Opposing Effects of Cat and Dog Ownership and Allergic Sensitization on Eczema in an Atopic Birth Cohort

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Objective To examine risk factors for eczema at age 4 years.

Study design Beginning at 1 year of age, infants of atopic parents (n = 636) had annual clinical evaluations and skin prick tests (SPTs) to 15 aeroallergens and milk and egg. Parents completed validated surveys on eczema and environmental exposures. House dust samples were evaluated for allergens and endotoxin. Eczema was defined as a parental report of scratching, and redness, ''raised bumps,'' or dry skin/scaling for 6 of the last 12 months.

Results At age 4 years, a total of 90 children (14%) had eczema. Not having a dog before 1 year of age and being dog SPT+ at 1, 2, or 3 years of age conferred a 4-fold higher risk for eczema at age 4 years (adjusted odds ratio [aOR] = 3.9 [1.6-9.2]; $P = .002$). Among dog owners, however, dog SPT+ was not associated with significantly increased risk (aOR 1.3 [0.3-6.8]; $P = .8$). Among children with cats before 1 year of age, cat SPT+ conferred significantly increased risk for eczema (aOR = 13.3 [3.1-57.9]; $P < .001$). Among non-cat owners, cat SPT+ was not associated with increased risk (aOR = 1.1 [0.5-2.7]; $P = .8$).

Conclusion Dog ownership significantly reduced the risk for eczema at age 4 years among dog-sensitized children, cat ownership combined with cat sensitization significantly increased the risk. *(J Pediatr 2011;158:265-71)*.

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Although time trends in the prevalence of eczema vary greatly by geographic location, the global burden of the disease has increased substantially over the last 3 decades.[1,2] World-wide, eczema affects 15% to 30% of children and 2% to 10% of adults.[2] Much attention has recently been focused on genetic variations associated with eczema (eg, filaggrin).[3] Nevertheless, the rapid rise in disease prevalence implies that environmental influences must play a critical role as well.[1]

Transient sensitization to food allergens is associated with childhood eczema; however, the relative importance of aeroallergen sensitization early in life is not well defined.[4,5] We and others have shown that dog ownership may reduce the risk for childhood eczema.[6,7] Although the protective effect of dog ownership may be mediated by elevated environmental endotoxin levels, evidence to support this conclusion is sparse. In addition, cat ownership has been associated with lower rates of atopic sensitization in some studies, while others have reported an increased risk for eczema among cat owners with filaggrin mutations.[8,9]

In this study, we investigated associations between early environmental exposures, including pet ownership patterns, house dust endotoxin levels, sensitization patterns, and the eczema phenotype. Our hypothesis was that early environmental exposures and sensitization patterns would be predictive of eczema at age 4 years. The Cincinnati Childhood Allergy & Air Pollution Study (CCAAPS) population is a high-risk, atopic birth cohort. Findings regarding eczema at age 3 years and younger have been reported elsewhere.[7] In this report, children with eczema at age 4 years were evaluated, because this group may represent a more severe phenotype at increased risk for persistence of eczema and the development of asthma.[10,11]

Methods

CCAAPS is a longitudinal birth cohort study on air pollution and allergy. Newborns in the Cincinnati metropolitan area were identified by public birth records from 2001 to 2003.[12,13] Infants living less than 400 m or greater than 1500 m from the nearest major highway or interstate were eligible for enrollment.[13] All 762 infants also had a parent with symptoms of asthma, allergic rhinitis, or eczema, and with at least one positive skin prick test (SPT) result to a panel of 15 aeroallergens.[12] Parents signed an informed consent, and the study was approved by the Institutional Review Board of the University of Cincinnati.

aOR	Adjusted odds ratio
CCAAPS	Cincinnati Childhood Allergy and Air Pollution Study
ECAT	Elemental carbon attributable to traffic
$PM_{2.5}$	Particulate matter less than 2.5 μm in diameter
SPT	Skin prick test
uOR	Unadjusted odds ratio

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Children were skin tested by trained clinicians for 15 aeroallergens, plus cow's milk and hen's egg, on a yearly basis from ages 1 through 4 years.[12] Parents completed yearly in-person surveys. Physical examinations and a clinician's assessment were performed on the same day as the in-person surveys. A home visit and environmental assessment were conducted before 1 year of age. House dust samples were collected from a 2 m^2 area of floor surface from the infant's primary living area with a Filter Queen Majestic vacuum cleaner (Health-Mor World Headquarters, Strongsville, Ohio) at a rate of 2 min/m^2. Monoclonal sandwich enzyme-linked immunosorbent assays were performed for Fel d 1, Can f 1, and Der f 1 concentrations in house dust.[14] Endotoxin and (1→3) β-D-glucan concentrations were determined with a *Limulus* amebocyte lysate assay.[15,16] Glucatell modification of the assay was used for (1→ 3) β-D-glucan and Pyrochrome modification for endotoxin.[15,16]

Personal elemental carbon attributable to traffic (ECAT), a marker of exposure to traffic related particles, was determined.[17] Briefly, particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) was collected at ambient monitoring stations.[18] Elemental carbon concentrations and absorption coefficients were determined. Multivariable UNMIX and chemical mass balance models were then used to determine ECAT at monitoring stations.[18] A land-use regression model was applied to estimate ECAT for locations where a child spent greater than 8 hours per week between ages 6 and 12 months.[17]

Two case definitions of eczema at age 4 years were established a priori. Eczema on the basis of parental report was modified from a validated questionnaire (International Study of Asthma and Allergies in Childhood) and included a parental report of scratching, and redness, "raised bumps," or dry skin/scaling for at least 6 of the last 12 months.[19] Clinician-diagnosed eczema was a global assessment measure based primarily on physical examination findings from a single office visit with one of several study clinicians. Physical examination findings considered to be consistent with eczema included erythema, papulation, excoriations, or lichenification. The parental report case definition served as the primary outcome measure because it reflected persistent findings for 6 of the previous 12 months and was adapted from a validated survey.[20] In addition, to avoid potentially misclassifying children who were positive for eczema on physical examination as control subjects, the comparison group for this analysis had neither a parental report nor a clinician's diagnosis of eczema. The clinician's diagnosis definition was also used in a sensitivity analysis to validate findings from the parental report. As a secondary outcome measure, we also evaluated a subgroup of children with "atopic eczema," defined as a parental report of eczema plus a positive SPT result at age 4 years.

Statistical Analysis

Potential covariates are listed in Table I (available at www.jpeds.com). A positive SPT result was defined as a wheal of 3 mm greater than the saline solution control, along with a flare at least as large as the accompanying wheal. Previous studies have shown that aeroallergen sensitization is less common before the age of 2 years, and up to 15% to 20% of young children may have transient responses on skin testing.[21,22] Although the predictive value of transient aeroallergen sensitization is unclear, it may be a measure of the ability to become sensitized and thus may have clinical relevance in terms of the presence or future development of atopic diseases such as eczema.[21] We therefore considered a child to have a positive SPT result for an aeroallergen if they had a single positive result for that allergen at ages 1, 2, or 3 years. Because previous studies found that sensitivity to egg at 1 year of age was predictive of atopic manifestations at later ages, and the prevalence and predictive value of egg SPT+ at ages 2 and 3 years were lower in this study, SPT results for egg at 1 year of age only were included in the multivariable model.[23]

Regardless of univariable findings, all potential covariates listed in Table I were initially included in the maximum estimated logistic regression model. Potential covariates were removed by backward elimination from the multivariable model on the basis of an alpha cut-off of 0.15. Variables that remained in the final model included the following: (1) history of parental eczema; (2) egg ingestion (on a single or multiple occasions) before 1 year of age; (3) SPT+ to egg at 1 year of age; (4) SPT+ to elm at ages 1, 2, or 3 years; and (5) the interaction terms for dog ownership (yes/no) before 1 year of age, and dog SPT+ at ages 1, 2, or 3 years; and (6) cat ownership (yes/no) before 1 year of age and cat SPT+ at ages 1, 2, or 3 years. A spline procedure was used to determine the effects of dog and cat allergen concentrations in house dust, with adjustment for other covariates in the multivariable model.[24]

Results

In total, 636 children completed the annual visit at age 4 years; 14% (n = 90) satisfied the definition of eczema on the basis of parental report, 17% (n = 107) met criteria for the clinician's diagnosis, and 75% (n = 477) did not have eczema by either case definition. Thirty-nine children (6%) satisfied both the parental report and clinician's diagnosis of eczema, 51 met criteria for eczema by parental report but not by clinician's diagnosis, and 68 met criteria by the clinician's diagnosis but not by parental report (Table II; available at www.jpeds.com). The prevalence of atopic eczema was 10% (n = 55). Data from the questionnaire were complete, and 635 children completed the physical examination. To avoid including children in the comparison group who were potentially misclassified (ie, positive for eczema by clinician's diagnosis but negative by parental report), 68 children were excluded a priori from the analysis.

Table III presents unadjusted findings for eczema on the basis of the parental report case definition. A history of eczema in either parent was a significant predictor of eczema at age 4 years (P = .002). High ECAT (elemental carbon attributable to traffic) in the first year of life trended towards a positive association with eczema at age 4 years (P = .07), and dog ownership before 1 year of age (P = .002) also

Table III. Characteristics of children with eczema at age 4 years*

Characteristic†	N Eczema/ N total (% with eczema)	Unadjusted odds ratio [95% CI]	*P* value
Male	52/310 (17%)	1.2 [0.7-1.8]	.5
African-American	24/131 (18%)	1.3 [0.8-2.1]	.4
History of parental eczema (either parent)	27/96 (28%)	2.5 [1.5-4.3]	.002
Dog ownership before 1 year of age‡	17/184 (9%)	0.4 [0.2-0.7]	.002
Cat ownership before 1 year of age‡	19/121 (14%)	1.0 [0.6-1.7]	.9
Diesel (ECAT)§		1.5 [0.8-2.6]	.07
Highest tertile	35/177 (20%)		
Lowest tertile	26/181 (14%)		
Egg ingestion before 1 year of age	54/383 (14%)	0.6 [0.4-1.0]	.05
Peanut/tree nut before age 3 years	64/447 (14%)	0.4 [0.2-0.7]	.002

*Total cohort size was 636 children at age 4 years; 90 children (14%) had eczema on the basis of parental report; 477 children were in the comparison group (no eczema by both parental report and clinician's diagnosis).
†Additional covariates that were not significantly predictive are listed in the text.
‡On the basis of home visit.
§Elemental carbon attributable to traffic; average over the first year of life.

conferred a significant protective effect. Egg ingestion before 1 year of age demonstrated a trend toward protection ($P = .05$). Peanut/tree nut ingestion before age 3 years conferred significant protective effects from eczema ($P = .002$). Potential covariates that were not significantly predictive included parental asthma; season of birth; parental income; parental education level; breast-feeding; day-care attendance; number of siblings; tobacco smoke exposure; house dust concentrations of endotoxin, dust-mite allergen, and β-glucan; and a parental report of cow's milk ingestion before 1 year of age. Unadjusted findings for SPTs are presented separately (**Table IV**; available at www.jpeds.com).

Results from a multivariable logistic regression analysis are presented in **Table V**. After adjusting for the environmental exposures and host characteristics described above, significant predictors of eczema at age 4 years were parental eczema ($P = .03$), SPT+ to egg at 1 year of age ($P < .001$), and SPT+ to elm tree pollen at ages 1, 2, or 3 years ($P = .03$). Findings for pet ownership and dog/cat SPT are not listed separately because of the presence of significant interactions involving these covariates. Without adjustment for interactions, dog ownership before 1 year of age was significantly protective from eczema ($P = .009$), and dog SPT+ at age 1, 2, or 3 years demonstrated a greater than 4-fold increased risk of eczema ($P = .003$). By themselves neither cat ownership before 1 year of age nor cat SPT+ at ages 1, 2, or 3 years were significantly predictive.

Egg ingestion before 1 year of age trended toward a protective effect from eczema at age 4 ($P = .08$). The timing of egg introduction was not related to egg SPT+. Early versus

Table V. Multivariable analysis to determine predictors of eczema at age 4 years*†

	N Eczema/ N total (% with eczema)	Adjusted odds ratio [95% CI]	*P* value
History of parental eczema	27/96 (28%)	2.2 [1.1-4.3]	.03
Egg ingestion before 1 year of age	54/383 (14%)	0.6 [0.3-1.1]	.08
Sensitization to egg (1 year of age)	23/58 (40%)	3.9 [1.8-8.7]	<.001
Sensitization to elm (ages 1, 2, or 3 years)	18/48 (38%)	2.8 [1.1-7.2]	.03
Interaction terms			
Dog in home		1.3§ [0.3-6.8]	.8
(before 1 year of page; n = 184)‡			
SPT+ to Dog (age 1, 2, or 3 years)	2/14 (14%)		
SPT- to Dog (age 1, 2, or 3 years)	14/160 (9%)		
No dog in home		3.9§ [1.6-9.2]	.002
(before 1 year of age; n = 325)			
SPT+ to Dog (age 1, 2, or 3 years)	17/30 (57%)		
SPT- to Dog (age 1, 2, or 3 years)	38/253 (15%)		
Cat in home		13.3§ [3.1-57.9]	<.001
(before 1 year of age; n = 121)‡			
SPT+ to Cat (age 1, 2, or 3 years)	7/13 (54%)		
SPT- to Cat (age 1, 2, or 3 years)	10/95 (11%)		
No cat in home		1.1§ [0.5-2.7]	.8
(before 1 year of age; n = 353)			
SPT+ to Cat (age 1, 2, or 3 years)	16/49 (33%)		
SPT- to Cat (age 1, 2, or 3 years)	39/304 (13%)		

*Total cohort size was 636 children at age 4 years; 90 children (14%) met criteria for eczema on the basis of parental report.
†Table V represents covariates that remained in the final model after backward elimination with an alpha cutoff of 0.15.
‡Sixteen (9%) children with eczema owned dogs; 17 (14%) owned cats; on the basis of home visit.
§Represents adjusted odds ratio for eczema based on the interaction between pet ownership and SPT.

delayed introduction of milk and peanuts/tree nuts were not predictive of eczema in the multivariable analysis.

Interaction between Dog Ownership and SPT Reactivity to Dog

We next examined the relationship between dog ownership and percutaneous sensitization to dog (Table V and Figure 1). Before 1 year of age, a total of 184 children owned dogs. Among children who had a dog before 1 year of age, dog SPT+ at age 1, 2, or 3 years did not significantly increase the risk for eczema at age 4 years. In contrast, children who did not own dogs (before 1 year of age), but were dog SPT+ (ages 1, 2, or 3 years), had an almost 4-fold increased risk of eczema at age 4 years ($P = .002$). Children who owned dogs and were dog SPT- had a slightly lower rate of eczema relative to those who did not own dogs (9% vs 15%); however, this result was not statistically significant. Maternal/paternal dog SPT status did not predict dog ownership. Dog ownership was also independent of dog SPT status in the first 3 years of life and of endotoxin levels.

To verify these findings, we examined the effects of dog allergen levels from house dust samples collected before 1 year of age on the presence of eczema at age 4 years (Table VI; available at www.jpeds.com). Children exposed to the highest tertile of dog allergen concentrations had a significantly lower risk of eczema (uOR 0.4 [0.2-0.7]; $P = .01$).

We next sought to determine whether the modifying effect of dog ownership might impact other SPTs as well. With eczema as the outcome, we found no interactions involving dog ownership and SPTs to allergens other than dog. A significant inverse relationship between dog ownership before 1 year of age and SPT positivity to cat at ages 1, 2, or 3 years (uOR 0.5 [0.3-0.8]; $P = .005$) was found, indicating that dog owners were less likely to become sensitized to cats. This relationship was independent of cat ownership or cat allergen levels.

Interaction between Cat Ownership and Skin Prick Test Reactivity to Cat

A similar analysis was performed for cat ownership and cat sensitization (Table V and Figure 2). Before 1 year of age, a total of 121 children lived with cats. In contrast to children living with dogs, children living with cats before 1 year of age who were SPT+ to cat at ages 1, 2, and 3 years were 13 times more likely to have eczema at age 4 years than those who were cat SPT- ($P < .001$). Among non-cat owners, no significant relationship was found between SPT positivity to cat and eczema at age 4 years ($P = .8$). Maternal/paternal cat SPT status was not predictive of cat ownership. Cat SPT+ at ages 1 through 3 years and cat ownership before 1 year of age were also independent of one another and were independent of endotoxin.

To verify the above findings, cat allergen levels from house dust samples collected at 8 months of age were assessed. Cat allergen levels alone were not predictive of eczema (Table VI). After adjustment for other covariates with a spline procedure, a positive trend between cat allergen exposure and eczema at age 4 years was found for levels up to 3.0 μg/g of dust ($P = .10$).[24]

Sensitivity Analysis

A sensitivity analysis was used to compare findings for different eczema definitions, as well as to determine the impact of excluding potentially misclassified children. Results were similar for most outcomes regardless of the eczema definition used, with the exception that the protective effect of dog ownership was less pronounced when the clinician's diagnosis of eczema was used (uOR 0.7 [0.5-1.2]; $P = .2$). Among the subgroup of children who met both the parental report and clinician's diagnosis definitions (n = 39), major findings were the same as those based on the parental report. Our conclusions were unchanged and precision was increased by including children who were positive for eczema on physical examination but negative by parental report in the comparison (no eczema) group. (Tables VII-IX; available at www.jpeds.com).

Analysis in African-Americans

Interactions between pet ownership and sensitization were not found in the African-American subpopulation, possibly because very few African-Americans owned pets (Table X; available at www.jpeds.com). Nevertheless, African-Americans who owned cats before age 1 year of age (n = 6; 3%) were 12

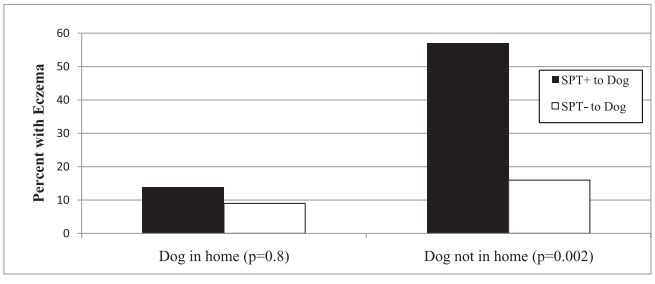

Figure 1. Relationship between dog ownership (before 1 year of age), SPT to dog (age 1, 2, or 3 years), and eczema (age 4 years) ($P = .002$).

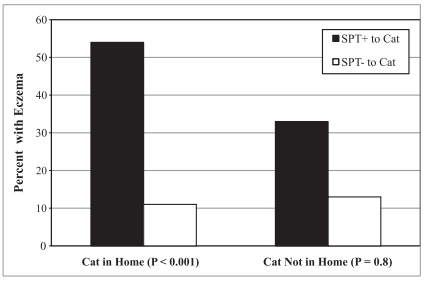

Figure 2. Relationship between cat ownership (before 1 year of age), SPT to cat (age 1, 2, or 3 years), and eczema (age 4 years) ($P < .001$).

times more likely to have eczema at age 4 years than those who did not (aOR 12.4 [1.2-133.7]; $P = .04$). In contrast, none of the African-Americans who owned dogs (n = 17; 9%) before 1 year of age had eczema at age 4 years. An analysis of atopic eczema (eczema plus a positive SPT) for the entire cohort can be found in **Table XI** (available at www.jpeds.com).

Discussion

Consistent with previous studies, children in the CCAAPS cohort with a history of parental eczema and SPT positivity to egg at 1 year of age were at significantly increased risk for eczema at age 4 years.[4,25] As previously reported, early dog ownership conferred a significant protective effect from eczema at age 4 years.[7,25] Also, consistent with recent reports, cat ownership by itself did not confer a significantly increased risk for eczema.[9] After adjustment for these and other known risk factors, several novel findings became apparent.

In this study, we identified significant interactions between pet ownership and sensitization to pets, with the outcome of eczema. We found that dog owners with early sensitization to dog were almost 4 times less likely to have eczema at age 4 years than non-dog owners. Thus early dog ownership significantly reduced the risk of eczema associated with dog sensitization. Although there was a trend toward a protective effect of dog ownership among children who were not sensitized to dog, this result was not statistically significant. In contrast to these findings, cat ownership significantly increased the risk for eczema among cat-sensitized children. The magnitude of this effect was pronounced as cat owners with early sensitization to cat were 13 times more likely to have eczema at age 4 years than non-cat owners. Sensitization to dogs or cats was independent of dog or cat ownership, respectively, presumably because of the ubiquity of dog and cat allergens in a variety of indoor environments. The aforementioned relationships were also independent of endotoxin levels.

It is tempting to attribute the protective effect of dog ownership to a natural form of immunotherapy, whereby constant exposure to high levels of dog antigen over time might induce tolerance to dog allergen in sensitized children. Consistent with the literature, early dog ownership was also protective from the development of SPT positivity to cat.[8] This suggests that dog ownership may have broader tolerogenic effects. T cell lines of dog-allergic subjects produce high levels of interleukin-10 and interferon-gamma, cytokines associated with the induction of tolerance, after stimulation with certain Can f 1 epitopes.[26] In addition, dog ownership in infancy has previously been associated with increased secretion of IL-10, along with a reduced risk for childhood eczema and decreased sensitization to foods and aeroallergens.[6] These effects appear to be independent of endotoxin levels.[20] In this study, dog ownership was independent of endotoxin levels, and endotoxin levels were unrelated to the presence of eczema. In addition, although we previously reported an interaction involving dog ownership and endotoxin levels with asthma at age one, we did not find evidence for an interaction involving endotoxin and dog ownership with eczema at age four.[16] It is therefore possible that dog antigens exert immune modulating effects distinct from those attributed to endotoxin.[20]

Why cat ownership accentuated the positive association between sensitization to cat and eczema rather than promoting tolerance is not clear. The novel finding that interactions between pet ownership and sensitization appear to be specific for dog or cat allergens suggests that animal exposures may exert antigen specific effects, the mechanisms for which are poorly understood. Recent studies have highlighted the positive association between exposure to cats and eczema among children with filaggrin mutations.[9] In contrast, dog ownership does not appear to increase the risk for eczema associated with filaggrin variants.[25] Further research regarding gene-environment interactions between genetic variants in skin barrier proteins and pet ownership may be particularly germane.

Recent studies indicate that delayed introduction of allergenic foods is unlikely to prevent eczema and other atopic diseases and that earlier introduction of these foods might be beneficial.[27] In this study, delaying egg introduction until after 1 year of age did not decrease the risk for eczema at age 4 years, and earlier introduction may have been protective. This finding was statistically significant for children with atopic eczema, arguably the group at highest risk for development of asthma (**Table XI**). Although the possibility of reverse causation related to food restriction because of parental food allergies or the presence of eczema in the first few months of life cannot be absolutely ruled out, our results do support recently modified guidelines not to delay egg introduction in children at high risk for atopic disease.[28] Findings regarding the timing of nut ingestion should be interpreted with caution, given that effects were not significant after adjustment for other covariates in the multivariable model.

While the role of food introduction and sensitization to foods in the development of eczema has received much attention, the association between aeroallergen sensitization and eczema early in life may be underappreciated.[5] One of the most important predictors of eczema at age 4 years was sensitization to American elm, a tree pollen, at age 1, 2, or 3 years. We previously reported that elm pollen was a less common sensitizer in infancy relative to other trees.[12] Elm remained a less common sensitizer through age 3 years (**Table IV**). Among children sensitized to elm, however, almost 40% had eczema, compared with 29% for oak, 23% for red cedar, and 21% for maple. Our findings may therefore indicate that children with eczema are prone to early sensitization to aeroallergens that are less frequent sensitizers in other children.

It has recently been suggested that exposure to traffic-related air pollutants may increase the risk for eczema.[29] In this study, elemental carbon attributable to traffic, a marker of diesel exposure, trended towards a positive association

with eczema in the univariable analysis. This finding was not replicated in the multivariable analysis, however, suggesting that confounding factors may explain the previously reported positive association between air pollution and eczema.

Although bias is a potential concern for studies involving pet keeping, there are several ways that bias was minimized in this study. First, dog and cat ownership and early sensitization to dogs and cats, respectively, were independent of one another. Pet keeping was unrelated to parental sensitization patterns. In addition, the prevalence of pet keeping in this high-risk birth cohort was very similar to the general population.[16] We adjusted for numerous other possible risk factors in the logistic regression model. Even though maternal smoking and socioeconomic status in particular have been cited as having an association with pet keeping, these factors did not impact our results. Furthermore, the sensitivity analysis conducted to validate our eczema definitions revealed similar findings regardless of the case definition used (**Tables VII-IX**).

Finally, it is difficult to speculate regarding the impact of our findings on non-atopic eczema, given that our cohort was enriched for atopy. Findings from the small subgroup of children with non-atopic eczema suggest that parental eczema may be the most important determinant of eczema among non-atopic children, and that other predictors of atopic eczema may not be as relevant to this group (**Appendix**; available at www.jpeds.com). In addition, findings regarding pet ownership and sensitization may not be applicable to African-Americans, given the small number of African-Americans who owned pets.

In conclusion, in this prospective birth cohort involving children of atopic parents, an interaction between pet ownership and pet sensitization was discovered that has not been previously reported. Early dog ownership attenuated the risk for eczema among children who are sensitive to dogs and early cat ownership accentuated the association between cat sensitization and eczema. In addition, we found that early sensitization to elm, a relatively uncommon sensitizer in young children, was strongly associated with the presence of eczema at age 4 years. Delayed introduction of egg beyond 1 year of age was not found to be protective from atopic eczema. ■

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50 Years Ago in *The Journal of Pediatrics*

The Effect of High Caloric Feeding on the Growth of Premature Infants

Snyderman SE. J Pediatr 1961;58:237-40.

Undernutrition continues to be a problem in the neonatal intensive care unit, with 90% of very low birth weight infants demonstrating growth failure at 36 weeks postmenstrual age.[1] Lower growth velocity is related to an increased risk of neurodevelopmental impairment.[2]

Snyderman, in the February 1961 issue of *The Journal,* asked whether calorically fortifying enteral feeding improved the linear growth and weight gain of premature infants. By increasing caloric intake to 155 to 180 cal/kg/day, daily weight gain improved by approximately 20 g/day. The investigators noted that the intervention group reached its goal discharge weight earlier and that "the babies all appeared plump and had unusually rounded cheeks for premature infants." However, there were no differences in linear growth as assessed with fibula length on serial radiography. The authors concluded that caloric fortification accelerated weight gain caused by fat deposition and resulted in earlier attainment of discharge weight. However, they questioned whether this accelerated weight gain benefited their patients.

Today, preterm infants routinely receive calorically dense formula or fortified breast milk to improve weight gain. However, optimal growth velocity remains unknown. It has been speculated that too much weight gain may affect the later development of adult cardiovascular disease, hypertension, and diabetes mellitus, especially in babies with intrauterine or postnatal growth restriction. It is hypothesized that the caloric restriction associated with these conditions results in epigenetic modifications and programming that manifest later as adult-onset disease. Additionally, although new growth curves derived from birth weights have been published,[3] whether these approximate appropriate postnatal growth remains unclear.[4] The question of whether high caloric feedings would be of benefit to premature infants was raised more than 50 years ago, yet today's clinicians still have no clear answers.

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Table I. Potential covariates (estimated maximum model)

Potential covariate	Age of child when data collected	Characteristics of variable
Sex	Enrollment	
Race	Enrollment	African-American versus all others
Parental income	Enrollment	9 categories, lowest = under $9999, highest = over $110 000; ordinal
Highest level of parental education attained	Enrollment	Categorical; analyzed separately by sex
History of parental eczema	Enrollment	Yes/No
History of parental asthma	Enrollment	Yes/No
Dog ownership	Before 1 year of age (home visit)	Yes/No
	Dog allergen (Can f 1) levels: home visit	Continuous and in tertiles
Cat ownership	Before 1 year of age (home visit)	Yes/No
	Cat allergen (Fel d 1) levels: home visit	Continuous and in tertiles
Endotoxin	Before 1 year of age (home visit)	Continuous and in tertiles
β-glucan	Before 1 year of age (home visit)	Continuous and in tertiles
Dust-mite (Der p 1)	Before 1 year of age (home visit)	Continuous and in tertiles
Season of birth	Enrollment	Winter: Dec-Feb; Spring: March-May; Summer: June-August; Fall: September-November; Ordinal
Breast-feeding	Age 2 years (questionnaire)	Yes/No and Months breastfed
Tobacco smoke exposure	Ages 1-4 years (questionnaire)	3 variables: (1) Total number of smokers (2) Cigarettes smoked in household (3) Cigarettes smoked by mother Analyzed as None versus Any, and Number of cigarettes smoked
Elemental carbon attributable to traffic	Average over first year of life	Measures exposure to traffic related particles; Continuous and in tertiles
Daycare attendance	Ages 1-4 years (questionnaire)	Yes/No (each year analyzed separately)
Number of siblings	Ages 1 and 2 years (questionnaire)	Analyzed as an ordinal and a continuous variable
SPTs	Ages 1-4 years	Positive = >3 mm above saline solution control, vs negative
Timing of food introduction	Age 6 months, Ages 1-4 years (questionnaire)	Egg & Milk: Before versus after 1, 2, 3, or 4 years of age, respectively Nut (peanut or tree nut): Before versus after 2 or 3 years of age, respectively
Interaction Terms		Interactions for dog or cat, respectively, and SPTs in multivariable model
Dog Ownership * Dog SPT Cat Ownership * Cat SPT	Age 1, 2, or 3 years for SPTs	

Table II. Number of children with eczema by parental report versus clinician's diagnosis

	No eczema by parental report	Eczema by parental report	Total
No eczema by clinician's diagnosis	477	51	528
Eczema by clinician's diagnosis	68	39	107
Total	545*	90	635†

*The total number of children with no eczema by parental report was 546 (545 are included in this comparison given that one child did not complete a physical examination).
†The total number of children who completed the annual visit at age 4 years was 636 (one child did not complete a physical examination).

Table IV. Sensitization patterns and eczema at age 4 years[#†]

SPT	N Eczema/N total (% with eczema)	Unadjusted odds ratio [95% CI]	*P* value
Any SPT positive at age 4 years	55/273 (20%)	1.9 [1.2-3.0]	.007
Food			
Egg at 1 year of age	23/58 (40%)	4.3 [2.4-7.8]	<.0001
Milk, age 1, 2, or 3 years	7/24 (29%)	2.4 [1.0-6.0]	.05
Animals			
Dog, age 1, 2, or 3 years	20/49 (41%)	4.8 [2.6-9.1]	<.0001
Cat, age 1, 2, or 3 years	24/67 (36%)	4.0 [2.4-7.3]	<.0001
Pollen			
Any tree, age 1, 2, or 3 years	37/170 (22%)	1.9 [1.2-3.0]	.01
Elm, age 1, 2, or 3 years	18/48 (37.5%)	4.0 [2.1-7.7]	<.0001
Oak, age 1, 2, or 3 years	16/55 (29%)	2.5 [1.3-4.8]	.004
Cedar, age 1, 2, or 3 years	17/75 (23%)	1.8 [1.0-3.3]	.06
Ragweed, age 1, 2, or 3 years	14/52 (27%)	2.3 [1.2-4.5]	.01
Fescue, age 1, 2, or 3 years	13/46 (28%)	2.4 [1.2-4.9]	.01
Timothy, age 1, 2, or 3 years	21/83 (25%)	2.1 [1.2-3.7]	.009
Mold			
Any mold, age 1, 2, or 3 years	28/129 (22%)	1.7 [1.0-2.9]	.04
Alternaria, age 1, 2, or 3 years	13/48 (27%)	2.2 [1.1-4.4]	.02

#Total cohort size was 636 children at 4 years; 90 children (14%) had eczema on the basis of parental report; 477 children were in the comparison group (no eczema by both parental report and clinician's diagnosis).
†SPT results that were not significantly predictive included: Dust-mite (n total = 99), Cockroch (n total = 76), *Aspergillus* (n total = 59), *Penicillium* (n total = 61), *Cladosporium* (n total = 53), and Maple (n total = 75).

Table VI. Dog and cat allergen levels as predictors of eczema at age 4 years[*†]

Allergen[‡]	N Eczema/N Total (% with Eczema)	Unadjusted Odds ratio [95% CI]	*P* value
Dog		0.4 [0.2-0.7]	.01
Highest tertile	12/144 (8%)		
Lowest tertile	59/294 (20%)		
Cat		1.1 [0.7-1.9]	.6
Highest tertile	28/177 (16%)		
Lowest tertile	33/230 (14%)		

*Total cohort size was 636 children at age 4 years.
†Eczema on the basis of parental report case definition.
‡From house dust samples collected at home visit (before 1 year of age).

Table VII. Part I of sensitivity analysis: multivariable analysis to determine predictors of eczema based on clinician's diagnosis at age 4 years[*†]

	N Eczema/ N Total (% with Eczema)	Adjusted odds ratio [95% CI]	*P* value
History of parental eczema	32/115 (28%)	2.4 [1.4-4.4]	.003
Egg ingestion before 1 year of age	71/426 (17%)	0.9 [0.5-1.6]	.7
Sensitization to egg (1 year of age)	27/72 (38%)	4.3 [2.2-8.5]	<.001
Sensitization to elm (ages 1, 2, and/or 3 years)	16/55 (29%)	2.1 [0.9-5.1]	.1
Interaction Terms			
Dog in home (before 1 year of age; n = 197)[‡]		2.6[§] [0.7-9.9]	.2
SPT+ to Dog (age 1, 2, or 3 years)	4/17 (24%)		
SPT− to Dog (age 1, 2, or 3 years)	24/180 (13%)		
No dog in home (before 1 year of age; n = 319)		1.8[§] [0.7-4.8]	.2
SPT+ to Dog (age 1, 2, or 3 years)	14/33 (42%)		
SPT- to Dog (age 1, 2, or 3 years)	51/286 (18%)		
Cat in home (before 1 year of age; n = 120)[‡]		7.4[§] [2.2-25.3]	.002
SPT+ to Cat (age 1, 2, or 3 years)	9/18 (50%)		
SPT- to Cat (age 1, 2, or 3 years)	14/102 (14%)		
No cat in home (before 1 year of age; n = 402)		0.6[§] [0.3-1.6]	.4
SPT+ to Cat (age 1, 2, or 3 years)	17/58 (29%)		
SPT- to Cat (age 1, 2, or 3 years)	55/344 (16%)		

*Total cohort size was 636 children at 4 years; 107 children (17%) met criteria for eczema on the basis of the clinician's diagnosis.
†Table represents covariates that remained in the final model after backward elimination with an alpha cut-off of 0.15.
‡Twenty-eight (26%) children with eczema on the basis of the clinician's diagnosis owned dogs; 23 (21%) owned cats; on the basis of the home visit.
§Represents adjusted odds ratio for eczema on based on the interaction between pet ownership and SPT.

Table VIII. Part II of sensitivity analysis: multivariable analysis to determine predictors of eczema based on both parental report and clinician's diagnosis at age 4 years*†

	N Eczema/N Total (% with Eczema)	Adjusted Odds ratio [95% CI]	*P* value
History of parental eczema	13/82 (16%)	1.8 [0.7-4.9]	.2
Egg ingestion before 1 year of age	28/357 (8%)	1.2 [0.5-2.8]	.8
Sensitization to egg (1 year of age)	13/48 (27%)	5.6 [2.2-14.4]	<.001
Sensitization to elm (age 1, 2, or 3 years)	9/39 (23%)	2.9 [1.0-8.5]	.06
Interaction terms			
Dog in home (before 1 year of age; n = 163)‡		3.8§ [0.4-36.4]	.3
SPT+ to Dog (age 1, 2, or 3 years)	1/13 (8%)		
SPT- to Dog (age 1, 2, or 3 years)	4/150 (3%)		
No dog in home (before 1 year of age; n = 257)		5.1§ [1.9-14.0]	.002
SPT+ to Dog (age 1, 2, or 3 years)	11/24 (46%)		
SPT- to Dog (age 1, 2, or 3 years)	18/233 (8%)		
Cat in home (before 1 year of age; n = 102)‡		7.7§ [1.5-38.6]	.02
SPT+ to Cat (age 1, 2, or 3 years)	4/10 (40%)		
SPT- to Cat (age 1, 2, or 3 years)	7/92 (8%)		
No Cat in home (before 1 year of age; n = 321)		1.1 §[0.4-3.0]	.9
SPT+ to Cat (age 1, 2, or 3 years)	8/41 (20%)		
SPT- to Cat (age 1, 2, or 3 years)	15/280 (5%)		

*Total cohort size was 636 children at age 4 years; 39 children (6%) met criteria for eczema on the basis of both the parental report and the clinician's diagnosis.
†Table represents covariates that remained in the final model after backward elimination with an alpha cut-off of 0.15.
‡Five (13%) children with eczema on the basis of both the parental report and the clinician's diagnosis owned dogs; 11(28%) owned cats; on the basis of the home visit.
§Represents adjusted odds ratio for eczema based on the interaction between pet ownership and SPT.

Table IX. Part III of sensitivity analysis: multivariable analysis to determine predictors of eczema based on parental report at age 4 years without exclusion of 68 children who were positive by clinician's diagnosis but negative by parental report*†

	N Eczema/ N Total (% with Eczema)	Adjusted Odds ratio [95% CI]	*P* value
History of parental eczema	27/115 (23%)	2.0 [1.1-3.7]	.03
Egg ingestion before 1 year of age	54/426 (13%)	0.6[0.3-1.1]	.07
Sensitization to egg (1 year)	23/72 (32%)	3.1[1.5-6.5]	.002
Sensitization to elm (ages 1, 2, and/or 3 years)	18/55 (33%)	2.7[1.2-6.1]	.01
Interaction terms			
Dog in home (before 1 year of age; n = 197)‡		1.3§ [0.3-6.5]	.7
SPT+ to Dog (age 1, 2, or 3 years)	2/17 (12%)		
SPT- to Dog (age 1, 2, or 3 years)	14/180 (8%)		
No dog in home (before 1 year of age; n = 319)		4.8 [2.1-10.8]	<.001
SPT+ to Dog (age 1, 2, or 3 years)	17/33 (52%)		
SPT- to Dog (age 1, 2, or 3 years)	38/286 (13%)		
Cat in home (before 1 year of age; n = 120)‡		7.3§ [2.1-25.0]	.002
SPT+ to Cat (age 1, 2, or 3 years)	7/18 (39%)		
SPT- to Cat (age 1, 2, or 3 years)	10/102 (10%)		
No Cat in home (before 1 year of age; n = 402)		1.1 [0.5-2.5]	.8
SPT+ to Cat (age 1, 2, or 3 years)	16/58 (28%)		
SPT- to Cat (age 1, 2, or 3 years)	39/344 (11%)		

*Total cohort size was 636 children at age 4 years; 90 children (14%) met criteria for eczema on the basis of the parental report definition *without* removal from the analysis of children who were negative for eczema by parental report but positive on the basis of the clinician's diagnosis. Children who were negative by parental report were included in the comparison (no eczema) group for this analysis regardless of findings from the clinician's diagnosis.
†Table represents covariates that remained in the final model after backward elimination with an alpha cutoff of 0.15.
‡Sixteen (9%) children with eczema on the basis of both the parental report and the clinician's diagnosis owned dogs; 17(14%) owned cats; on the basis of the home visit.
§Represents adjusted odds ratio for eczema based on the interaction between pet ownership and SPT.

Table X. Multivariable analysis of predictors of eczema based on parental report at age 4 years in African-Americans*

	Adjusted odds ratio [95% CI]	*P* value
History of parental eczema	2.2 [0.4-10.9]	.3
Egg ingestion before 1 year of age	0.3 [0.07-1.4]	.1
Sensitization to egg (1 year of age)	1.8 [0.3-9.2]	.5
Sensitization to elm (ages 1, 2, or 3 years)	1.8 [0.3- 10.2]	.5
Dog ownership before 1 year of age	Cannot estimate†	
Sensitization to dog (ages 1, 2, or 3 years)	4.5 [1.1-18.2]	.04
Cat ownership before 1 year of age‡	12.4 [1.2-133.7]	.04
Sensitization to cat (ages 1, 2, or 3 years)	1.4 [0.4-5.5]	.7

*The African-American subpopulation included 131 children at age 4 years; 24 had eczema based on the parental report.
†Unable to estimate the effect of dog ownership or assess for an interaction with sensitization due to the low prevalence of dog ownership in the African-American subpopulation (17 African-Americans owned dogs before one; none of the dog owners had eczema).
‡Six African-American children owned cats before age 1 year of age; 3 of these had eczema at age 4 years. The interaction between cat and cat-ownership was not calculated because of collinearity between these variables in the African-American subpopulation.

Table XI. Multivariable analysis to determine predictors of atopic eczema at age 4 years*

	Adjusted odds ratio [95% CI]	*P* value
History of parental eczema	2.0 [0.8-4.8]	.14
Egg ingestion before 1 year of age	0.4 [0.2-0.9]	.03
Sensitization to egg (1 year of age)	6.5 [2.5-16.7]	<.001
Sensitization to elm (age 1, 2, or 3 years)	4.4 [1.6-12.0]	.004
Interaction terms		
Dog in home (before 1 year of age)†		
SPT+ vs SPT- to Dog (age 1, 2, or 3 years)	2.4 [0.3-17.0]‡	.4
No dog in home (before 1 year of age)		
SPT+ vs SPT- to Dog (age 1, 2, or 3 years)	5.0 [1.8-13.9]‡	.002
Cat in home (before 1 year of age)†		
SPT+ vs SPT- to cat (age 1, 2, or 3 years)	10.3 [2.5-43.2]‡	.001
No cat in home (before 1 year of age)		
SPT+ vs SPT- to Cat (age 1, 2, or 3 years)	1.4 [0.5-4.2]‡	.6

*Total cohort size was 636 children at age 4 years; Atopic eczema was defined as parental report of eczema plus a positive SPT at age 4 years (n = 55 children).
†On the basis of home visit.
‡Represents adjusted odds ratio for atopic eczema on the basis of the interaction between pet ownership and SPT.

Appendix

Sensitivity Analysis of Eczema Definition

Despite low agreement between the parental report and clinician's diagnosis (kappa = 0.3), most results were the same with either outcome definition (**Tables V** and **VII**). With the clinician's diagnosis, a history of parental eczema and egg SPT+ at 1 year of age were still predictive of eczema at age 4 years (aOR 2.4 [1.4-4.4]; $P = .003$ and 4.3 [2.2-8.5]; $P < .001$, respectively). The significant interaction between cat ownership and positive cat SPT (ages 1-3 years) was also present with the clinician's diagnosis eczema definition (aOR 7.4 [2.2-25.3]; $P = .002$ among cat owners with cat SPT+ vs aOR 1.1[0.4-3.0]; $P = .9$ among non-cat owners with cat SPT+).

Perhaps of greatest relevance, all of the findings from the parental report case definition were replicated in the subgroup of children who had eczema by both parental report and the clinician's diagnosis (**Table VIII**). The significant association between egg SPT+ at 1 year of age and eczema at age 4 years (aOR 5.6 [2.2-14.4]; $P < .001$), and the significant interaction involving cat and cat SPT were present in this subgroup (aOR 7.7 [1.5-38.6]; $P = .02$ among cat owners with cat SPT+ vs 1.1[0.4-3.0]; $P = .9$ among non-cat owners with cat SPT+). The same was true for dog and dog SPT (aOR 3.8 [0.4-36.4]; $P = .3$ among dog owners with dog SPT+ vs 5.1 [1.9-14.0]; $P = .002$ among non-dog owners with dog SPT+).

As a separate sensitivity analysis, we evaluated the impact of including children in the comparison (no eczema) group who were negative for eczema on parental report but positive by the clinician's diagnosis (**Table IX**). Conclusions for all outcomes in the multivariable analysis were unchanged, and confidence intervals were smaller (precision was increased) when we added back these 68 children who had been excluded a priori because of concerns for misclassification.

Predictors of Atopic Eczema at Age Four Years

Atopic eczema (n = 55) was analyzed with adjustment for covariates described in the results section (**Tables I** and **III**). Results were similar to those with eczema alone (**Table XI**). The positive associations between sensitization to egg and atopic eczema, and between elm and atopic eczema were stronger (aOR 6.5 [2.5-16.7]; $P < .001$ and aOR 4.4 [1.5-12.7]; $P = .006$, respectively) than for eczema alone. The protective effect of early egg introduction was statistically significant in this subgroup (aOR 0.4 [0.2-0.9]; $P = .03$). Statistically significant effect modification by dog ownership on dog SPT was also present. As before, children with no dog who were dog SPT+ were at significantly increased risk for atopic eczema (aOR 5.0 [1.8-13.9]; $P = .002$). The significant interaction between cat ownership and cat SPT was also replicated. The effect of parental eczema was no longer statistically significant. In a separate analysis, we found that parental eczema was the only predictor that trended toward significance among children with non-atopic eczema at age 4 years (n = 45; aOR 2.1 [0.9-5.0]; $P = .09$).