Childhood Asthma Morbidity Study

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Table 1

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

		Kitchen (n=144)	
Outcome		OR (95% CI)	Interaction p^e
Breathing difficulty			
Not exposed/not sensitized ^c	Ref		0.71
Exposed/not sensitized		3.36 (1.41 – 8.01)	
Not exposed/sensitized		0.76 (0.33 – 1.76)	
Exposed/sensitized		3.26 (1.25 – 8.49)	
Bothered by asthma			
Not exposed/not sensitized	Ref		0.99
Exposed/not sensitized		3.19 (1.31 – 7.77)	
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)	
Not exposed/sensitized		0.75 (0.30 – 1.85)	
Exposed/sensitized		4.76 (1.77 – 12.75)	
Evening inhaler use			
Not exposed/not sensitized	Ref		0.12
Exposed/not sensitized		5.25 (2.13 – 12.98)	
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)	
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)	
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 (β)^b			
Not exposed/not sensitized	Ref		0.05

Kitchen (n=144)		
Outcome	OR (95% CI)	Interaction p^e
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)	

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

^b. FeNO: 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.

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

^d. Not exposed/not sensitized (n=84), Exposed/not sensitized (n=16); Not exposed/sensitized (n=35); Exposed/sensitized (n=9)

^e. Significance level for interaction was defined as $p < 0.10$; OR: Odds Ratio.

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

Table 2

Dog-sensitized patients (n=44)		Allergen or animal presence unadjusted			Allergen and animal presence adjusted		
Outcome		OR (95% CI)	p-value		OR (95% CI)	p-value	
Breathing difficulty	Animal presence	1.22 (0.56 – 2.69)	0.62	Animal presence	0.65 (0.24 – 1.80)	0.41	
	Allergen	1.64 (1.20 – 2.24)	<0.01	Allergen	1.85 (1.15 – 2.96)	0.01	
Bothered by asthma	Animal presence	0.99 (0.42 – 2.30)	0.98	Animal presence	0.72 (0.28 – 1.86)	0.49	
	Allergen	1.28 (0.84 – 1.94)	0.25	Allergen	1.40 (0.84 – 2.32)	0.20	
Activity limited by asthma	Animal presence	1.11 (0.50 – 2.48)	0.80	Animal presence	0.48 (0.17 – 1.32)	0.16	
	Allergen	1.74 (1.36 – 2.24)	<0.01	Allergen	2.15 (1.41 – 3.27)	<0.01	
Morning inhaled use	Animal presence	0.64 (0.22 – 1.90)	0.42	Animal presence	0.53 (0.21 – 1.31)	0.17	
	Allergen	1.02 (0.38 – 2.73)	0.97	Allergen	1.23 (0.45 – 3.35)	0.69	
Nocturnal symptoms	Animal presence	0.54 (0.25 – 1.16)	0.11	Animal presence	0.36 (0.14 – 0.92)	0.03	
	Allergen	1.14 (0.80 – 1.61)	0.46	Allergen	1.51 (0.96 – 2.38)	0.07	
School absent	Animal presence	0.31 (0.05 – 2.02)	0.22	Animal presence	0.15 (0.02 – 1.00)	0.05	
	Allergen	1.26 (0.69 – 2.29)	0.45	Allergen	1.94 (0.94 – 4.00)	0.08	
FeNO (β) ^a	Animal presence	0.14 (–0.23 – 0.51)	0.46	Animal presence	0.13 (–0.24 – 0.50)	0.49	
	Allergen	0.05 (–0.20 – 0.31)	0.69	Allergen	0.01 (–0.24 – 0.27)	0.92	
Dog non-sensitized patients (n=100)							
Outcome		OR (95% CI)	p-value		OR (95% CI)	p-value	
Breathing difficulty	Animal presence	1.17 (0.61 – 2.24)	0.63	Animal presence	0.86 (0.43 – 1.73)	0.67	
	Allergen	1.45 (1.06 – 1.99)	0.02	Allergen	1.50 (1.06 – 2.13)	0.02	
Bothered by asthma	Animal presence	1.29 (0.66 – 2.49)	0.46	Animal presence	0.98 (0.47 – 2.03)	0.95	
	Allergen	1.42 (1.04 – 1.95)	0.03	Allergen	1.43 (1.01 – 2.02)	0.04	
Activity limited by asthma	Animal presence	1.09 (0.52 – 2.27)	0.82	Animal presence	0.82 (0.38 – 1.79)	0.63	
	Allergen	1.39 (1.00 – 1.92)	0.05	Allergen	1.45 (1.04 – 2.04)	0.03	
Morning inhaled use	Animal presence	1.03 (0.39 – 2.71)	0.96	Animal presence	0.56 (0.21 – 1.47)	0.24	
	Allergen	1.67 (1.09 – 2.55)	0.02	Allergen	1.92 (1.26 – 2.91)	<0.01	
Nocturnal symptoms	Animal presence	0.98 (0.51 – 1.87)	0.95	Animal presence	0.82 (0.36 – 1.85)	0.64	
	Allergen	1.20 (0.86 – 1.68)	0.27	Allergen	1.26 (0.83 – 1.92)	0.28	

Dog-sensitized patients (n=44)					
Outcome	Allergen or animal presence unadjusted			Allergen and animal presence adjusted	
		OR (95% CI)	p-value	OR (95% CI)	p-value
School absent	Animal presence	0.76 (0.36 – 1.60)	0.47	Animal presence	0.66 (0.28 – 1.58)
	Allergen	1.07 (0.80 – 1.43)	0.64	Allergen	1.18 (0.85 – 1.64)
FeNO (p)	Animal presence	-0.05 (-0.23 – 0.14)	0.61	Animal presence	-0.03 (-0.23 – 0.18)
	Allergen	-0.04 (-0.12 – 0.05)	0.40	Allergen	-0.03 (-0.12 – 0.06)

^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 exposure, and number of allergic sensitizations

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