

Letter to the Editor

Cat ownership, cat allergen exposure, and trajectories of sensitization and asthma throughout childhood*To the Editor:*

For almost 2 decades, cat exposure has been linked to a number of different and often contradictory outcomes. Several birth cohorts reported increased risk of cat-specific sensitization in preschool children with increasing early-life cat allergen exposure.¹⁻³ In contrast, a protective effect of high allergen exposure on cat sensitization, with a bell-shaped dose-response relationship, has been reported in cross-sectional studies in older children and adults.^{4,5} Similar inconsistencies have been reported on the association between cat ownership and cat-specific sensitization.^{1,6,7} We hypothesized that the effect of early-life cat exposure on sensitization differs (1) over time, rendering the generalization of effects from cross-sectional analyses at specific age points potentially misleading; (2) for different allergenic proteins from cat; and (3) between children with different risk of allergy.

To address our hypotheses, we investigated the effect of cat exposure in the first year of life on longitudinal trajectories of sensitization and asthma throughout childhood in a population-based birth cohort in which skin prick tests (SPTs) and IgE to cat allergens Fel d 1, 2, and 4 (ImmunoCAP ISAC) were available at 6 time points (ages 1, 3, 5, 8, 11, and 16 years). We defined SPT sensitization as a wheal diameter of greater than or equal to 3 mm; for component-resolved diagnostics (IgE/CRD), we considered a child being sensitized if the IgE level was more than 0.3 ISU to at least 1 component. We ascertained cat ownership in infancy using questionnaires, and quantitated Fel d 1 in dust samples collected in homes within the first year of life using ELISA ($\mu\text{g/g}$). We carried out longitudinal analyses using generalized estimation equations (GEEs). We generated prototypical trajectories of sensitization from infancy to adolescence on the basis of mean predicted values of the multivariate GEE model, with an interaction between cat ownership and time.

We analyzed data for 1004 of 1051 children in the observational cohort who had confirmed exposure in infancy, and at least 1 valid sensitization measurement. Table E1 in this article's Online Repository at www.jacionline.org presents the demographic and clinical characteristics of study participants. In cross-sectional analyses, cat ownership in infancy was associated with a significantly higher risk of cat sensitization in preschool age, but not thereafter (see Fig E1 in this article's Online Repository at www.jacionline.org). In the multivariable longitudinal model (Fig 1; see Table E2 in this article's Online Repository at www.jacionline.org), early-life cat ownership significantly increased the risk of sensitization to cat (odds ratio [OR], [95% CI]: SPT, 2.50 [1.37-4.55], $P = .003$; IgE/CRD, 3.13 [1.62-6.07], $P = .001$). However, there was a significant interaction between early-life cat ownership and time, in that compared with cat owners, among children without a cat the annual increase in the

rate of SPT sensitization from 1 to 16 years was 6% higher (95% CI, 1% to 11%; $P = .02$), and for IgE/CRD sensitization 8% higher (95% CI, 2% to 14%; $P = .005$). Most children with a cat in the home who developed cat sensitization during childhood did so by age 1 year. After age 1 year, the sensitization rate among cat owners either increased very slowly (SPT, Fig 1, A), or remained unchanged (IgE/CRD, Fig 1, B). In contrast, for children without a cat, the preschool sensitization rate was low, but their trajectory over time was markedly different, with a significantly higher increase in sensitization with increasing age. By adolescence, there was no difference in the point prevalence of cat sensitization between cat owners and those not owning a cat (Fig 1).

Cat ownership significantly increased the risk of sensitization to Fel d 1 and Fel d 4, but not Fel d 2, with a significant interaction between cat ownership and time in relation to the development of IgE to Fel d 1 ($P = .008$), marginal for Fel d 4 ($P = .06$), but not for Fel d 2 ($P = .39$) (Fig 1, C).

We measured Fel d 1 in 939 homes. In cross-sectional analyses, an increase in Fel d 1 exposure in infancy significantly increased the likelihood of sensitization in preschool age, but not thereafter (see Table E3 in this article's Online Repository at www.jacionline.org). In the multivariable GEE model, there was a significant association between early-life Fel d 1 exposure and the development of sensitization to cat (see Table E4 in this article's Online Repository at www.jacionline.org); the increase in risk per logarithmic unit increase in Fel d 1 concentration was 15% for SPT (95% CI, 4% to 28%; $P = .008$) and 22% for IgE/CRD (95% CI, 10% to 36%; $P < .001$). However, as with cat ownership, we observed a significant interaction between Fel d 1 exposure and time, in that the effect of early-life exposure significantly decreased with increasing age (SPT: OR [95% CI], 0.99 [0.98-1.00], $P = .04$; IgE/CRD: 0.98 [0.98-0.99], $P < .001$).

Sensitization rates were consistently higher among high-risk children of atopic parents, but the rate of change over time in relation to cat ownership or allergen exposure did not significantly differ between the high- and low-risk children (Fig 2; Tables E2-E4). Finally, there was no effect of cat ownership on sensitization to allergens other than cat, and no significant effect on asthma (see Fig E2 in this article's Online Repository at www.jacionline.org). Fel d 1 exposure in infancy was not significantly associated with the development of asthma (0.98 [0.89-1.07]; $P = .61$). The absence of any association between cat exposure and asthma is consistent with a pooled analysis of 11 European birth cohorts,⁶ and suggests that early-life exposure to cat exerts cat allergen-specific immune responses.

In our population, 18% of cat owners removed their cat between pregnancy and the first birthday of their child. When we adjusted our analyses for contemporaneous exposure, there was very little difference in the results. Limitations of our study are discussed in this article's Online Repository at www.jacionline.org.

Our findings highlight the changing nature of the association between early-life cat exposure and specific sensitization during childhood, and the key role of the time of the assessment of outcomes. These results can explain most inconsistencies in the previous literature. For example, most reports from birth-cohort

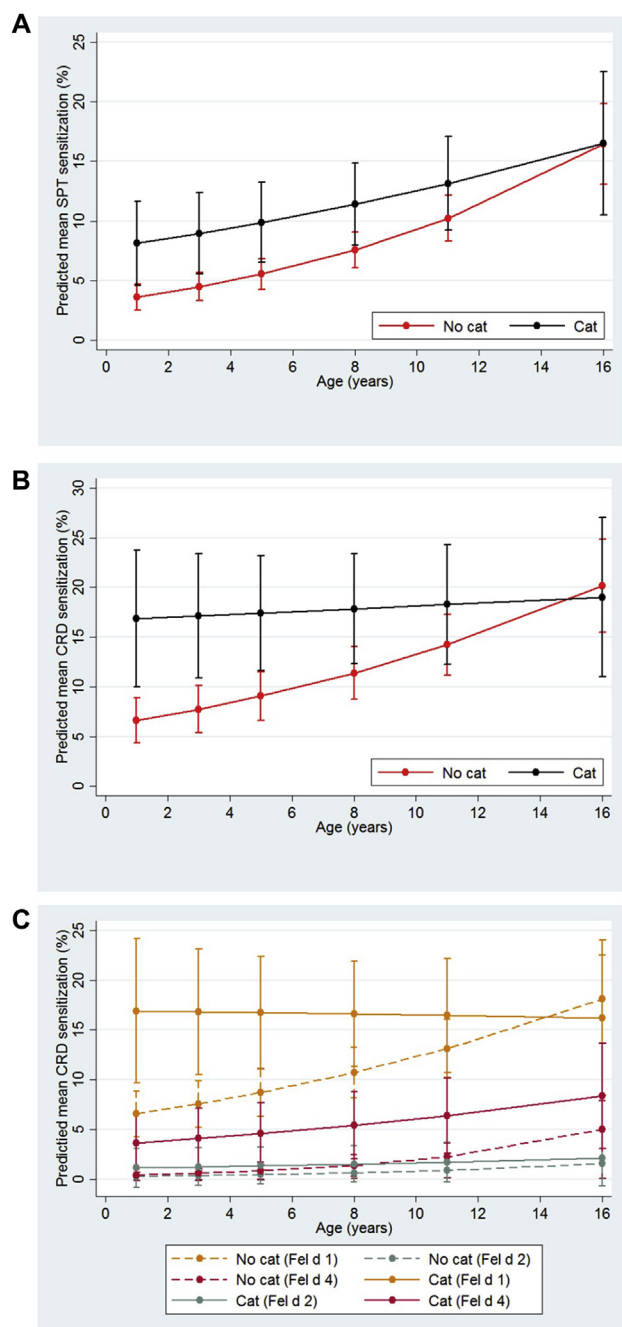


FIG 1. Longitudinal trajectories of cat sensitization among children who lived in a home with a cat in early life and those who did not. Predicted value of mean response is shown in graphical format along with 95% CIs. **A**, SPT sensitization. **B**, CRD sensitization to cat. **C**, CRD components.

studies have assessed sensitization in preschool age, and have identified cat ownership as a risk factor, along with a linear dose-response relationship between cat allergen exposure and specific sensitization.^{1-3,8} Cross-sectional and case-control studies in older children and adults have found either no association or a protective effect of cat exposure.^{4,5,9} This is entirely consistent with our sensitization trajectories. The sensitization rate at age 16 years in our study was numerically lower among children who had a cat in early life, but this difference was not statistically

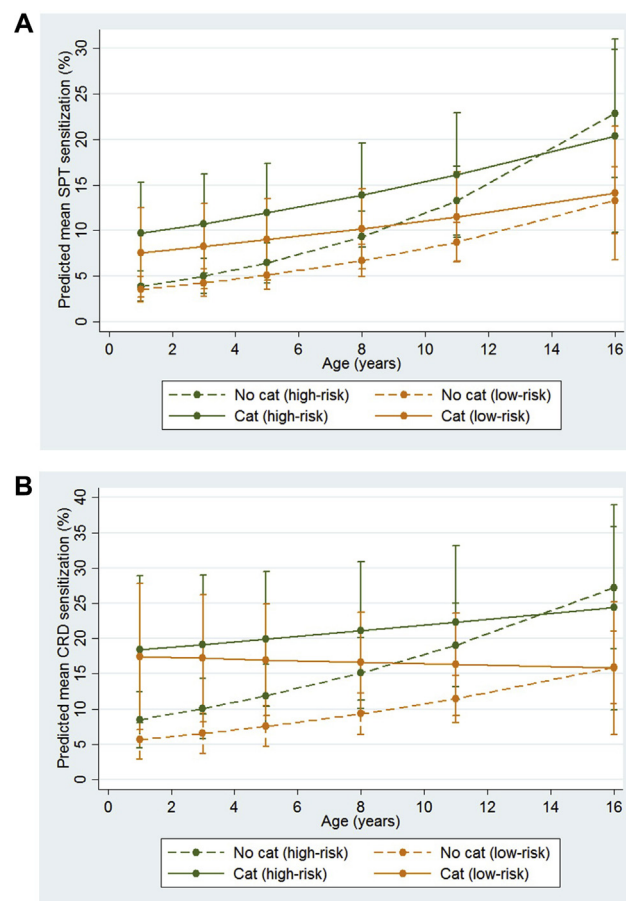


FIG 2. Longitudinal trajectories of cat sensitization among high- and low-risk children who lived in a home with a cat in early life and those who did not. Predicted value of mean response is shown in graphical format along with 95% CIs. High-risk group: Both biological parents with at least 1 positive SPT result at recruitment. **A**, SPT sensitization. **B**, IgE/CRD sensitization.

significant. We propose that if we extrapolate our data to adulthood, with projected sensitization rates of 25% to 30%, a significant protective effect of cat ownership would be seen. Thus, exposure to cat can confer either an increase in risk, or protection, or will have no effect, depending on the age of the assessment, study design, and the choice of the study population. Therefore, the fact that the findings of previous studies are apparently contradictory does not make them incorrect, but is a consequence of markedly different trajectories of cat sensitization through life-course between early-life cat owners compared with individuals without a cat.

We thank the children and their parents for their continued support and enthusiasm. We greatly appreciate the commitment they have given to the project. We also acknowledge the hard work and dedication of the study team (postdoctoral scientists, research fellows, nurses, physiologists, technicians, and clerical staff).

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