

Effect of prenatal indoor pet exposure on the trajectory of total IgE levels in early childhood

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Background: The presence of pets in a home during the prenatal period and during early infancy has been associated with a lower prevalence of allergic sensitization and total IgE levels in middle childhood. No studies have examined the effect of pet exposure in a population-based cohort by using multiple early-life measures of serum total IgE.

Objective: We sought to examine within-individual longitudinal trends in total IgE levels during early childhood and assess the effect of indoor prenatal pet exposure on those trends. Also, we sought to use a statistical method that was flexible enough to allow and account for unequally spaced study contacts and missing data.

Methods: Using the population-based Wayne County Health, Environment, Allergy and Asthma Longitudinal Study birth cohort (62% African American), we analyzed 1187 infants with 1 to 4 measurements of total IgE collected from birth to 2 years of age. Effects of pet exposure on the shape and trajectory of IgE levels were assessed by using a multilevel longitudinal model, accommodating repeated measures, missing data, and the precise time points of data collection.

Results: The best-fit shape to the trajectory of IgE levels was nonlinear, with an accelerated increase before 6 months. Total IgE levels were lower across the entire early-life period when there was prenatal indoor pet exposure ($P < .001$). This effect was statistically significantly stronger in children delivered by means of cesarean section versus those delivered vaginally ($P < .001$ and $P < .06$, respectively) and in those born to non-African American ($P < .001$) versus African American ($P < .3$) mothers.

Conclusion: Pet exposure and delivery mode might be markers of infant exposure to distinct microbiomes. The effect of exposures might vary by race, suggesting a differential effect by ancestry. (J Allergy Clin Immunol 2011;■■■■:■■■■-■■■■.)

Key words: Total IgE, cohort, longitudinal, multilevel model

Allergic sensitization, allergies, and asthma have been increasing in prevalence over the last half century among children residing in westernized countries.¹⁻³ One theory, the hygiene hypothesis, posits that decreased exposure to infections during early life results in an immunologic shift toward an allergic phenotype.⁴ A refined version of this hypothesis is based on microbial ecology, suggesting that exposure to a distinct microbial community composition of home environments with certain characteristics, such as indoor pets, during pregnancy and infancy affects the developing immune system.⁵⁻⁷

The production of IgE in response to innocuous substances is the hallmark of allergic disease: as more IgE is produced, total IgE levels increase.⁸ The total IgE level has been associated with risk for asthma in children in westernized countries.^{9,10} Although a number of studies have reported cross-sectional associations between early-life allergic disease risk factors and total IgE levels, few have examined the effects of such factors on intraindividual IgE levels over time by using repeated measures during infancy in a large population-based birth cohort. None have accommodated together 2 specific analytic challenges associated with birth cohort studies, the exclusion of subjects with missing data because of the difficulties of collecting blood samples from infants and the varying collection points by time since birth because of scheduling compromises, even though the precise age at which a measurement is taken is critical because IgE levels are rapidly changing during this time period. Using an analytic approach that addresses these potential biases, we assessed the effect of exposure to pets on the trajectory of IgE development in the first 2 years of life in a racially diverse birth cohort based in metropolitan Detroit, Michigan.

METHODS

Study population

The Wayne County Health, Environment, Allergy and Asthma Longitudinal Study is a birth cohort from southeastern Michigan designed to examine the relationship of environmental factors to the subsequent development of atopic and allergic diseases in childhood. The cohort was based in the Henry Ford Health System. The population served has been shown through census data to be representative of the Detroit metropolitan area. Through an electronic medical claims database, potentially pregnant women were identified through the use of the International Classification of Diseases–Ninth

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Abbreviation used

MLM: Multilevel longitudinal model

Revision for visits to one of 5 obstetric clinics. To be eligible for the study, women needed to be between 21 and 49 years of age and live in a predefined cluster of ZIP codes that included both urban and suburban Detroit, Michigan (see Fig E1 in this article's Online Repository at www.jacionline.org for study area map). By including not only the city of Detroit (82% African American based on 2000 Census data) but also suburbs that range from 1% African American to 68% African American, we expected to recruit subjects from highly variable socioeconomic and racial backgrounds. Medical records were then reviewed to confirm pregnancy and to determine whether the pregnancy had progressed beyond the first trimester (calculated by estimated due date or last menstrual period). Women in their first trimester of pregnancy qualified for the study if they remained pregnant into their second trimester and still met other study criteria. We chose the second trimester restriction to decrease the chance of miscarriage/spontaneous abortion. Women who met the above criteria were then officially enrolled in the study if they read and signed the study's informed consent form, indicated their intention of living in the area for at least 2 years, completed the predelivery interview, and were delivered of at least 1 live birth. We recorded 5 stillborn children (not in study) and no instances of a multiple birth during which 1 or more children died. For the 16 twin deliveries (no other multiple births in study), the firstborn child was designated the study child. Recruitment was completed between August 2003 and November 2007. Each follow-up contact included an interviewer-administered questionnaire and was planned for 1, 6, 12, and 24 months after the child's birth. All questionnaires included questions on the type of household pets, and for dogs and cats, more detailed information, such as the average time spent indoors for each pet, was captured.

This research was approved by the Henry Ford Hospital Institutional Review Board.

Total IgE levels

The outcome of interest is the within-child pattern of total IgE development by using blood collected at birth (cord) and at approximately 6, 12, and 24 months of age. Total IgE levels were measured with the Pharmacia UniCAP system (Phadia, Portage, Mich) by using the manufacturer's protocols. The high-sensitivity protocol providing an assay range of 0.1 to 100 IU/mL IgE was used for the cord blood and 6-month samples, whereas the standard protocol was used for 12- and 24-month samples. The high-sensitivity assay protocol was used for the earlier time points to minimize the number of samples with IgE levels of less than the lower limit of assay calibration. One percent of all samples were reanalyzed in a different assay run on a different day, enabling us to calculate an interassay coefficient of variation of 6.7%. One hundred forty-seven (19.7%) of the cord blood samples and 1 of the 6-month samples had undetectable measures and were assigned a value of 0.05 IU/mL.

Pet exposure

A pet was defined as a cat or dog only (other types of pets were uncommon). We defined prenatal pet exposure as the mother answering yes to the following question: "Since the time you learned you were pregnant have you owned or cared for any pets for more than 1 week in your home?" We considered only those reporting pets being kept indoors for at least 1 hour daily as exposed.

Other early-life factors

Maternal race was based on self-report during the enrollment interview. Women were grouped as either being African American or not; because of sample size, the non-African American group was not further subdivided. Maternal allergic history was defined as positive if she reported ever having a doctor's diagnosis of hay fever or allergic rhinitis. Women were also asked to report the outcome of all prior pregnancies.

Information on maternal smoking or living with smokers and the child's exposure to tobacco smoke after delivery was also collected before delivery and at the time of blood sampling at 6, 12, and 24 months postpartum. Delivery type (vaginal or cesarean section) was collected from the medical record.

The number of days per week or month that the child spent 4 or more hours outside the home, defined as visiting a family, friend, or babysitter's house or child care facility, was recorded at postpartum interviews. The average numbers of other children and pets at such locations were also recorded, and routine exposure was defined as 3 or more visits per week. We created 4 indicator variables to examine potential effects of routine external exposures: 1 or more children, presence of a pet or pets, either, and both.

Statistical analysis

Multilevel modeling techniques use all available data in the analyses. This means that children missing 1 or more IgE measurements were not excluded from analyses, thus addressing a common analytic challenge in asthma cohort studies/longitudinal analyses. Of the 1258 subjects enrolled, 1187 (94%) had a total IgE measure for at least 1 of the scheduled collection times (cord blood or 6, 12, or 24 months of age), and 825 (66%) had 2 or more IgE values. IgE levels were log-transformed before inclusion in the model because of the skew of the data.

Multilevel longitudinal models (MLMs) were fit by using full maximum likelihood methods and included both random and fixed effects (PROC MIXED, SAS version 9.2, release 2; SAS Institute, Inc, Cary, NC) to assess the trajectory (rate and direction of change over time) of IgE development and between-individual change to assess the effects of early-life exposures. Random effects account for the correlation within individuals (repeated measures). The age of each child at each visit is included as a variable in the individual-specific component of the multilevel model to allow and account for unequal spacing of collection points, thus addressing another commonly occurring situation in many research studies in which planned study contacts occur over a window of time. This study's intent was to contact every child at 6, 12, and 24 months of age, yet visits actually occurred over a range of ages. Because of the young age of the subjects and the apparent rapid change in IgE levels for many subjects over this time period, MLMs are an appropriate choice.

For illustrative purposes, Fig 1 is a profile plot of a 5% random selection of subjects, which indicates a fair amount of variation in the starting point (intercept), rate (slope), and shape of the trajectory (possible higher-order terms). Visual inspection of all subject's trajectories (each line is constructed by connecting 1 child's log-transformed IgE levels at each age measured; single dots represent children with only 1 IgE measurement) showed that most were markedly nonlinear. The inspection process, through this type of graphing, can be helpful to assess whether and where variability in individual growth curves might exist for the data but is not deterministic. The 6-month time point

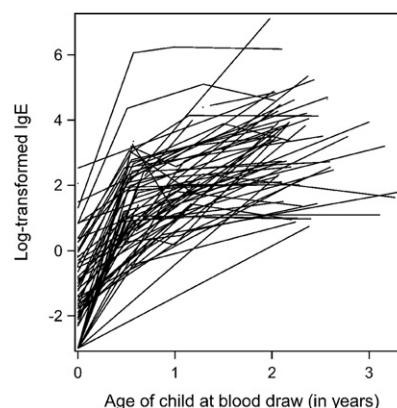


FIG 1. Profile plot of 5% randomly selected subjects. Each *line* is a "connect-the-dots" depiction of the log-transformed IgE values by age for 1 unique child. *Single dots* represent children with only 1 IgE measurement.

appeared to be the natural choice for the point at which the rate (or slope) of increase changed (sometimes called “change point”), but we also tested to see whether using the 1-year time point was able to explain more of the variability (ie, better fit); it did not.

A 2-segment linear (piecewise) model was found to have the best fit (see the Methods section in this article’s Online Repository at www.jacionline.org). Indoor pet exposure was included as a main effect and was also tested for an interaction with the age of the child. Indoor pet exposure was evaluated as a baseline exposure variable, as well as a time-varying exposure variable (one that can change over time), because we had reports about pet exposure at each time that IgE levels were measured.

Effect modification for *a priori* selected variables was tested by means of inclusion of an interaction term ($P < .10$) and inspection of stratified models. Maternal race, smoke exposure during pregnancy, mode of delivery, firstborn status, first pregnancy, child’s sex, and maternal history of allergy were tested for both effect modification and confounding of the association between indoor pets and the pattern of total IgE levels over early life.

RESULTS

Cohort’s characteristics

The average age of the mother at the time of the child’s birth was 29.5 years (SD, 5.3 years), and 62.2% ($n = 738$) self-reported their race as African American. Of the 1187 subjects, 35.4% ($n = 420$) had at least 1 indoor pet at the prenatal interview, 16.6% ($n = 197$) had at least 1 indoor cat and 24.3% ($n = 289$) had at least 1 indoor dog, and 5.6% ($n = 66$) had both cats and dogs. Thirty-seven percent ($n = 436$) of the babies were delivered by means of cesarean section, and 36.5% ($n = 433$) were firstborn children. Children whose mothers reported at least 1 indoor pet at the predelivery interview were more likely to be exposed to smoke during pregnancy, be firstborn, and have a mother of non-African American ethnicity (Table I). The non-African American mothers ($n = 449$) were 86% white, 7% Asian, and 7% other.

Shape of trajectory

Fig 2 shows the mean predicted piecewise model of IgE levels over time (within-individual change). The slope, or rate of change, between the cord blood measurement and the 6-month time point is significantly steeper than the slope after the 6-month time point ($P < .001$). The average change in total IgE level from cord blood to age 6 months estimated by the regression model is a 25.8-fold increase (95% CI, 23.3-fold to 28.5-fold) in the geometric mean from cord blood to 6 months ($P < .001$). Fig 2 shows that the regression model estimates an average total IgE

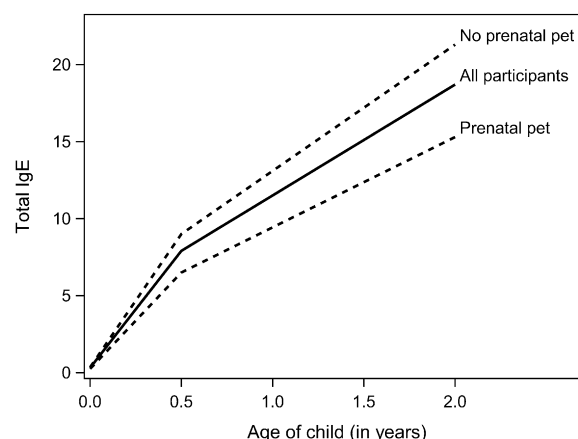


FIG 2. Predicted mean plot of the trajectory from the 2-piece random effects model.

level of 0.30 IU/mL at birth and 7.74 IU/mL at the 6-month time point, corresponding to a 25.8-fold increase ($7.74/0.30$). If there were no missing data and the timing of study contacts did not differ among subjects, this estimate of a 25.8-fold increase (equivalent to a 2580% increase) would directly correspond to the ratio of the (cross-sectional) geometric means at birth and the 6-month visit (see Table E1 in this article’s Online Repository at www.jacionline.org): a geometric means of 0.31 IU/mL at birth and 7.4 IU/mL at the 6-month visit is a (cross-sectional) 23.9-fold ($7.4/0.31$) increase. In contrast to the estimated 25.8-fold increase in the first 6 months, the estimated average fold increase in the post-6-month age period was 1.51-fold (95% CI, 1.48-fold to 1.59-fold) per 6-month interval (Fig 2). Thus, for example, for a child with a 6-month total IgE level of 7.7 IU/mL, we would expect, on average, an 11.6 IU/mL total IgE level at 12 months of age.

Effect of prenatal indoor pets

Overall, a constant statistically significant pet effect was found over the complete trajectory (Table II; regression coefficient = -0.33 [SE, 0.07], $P < .001$). This means that the total IgE trajectory is an estimated and unvarying 28% lower in the group of children with prenatal pet exposure versus that seen in those who did not have prenatal pet exposure. Addition of the time-varying postnatal indoor pet exposure variable to the model was not statistically significant ($P = .50$), suggesting that subsequent pet exposure did not add any additional information to the model once prenatal pet status was determined. We further explored this by creating variables for loss of pet and gain of pet, and although neither was statistically significant, the numbers were small ($n = 83$ and $n = 55$, respectively). The number of pets was not found to be significant ($P = .84$). Separating the pet exposure into indoor dog and indoor cat variables resulted in no statistically significant difference for the effect of pet type (all $P \geq .5$; see Table E2 in this article’s Online Repository at www.jacionline.org).

Modification of prenatal pet effect

Male sex, maternal African American race, mode of delivery, mother’s history of doctor-diagnosed allergy or asthma, being firstborn or first pregnancy, and prenatal maternal or other

TABLE I. Sample characteristics ($n = 1187$)

	Indoor pet at PD ($n = 420$)	No indoor pet at PD ($n = 727$)	<i>P</i> value
Mother’s age (y), mean (SD)	29.7 (5.1)	29.4 (5.3)	.30
African American race, no. (%)	186 (44.3)	552 (72.0)	<.001
Mother’s allergic history,* no. (%)	127 (30.5)	213 (27.8)	.34
Mother smoked, no. (%)	67 (16.0)	72 (9.4)	.001
ETS during pregnancy, no. (%)	131 (31.2)	196 (25.6)	.038
Delivery by means of cesarean section,† no. (%)	144 (34.6)	292 (38.5)	.19
Male sex (baby), no. (%)	217 (51.7)	375 (48.9)	.36
Firstborn, no. (%)	175 (41.7)	258 (33.6)	.006

ETS, Environmental tobacco smoke; PD, predelivery.

*Four with missing information.

†Thirteen with missing information.

TABLE II. Estimated regression coefficients (b) and SEs for the model of log-transformed IgE levels over time

Strata	Independent variable	b* (SE)	Expected decrease in total IgE with pet exposure†	P value
All	Prenatal indoor pet exposure	−0.33 (0.07)	28%	<.001
Type of delivery				
Vaginal	Prenatal indoor pet exposure	−0.18 (0.09)	16%	.055
Cesarean section	Prenatal indoor pet exposure	−0.57 (0.12)	43%	<.001
Race				
African American	Prenatal indoor pet exposure	−0.11 (0.10)	10%	.30
Non-African American	Prenatal indoor pet exposure	−0.40 (0.11)	33%	<.001

*Because of the log-transformation of total IgE levels, the regression coefficient can be interpreted as the average difference in log-transformed total IgE levels between children with prenatal indoor pet exposure versus children without prenatal indoor pet exposure.

†An easier interpretation is to use the formula $(e^b - 1) \times 100$, where b is the regression coefficient.

household member smoke exposures were assessed to see whether they modified the association between pet exposure and total IgE trajectory. A statistically significant interaction was found between prenatal indoor pet exposure and mode of delivery ($P = .009$). The protective effect of pet exposure on IgE trajectory was significantly greater in those delivered by means of cesarean section (regression coefficient = -0.57 [SE, 0.12], $P < .001$) compared with that seen in children delivered vaginally (regression coefficient = -0.18 [SE, 0.09], borderline statistical significance of $P = .055$). The regression coefficients translate to a 43% decrease in total IgE levels among children born by means of cesarean section compared with a 16% overall decrease for children born vaginally. Table III shows that women who underwent cesarean delivery tended to be older and have a firstborn female child; however, adjusting for these factors did not substantially alter the findings.

Additionally, there was evidence that maternal race was an effect modifier (interaction $P = .06$). The protective pet effect was only statistically significant within the non-African American women (associated 33% decrease, $P < .001$) compared with the children of African American women (associated 10% decrease, $P = .30$). African American women in this study were more likely to be younger and to be exposed to environmental tobacco smoke and less likely to have a pet or pets in the household (Table III). The remaining early-life factors (male sex, firstborn or first pregnancy, mother's history of doctor-diagnosed allergy or asthma, and prenatal environmental tobacco smoke) were not found to be effect modifiers (all interaction $P > .45$). Also, there was no strong evidence of confounding by these same early-life factors (all change in effects $< 20\%$).

Early exposures outside the home

At the 6-month visit, 31.8% ($n = 249$) of children had routine exposure to children outside the home, and 11.4% ($n = 89$) of children had routine exposure to pets outside the home. Routine exposure to other children, pets, or both external to the home environment did not significantly affect the trajectory of IgE levels after 6 months of age.

DISCUSSION

Our study demonstrates that the trajectory of IgE levels in early life is affected by the presence of pets in the home during pregnancy and that the magnitude of this effect varies by the mode of delivery and self-reported race. Studies in multiple settings have evaluated the effects of both early-life pet exposure¹¹⁻¹⁵ and mode of delivery^{16,17} on the risks of allergic disease. Although previous studies are not uniform, many suggest that early-life pet exposures are associated with decreased risk of allergic disease¹⁸ and that delivery by means of cesarean section is associated with increased risk.¹⁹ Furthermore, it is well established that African American children and adolescents have higher IgE levels than other racial groups.²⁰

The biological mechanism explaining the effects of pets on allergy development is unknown. We hypothesize that indoor pet ownership is associated with exposure to distinct, more broadly diverse bacterial populations in the home environment and that this broadly diverse exposure influences early infant development of immune function in a manner that decreases the risk of allergy and atopic asthma. Our previous study supports this hypothesis, demonstrating that house dust from homes with dogs

TABLE III. Sample characteristics by race and mode of delivery

	Comparisons by maternal race			Comparisons by mode of delivery		
	African American mother (n = 738)	Non-African American (n = 449)	P value	Cesarean section (n = 436)	Vaginal (n = 738)	P value
Mother's age (y), mean (SD)	29.0 (5.3)	30.3 (5.0)	<.001	30.6 (5.3)	28.8 (5.1)	<.001
Indoor pet, no. (%)	186 (25.2)	234 (52.7)	<.001	144 (33.0)	272 (36.9)	.19
African American race, no. (%)				284 (65.1)	446 (60.4)	.11
Mother's allergic history, no. (%)	224 (30.5)	116 (25.9)	.09	116 (26.6)	219 (29.8)	.24
Mother smokes, no. (%)	80 (10.8)	59 (13.1)	.23	53 (12.2)	84 (11.4)	.69
ETS, no. (%)	220 (29.8)	107 (23.8)	.025	110 (25.2)	209 (28.3)	.25
Delivery by means of cesarean section, no. (%)	284 (38.9)	152 (34.2)	.11			
Male sex (baby), no. (%)	366 (49.6)	226 (50.3)	.80	198 (45.4)	389 (52.7)	.016
Firstborn, no. (%)	264 (35.8)	169 (37.6)	.52	177 (40.6)	253 (34.3)	.030

ETS, Environmental tobacco smoke defined as an adult in the household who smokes at least 1 cigarette per day inside the home.

possessed significantly greater bacterial diversity than house dust from homes without pets.⁷ Delivery by means of cesarean section, which has been associated with as much as a 20% increase in the risk for allergic disease development,²¹ has been associated with distinct gastrointestinal microbiota deficient in *Lactobacillus* species and dominated by *Clostridium* and *Escherichia* species.^{22,23} It is possible that an enhanced household bacterial diversity provided by pets would have a greater effect on such babies. Indeed, in a Finnish study the beneficial effects of bacterial probiotics on the risk of allergic sensitization was only apparent among children delivered by means of cesarean section.²⁴ We speculate that subjects with a predominant African ancestry and therefore an evolutionary history founded in an equatorial climate with a relatively voluminous and presumably highly diverse microbial burden might have a preponderance of genetic variants that render a differential susceptibility to the effects on IgE levels of microbial exposures afforded by household dogs and cats.

Few longitudinal studies of IgE levels have taken maximum statistical advantage of the repeated measures within children. A recent exception is a publication from the Multi-Centre Allergy Study; however, their primary focus was to compare trends of total IgE levels with trends of allergen-specific IgE levels.²⁵ Although only participants with complete data over time (6% of the total sample) were analyzed in this report and very different statistical methods were used, our results were consistent with theirs in showing a rapid increase in IgE levels during early childhood. By using a random-effects model, the Tucson Children's Respiratory Study showed trends of general increase through childhood that were affected by breast-feeding and maternal total IgE levels, but there was only 1 postnatal data collection point in infancy.²⁶ Most relevant are the results from Rothers et al²⁷ from another Tucson-based birth cohort. Using samples collected at 3 months and 1, 2, and 3 years of age in a cohort of 362 children and again deploying a random-effects model, they reported that day care attendance by age 3 months was associated with decreased total IgE levels, although only among children whose mothers were atopic, asthmatic, or both, another example of effect modification. The MLM method used in this article differs from the random-effects model in that it accounts for measures at different time points and is focused on the evaluation of within-individual change, as well as allowing the inclusion of subjects with missing data.

Examination of factors affecting early within-person total IgE level trends over time is important because it might provide insight into immune mechanisms that increase the risk of clinical allergic disorders. In addition to the association between high total IgE levels and atopic dermatitis and allergic rhinitis, numerous studies have reported higher IgE levels among children with asthma, wheezing, or both.^{9,10,28,29} As we follow the children in our cohort over time, we will be able to examine whether certain longitudinal patterns of total IgE levels are associated with increased risk of subsequent allergic disorders and asthma.

The large size of our sample and its inclusion of a high proportion of African Americans were assets of our study. A potential limitation of our study is that we used the 6-month time point as the change point. The model might have changed if a 3- or 9-month blood collection had been completed. A test for a change point at the 1-year time point was not significant. In any case this did not affect the ability of our methods of analysis to detect a dramatic increase in total IgE levels in the first 6 months

of life and to analyze the effects of early-life exposures on this increase. Our analysis nonetheless does not permit the conclusion that 6 months is necessarily the optimal time point for early-life blood collection in future studies.

Additionally, no testing was done to rule out maternal contamination of the cord blood. However, it has been argued this is unnecessary because maternal IgE does not cross the placenta during gestation and the fetus is capable of producing IgE by the 11th week of gestation.³⁰ Furthermore, we repeated the analyses excluding the cord blood measurement and obtained extremely consistent results, both overall and when stratified by delivery mode and maternal race. The overall model excluding the cord blood measurement resulted in an estimated 27% decrease with indoor pet exposure compared with the 28% decrease in the model containing cord blood measurements.

In summary, our data are evidence in support of the hypothesis that prenatal pet exposure affects a child's very early-life immune status, resulting in a lower peripheral blood total IgE trajectory. The use of MLMs and all of their advantages facilitated this within-person analysis.

We thank all the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) study families for their past and future contributions. We also thank WHEALS research, laboratory, and field staff: without your dedication, this study would not have been possible.

Key messages

- Prenatal pet exposure has a protective effect on the trajectory of total IgE levels in early childhood, and this effect appears to be greater among babies delivered by means of cesarean section and those of non-African American race.
- Longitudinal studies in which unequally spaced study contacts often occur, deliberate or not, can be readily modeled with existing statistical software, and this might be of particular importance in early life or any situation in which rapidly occurring changes exist.
- The results are consistent with the hypothesis that pet exposure and delivery mode might be markers of infant exposure to distinct microbiomes.

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METHODS

Model-fit details

A series of nested and increasingly complex linear and nonlinear models were fit to determine the best-fitting individual trajectory model for our data. We started with a fit of a horizontal straight line (mean model, indicating no change over time). We then compared the fit of this model to both the linear, curvilinear, and piecewise models using a deviance statistic. Model fit was further assessed by means of comparison of the Akaike information criterion.^{E1}

A 2-segment linear (piecewise) model was found to have the best fit. The piecewise model was parameterized as a deviation model to test whether the 2 slopes (or “pieces”) differed and subsequently reparameterized as a 2-slope model for purposes of interpretation and further modeling. Indoor pet

exposure was included in the linear piecewise model as a main effect and was also tested for an interaction with the age of the child.

Effect modification for *a priori*-selected variables was tested by means of inclusion of an interaction term and inspection of stratified models. A 2 *df* deviance statistic was used to test whether the factor had an effect on either of the slopes by comparing this model with the individual trajectory model, where only the main effect was included. If the test was not significant (ie, $P > .1$), then both interaction terms were excluded. Confounding was tested by using a change in effects criteria ($\geq 20\%$).

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TABLE E1. Cross-sectional total IgE levels by prenatal indoor pet exposure

Scheduled time points	Indoor pet before delivery (n = 420)	No indoor pet before delivery (n = 727)	All (n = 1258)
Cord blood	0.35 (0.32-0.39), n = 681	0.25 (0.22-0.29), n = 382	0.31 (0.29-0.34), n = 1063
6 mo*	8.3 (7.1-9.8), n = 183	6.2 (5.1-7.5), n = 282	7.4 (6.6-8.4), n = 465
12 mo†	13.6 (11.5-16.0), n = 200	10.4 (8.6-12.7), n = 286	12.2 (10.7-13.8), n = 486
24 mo‡	22.9 (19.8-26.5), n = 229	19.4 (16.3-23.2), n = 381	21.6 (19.3-24.1), n = 610

*Actual time of contact ranged from 5.5 to 10.5 months, with a median of 6.6 months.

†Actual time of contact ranged from 11.5 to 25.2 months, with a median of 12.5 months.

‡Actual time of contact ranged from 20.2 to 61.2 months, with a median of 25.9 months.

TABLE E2. Estimated regression coefficients (b) and SEs for the model of log-transformed IgE levels over time

Independent variable	b* (SE)	Expected decrease in total IgE level with pet exposure†	P value
Prenatal indoor dog exposure	−0.23 (0.08)	21%	.006
Prenatal indoor cat exposure	−0.24 (0.16)	21%	.013
Prenatal outdoor dog exposure	0.14 (0.21)	NA	.50
Prenatal outdoor cat exposure	0.01 (0.73)	NA	.99

NA, Not applicable.

*Because of the log-transformation of total IgE levels, the regression coefficient can be interpreted as the average difference in log-transformed total IgE levels between children with prenatal indoor pet exposure versus children without prenatal indoor pet exposure.

†An easier interpretation is to use the formula $(e^b - 1) * 100$, where b is the regression coefficient.