

Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy

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Background: Influence of household pets in the development of childhood asthma or atopy has been controversial.

Objective: The purpose of this study was to investigate whether pet exposure in early life decreases the subsequent risk of frequent wheezing and/or allergic sensitization.

Methods: This was a prospective observational birth cohort study. The setting was a large health maintenance organization in Tucson, Ariz; the subjects were a population sample of 1246 newborns enrolled at birth and followed prospectively to age 13 years. The main outcome measures were as follows: time to first report of frequent wheezing (>3 episodes in the past year), skin prick test reactivity at 6 years and 11 years of age, and total serum IgE at 9 months, 6 years, and 11 years of age.

Results: Children living in households with ≥ 1 indoor dogs at birth were less likely to develop frequent wheeze than those not having indoor dogs ($P = .004$). This inverse association was confined to children without parental asthma (hazard ratio = 0.47; $P < .001$ [Cox regression]) and was not evident for children with parental asthma (hazard ratio = 0.96; $P = .87$). Adjustment by potential confounders did not change the results. Indoor cat exposure was not significantly associated with the risk of frequent wheezing. Neither cat exposure in early life nor dog exposure in early life was associated with skin prick test reactivity or total serum IgE at any age.

Conclusion: Dog exposure in early life might prevent the development of asthmalike symptoms, at least in low-risk children with no family history of asthma. Nevertheless, early pet exposure does not seem to significantly influence the development of allergic sensitization. (*J Allergy Clin Immunol* 2001;108:509-15.)

Key words: Asthma, wheezing, atopy, allergy, epidemiology, risk, children, cat, dog, pets, IgE

Abbreviation used
HR: Hazard ratio

The prevalence of asthma has been increasing during the last few decades.¹ A variety of factors have been suggested to explain this phenomenon, but it is increasingly clear that environmental factors play a crucial role.² Most research into the determinants of childhood asthma has focused on risk factors of asthma, unexpected findings on preventive factors often being discounted. For example, the results of 2 studies suggesting an inverse association between indoor pets and the risk of asthma or atopy were dismissed by their authors as being due to chance or confounding.^{3,4} Two more recent studies^{5,6} that found a similar inverse relation have been interpreted as demonstrating true associations, either reflecting induction of immunologic tolerance⁵ or supporting the "hygiene hypothesis."⁶ Supporters of this hypothesis contend that microbes or their products stimulate the developing immune system in the direction of a T_H1 response, whereas lack of exposure to these substances results in a default to a preexisting T_H2 pattern.⁷

However, current evidence supporting the protective effect of pets on the risk of asthma or atopy is relatively weak. Existing studies have either selected high-risk populations⁴ or been cross-sectional and thus subject to recall bias.^{5,6} No prospective studies with a long-term follow-up have thus far been published. Therefore, we used data from the Tucson Children's Respiratory Study, a prospective birth cohort initiated in the early 1980s,⁸ to test the hypothesis that pet exposure in early life is protective against the development of frequent wheezing and/or allergic sensitization.

METHODS

A cohort of 1246 healthy babies were enrolled at birth in the Tucson Children's Respiratory Study between 1980 and 1984.⁸ Information regarding household pets was collected at enrollment (ie, soon after the baby was born). Similarly, data on potential confounders (defined below) were obtained from parents by questionnaire at enrollment; maternal smoking in infancy was ascertained when the children were 2 years old. Follow-up questionnaires asking about respiratory symptoms were completed by the parents when the children were 2, 3, 6, 8, 11, and 13 years old.

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Pet exposure was assessed in infancy and at 3 and 6 years of age. Exposure was defined on the basis of answers to the following question: "How many pets are there in the household, either kept inside or out?" Pets were listed, and separate columns were provided for the numbers of pets kept indoors and outdoors. Only a small number of households kept animals other than dogs or cats, so other animals were not considered. Cats and dogs were analyzed separately, and only indoor pets were considered.

Frequent wheezing was the main outcome variable, defined as >3 episodes of wheezing in the past year. The risk time was defined as the age of the child when the first questionnaire reporting frequent wheezing was completed. Those who never developed frequent wheeze were included through the last age at which they completed a questionnaire; otherwise, they were censored at 13 years of age. When the first questionnaire reporting frequent wheezing was preceded by a missing questionnaire, the time to first frequent wheezing was defined as the age midway between the age at the time of the last questionnaire completed and the age at the time of the questionnaire first reporting frequent wheeze.

Allergic sensitization was measured by skin prick testing (at ages 6 and 11 years) and serum total IgE (at 9 months, 6 years, 11 years). Skin prick tests were performed through use of 7 local aeroallergens (*Alternaria alternata*, house dust mix, Bermuda grass, careless weed, mesquite tree, mulberry tree, and olive tree). At 11 years of age, cat dander and *Dermatophagoides farinae* were added to the allergen panel.⁹ At each age, skin prick test positivity was defined as having one or more wheals ≥ 3 mm in diameter. Total serum IgE was measured through use of a paper radioimmunosorbent test.¹⁰

Potential confounders included the following: parental history of asthma (asthma diagnosed in either parent); parental history of hay fever (hay fever diagnosed in either parent); maternal smoking during infancy (yes/no); number of older siblings (0 or ≥ 1); attendance at a large group day care facility (> 5 children) at <6 months of age; maternal education (≤ 12 years or >12 years of education); and parental ethnicity (both parents being Hispanic or at least 1 parent being white).

The data were analyzed through use of Stata Statistical Software (StataCorp, College Station, Tex).¹¹ For categorical variables, the χ^2 test was used for statistical comparisons when appropriate. Serum IgE values were log-transformed because of the right-skewness. One-way ANOVA was used to assess relations with geometric mean total IgE. Standard regression methods (linear and logistic) were used for multivariate analysis when appropriate. Kaplan-Meier survival curves with log-rank tests were fitted to examine the association between pet exposure and development of frequent wheeze. Survival models used time to the first frequent wheezing episode as a dependent variable. To adjust for potential confounders, multivariate Cox regression models were used. An interaction term between pet exposure and parental history of asthma was included in the models to assess possible effect modification by parental asthma. Additional longitudinal analyses included the random effects model (for IgE) and the general estimating equation model (for skin prick testing).¹¹

The study was approved by the University of Arizona Institutional Review Board. Informed consent was obtained from the parents before their children were entered into the study, when blood was drawn, and when skin prick tests were performed.

RESULTS

Characteristics of the study population

The original cohort included 1246 subjects, 14 (1%) of whom were missing data on early pet exposure. Enrollment questionnaires were completed at a median age of 2 weeks;

>95% of the questionnaires were completed in the first month of life. Data regarding frequent wheeze were available on 1076 children (86%). Skin prick test data were available for 737 and 613 children at 6 years and 11 years, respectively, and total serum IgE data for 829, 534, and 462 subjects at 9 months, 6 years, and 11 years, respectively.

Children with and children without complete data did not differ with respect to sex or family history of asthma. Hispanic children and those with mothers with less education tended to be more likely to have missing data on frequent wheeze. Skin prick test data were more often missing among children with mothers with less education. No significant differences were found in other background characteristics (data not shown).

The associations between potential confounders and the main exposure variable are shown in Table I. Almost 400 subjects had indoor dogs (32.2%), and 275 had indoor cats (22.3%). Small families, non-Hispanic families, and families with better educated or smoking mothers had more indoor cats and/or dogs. In contrast, pet ownership showed no relation to the child's sex or to parental history of asthma or hay fever.

Cumulative incidence of frequent wheezing

A total of 237 (22%) of the children developed frequent wheezing during the study period. Median age (25th-75th percentile) at the first report of frequent wheezing was 4.0 (1.8-8.2) years.

Association between frequent wheeze and indoor pet exposure

There was a significant inverse association between dog exposure in infancy and the risk of developing frequent wheeze. Because having 1 and having ≥ 2 dogs gave similar survival estimates, these strata were collapsed into a single stratum (Fig 1). Cumulative incidence of frequent wheeze was 17.1% in those with ≥ 1 dogs in infancy; this compared with 24.6% in those who did not have household dogs. The inverse association was seen mainly in children without parental asthma (Fig 2, A); no significant association was seen in children with parental asthma (Fig 2, B).

For cat exposure in infancy, there was a nonsignificant ($P = .17$) inverse association with frequent wheeze in the whole population, the shape of the Kaplan-Meier curve being similar to that seen for dogs. The association remained nonsignificant after stratification by parental asthma (data not shown).

Cox regression (Table II) indicated that even after adjustment for confounders, dog exposure in early life was associated with decreased risk (hazard ratio [HR] = 0.53, $P < .01$) of frequent wheeze among the children without parental asthma. There was no evidence of confounding with day care attendance in early life, and no interaction between dog exposure and day care was found. In addition, the apparent protective effect was evident for both children with and children without atopy (HR = 0.47 [0.24-0.91] and HR = 0.56 [0.32-0.98], respectively). Adjusting for confounders did not alter the lack of associ-

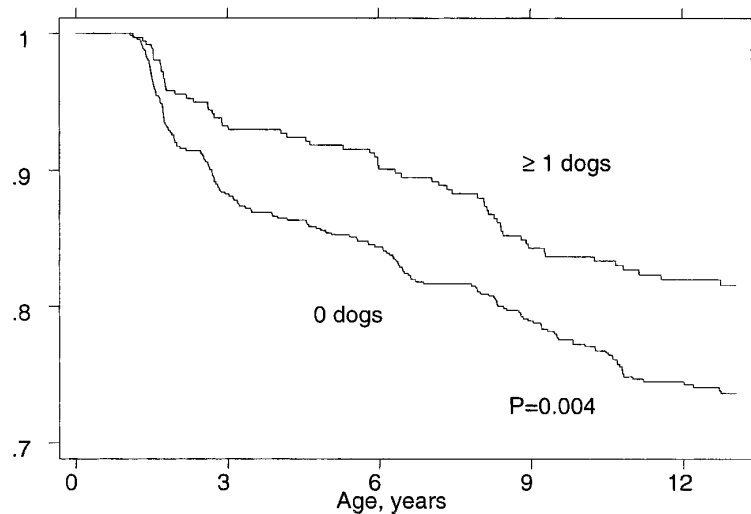


FIG 1. Kaplan-Meier survival estimates for frequent wheezing, by indoor dog exposure in infancy. P value is unadjusted (log-rank test).

TABLE I. Percent of subjects with 0, 1, or ≥2 indoor cats and/or dogs at enrollment, by various baseline characteristics

	No cats or dogs (n = 677)	1 cat or dog (n = 273)	≥2 cats or dogs (n = 282)	P value
Sex				.37
Male (n = 603)	55.2	23.4	21.4	
Female (n = 629)	54.7	21.0	24.3	
Parental MD asthma				.45
No (n = 849)	53.9	23.2	22.9	
Yes (n = 248)	54.8	19.8	25.4	
Parental MD hay fever				.59
No (n = 456)	56.1	21.5	22.4	
Yes (n = 659)	53.0	22.6	24.3	
Number of older siblings				<.001
0 (n = 513)	45.4	25.2	29.4	
≥1 (n = 719)	61.7	20.1	18.3	
Maternal education				<.01
≤12 years (n = 394)	61.9	18.6	19.6	
>12 years (n = 847)	51.8	23.8	24.5	
Ethnicity				<.001
Hispanic parents (n = 236)	81.8	10.0	8.2	
≥1 Non-Hispanic parent (n = 1010)	48.8	25.0	26.3	
Maternal smoking in infancy				<.001
No (n = 782)	55.8	23.6	20.6	
Yes (n = 255)	43.3	20.1	36.6	

MD, Physician-diagnosed.

ation between dog exposure and frequent wheeze for children with parental asthma (HR = 1.19, $P = .44$).

When the data were analyzed cross-sectionally instead of through use of longitudinal survival analysis, the results remained similar but the statistical power decreased. For example, odds ratios for frequent wheeze (among the children without parental asthma) by indoor dog exposure in infancy at 6, 8, and 11 years were 0.54 ($P = .12$), 0.55 ($P = .20$), and 0.46 ($P = .03$), respectively.

Effect of changes in pet ownership

Household pet ownership often changes over time. We thus looked at the timing of dog ownership in relation to

the development of frequent wheeze; we especially wanted to know whether removal of the dog from the home had any impact on symptom development. In the whole study population, the children who consistently had dogs throughout childhood had the lowest risk of developing frequent wheeze, and those who never had dogs had the highest risk (Fig 3). Interestingly, removal of the dog(s) by the child's third or sixth birthday was associated with a subsequent increase in the risk of frequent wheeze (Fig 3). Unfortunately, we do not know the exact times between birth and 3 years of age when the families removed the dogs—ie, whether the removal occurred before or after the development of symptoms within this

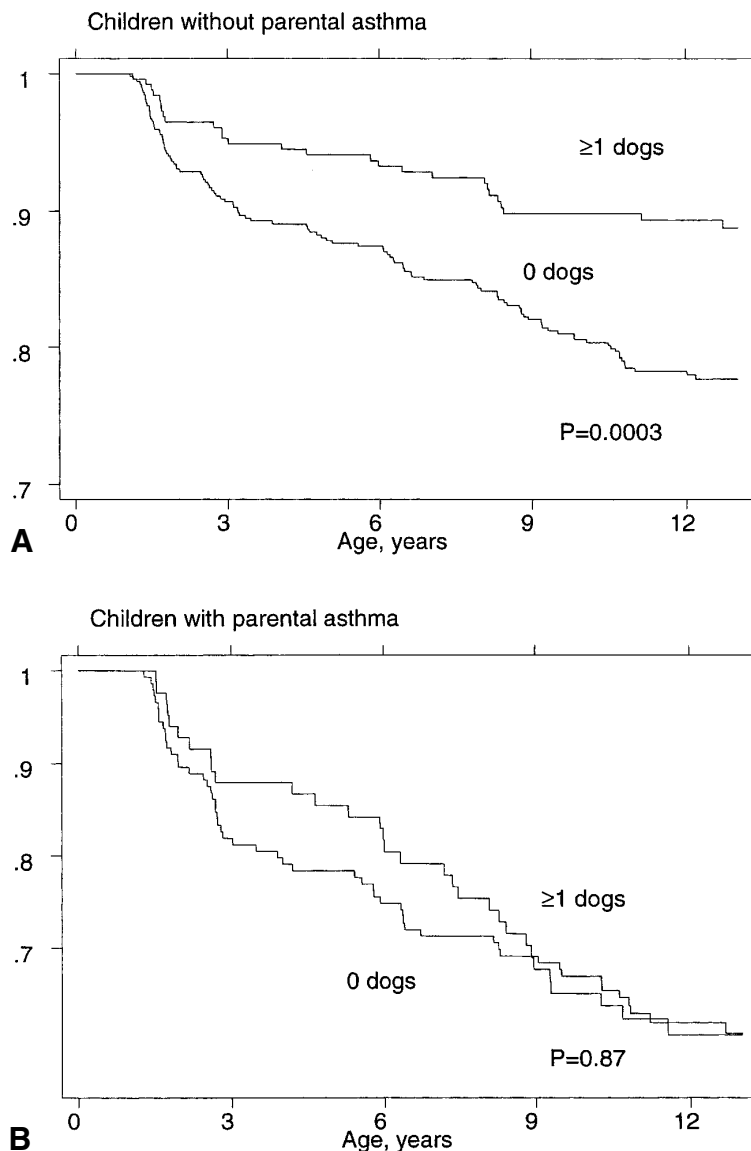


FIG 2. Kaplan-Meier survival estimates for frequent wheezing among children without (A) and children with (B) parental histories of asthma, by indoor dog exposure in infancy. *P* values are unadjusted (log-rank test).

subgroup. Among families removing dogs by the child's sixth birthday, however, the increased incidence of frequent wheeze clearly occurred after removal of the dog. Excluding children with occasional missing values or intermittent dog ownership after infancy did not significantly change the results. Removal of the dog(s) by the age of 3 or 6 years increased the subsequent risk of frequent wheeze principally among children with parental asthma (data not shown).

Association between atopy and indoor pet exposure

Neither dog nor cat exposure in infancy was associated with skin prick test positivity (Table III). When the

data were analyzed longitudinally through use of a general estimating equation model, there was still no relation to skin test response (not shown). There was also no relation of dog (or cat) exposure and early skin sensitization to *Alternaria*, nor was there any interaction between exposure and atopy. Likewise, no association was found between cat exposure in infancy and specific skin sensitization to cat at the age of 11 years.

Early exposure to a dog (or cat) also showed no relation to total serum IgE (Table III) at any age. The results on IgE remained the same when analyzed longitudinally through use of a random effects model. Stratification by parental asthma did not change the results for either skin test response or IgE (data not shown).

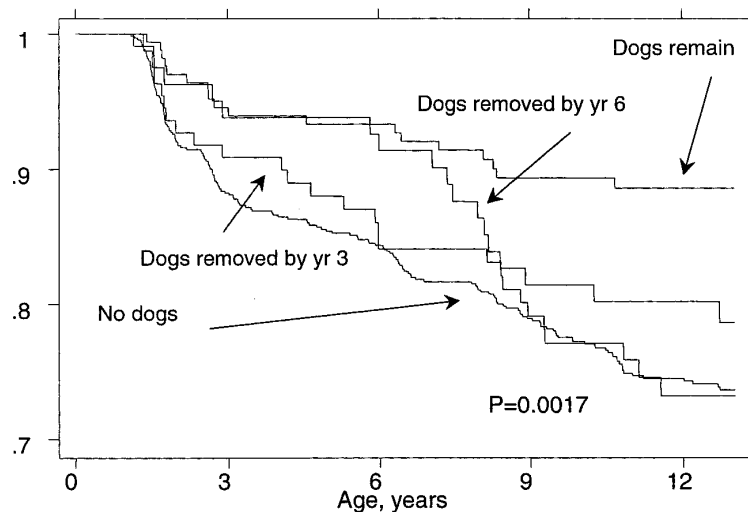


FIG 3. Kaplan-Meier survival estimates for frequent wheezing, by indoor dog exposure throughout childhood. Groups: *No dogs*, no dogs at enrollment or thereafter; *Dogs removed by yr 3*, dogs present at enrollment but removed by year 3; *Dogs removed by yr 6*, dogs at enrollment but removed by year 6; *Dogs remain*, Dogs at enrollment and thereafter. P value is unadjusted (log-rank test).

DISCUSSION

The major finding of the present study is that exposure to dogs in early life might be protective against the subsequent development of frequent wheezing. This was especially evident among children with no parental history of asthma. The lack of a relation between exposure to dogs and the development of asthma in children with parental history of asthma could reflect the fact that asthmatic parents avoid this exposure. Alternatively, any protective effect of exposure to dogs might be overwhelmed by strong hereditary susceptibility.

Our definition of asthma was based on rather severe symptoms, as suggested for the epidemiologic studies assessing the risk factors of asthma.¹² Exposure to dogs in infancy was defined as having indoor dog(s). If this proxy were an inaccurate measure of the true dog exposure, it would only have biased the risk estimates toward the null, potentially underestimating the true protective effect.¹³ Risk estimates for frequent wheezing were unchanged after adjustment (Cox regression), suggesting that the results are not likely to be explained by confounding, and they were stable over time (cross-sectional analysis), suggesting that the results were not unduly influenced by the use of survival analysis that considered only the first event.¹⁴

Exposure to various microbes or their products (such as endotoxin) in early life might decrease the subsequent risk of asthma and/or allergic disease.⁷ According to this hypothesis, microbial exposure might affect the developing immune system by preferential selection of T_H1 clones. Several recent cross-sectional studies have reported a decreased risk of asthma and allergy among farmers' children, especially those exposed to livestock.¹⁵⁻¹⁸ Similarly, endotoxin levels might be higher in

TABLE II. Risk of frequent wheeze by the number of indoor dogs in infancy, stratified by parental asthma

	Unadjusted * HR (95% CI)	Adjusted† HR (95% CI)
No parental asthma		
0 dogs‡	1.00	1.00
≥1 dogs	0.47 (0.31-0.72)***	0.53 (0.34-0.81)**
Parental asthma		
0 dogs‡	1.00	1.00
≥1 dogs	0.96 (0.62-1.50) (NS)	1.19 (0.76-1.88) (NS)

Risk estimates are presented as hazard ratios with 95% CIs (Cox regression).

NS, Not significant.

*Only dogs, parental asthma, and their interaction in the model. (Interaction between dogs and parental asthma was significant at $P = .021$.)

†Adjusted for sex, ethnicity, skin prick test positivity at year 6, number of siblings, maternal education, maternal smoking, and parental hay fever (indicator method for missing values used; model includes the same 1010 subjects as in the previous column). (Interaction between dogs and parental asthma after adjustment was significant at $P = .010$.)

‡Reference category.

*** $P < .01$.

** $P < .001$.

homes with indoor pets than in homes without pets.⁷ These findings suggest that endotoxin might be a common protective factor against asthma and allergy, found both in households with pets and on farms with livestock.¹⁹ In contrast to findings in previous studies,^{6,16,18} however, we found no association between early exposure to dogs and development of allergic sensitization (as measured by total serum IgE and skin prick test reactivity), irrespective of the family history of asthma. Our results suggest that microbial exposure, with dogs as either a source or a surrogate marker for exposure, might have an airway-specific effect, inhibiting the occurrence of airway inflammation and the development of asthma.

TABLE III. Pet ownership in infancy, by total serum IgE concentrations and skin prick test positivity at different ages

No. of pets in infancy	Total serum IgE (IU/mL)						Skin prick test result positive*	
	9 mo		6 y		11 y		6 y	11 y
	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	OR (95% CI)	OR (95% CI)
Dogs								
0	3.94 (3.5-4.4)	547	35.73 (30.0-42.5)	373	63.06 (51.5-77.2)	312	1.0	1.0
1	4.19 (3.4-5.2)	173	39.53 (27.7-56.4)	101	70.95 (47.1-106.8)	90	1.02 (0.70-1.49)	1.31 (0.85-2.0)
≥2	3.61 (2.8-4.6)	109	34.62 (21.8-55.1)	59	45.4 (26.8-77.0)	59	0.97 (0.61-1.55)	0.99 (0.60-1.64)
Cats								
0	4.14 (3.7-4.6)	644	38.36 (32.5-45.2)	414	62.45 (51.8-75.3)	366	1.0	1.0
1	3.40 (2.7-4.3)	113	27.49 (17.9-42.2)	71	54.64 (32.9-90.7)	68	0.84 (0.54-1.31)	0.96 (0.60-1.54)
≥2	3.25 (2.4-4.4)	72	33.99 (20.1-57.5)	48	74.49 (32.9-168.6)	27	0.94 (0.56-1.60)	0.96 (0.53-1.72)

*Any positive skin prick test reaction.

It is possible that exposure to microbial agents beginning immediately after birth has effects that are different from those of exposure to microbial products that occurs after exposure to ubiquitous allergens,^{20,21} which could explain the conflicting findings of previous studies.^{22,23} It is also likely that the length of the postnatal microbial exposure needed for a balanced maturation of the immune system depends on inherited predisposition.²⁴ Among low-risk children, in whom immunologic maturation develops faster than in high-risk children, the "immunologic window" for environmental effects might be short relative to that in high-risk infants, who require greater exposure. Similarly, our finding that removal of dog exposure had a greater impact among children with parental asthma suggests that the possible protective effect had already occurred among the low-risk infants.

Indoor pets are also a reservoir for and source of allergens. Research from Sweden indicates that indoor pet allergens are ubiquitous, indoor allergens being widely distributed within the community and within homes.^{20,21} A transient IgE response to these surrounding allergens is a normal phenomenon.²⁵ Among children with atopic heredity, however, the IgE response persists and increases because of a failure to induce tolerance. Some studies have suggested a dose response between exposure to allergens at home and the level of allergic sensitization.²⁶ However, allergen avoidance trials focusing on primary prevention have not provided convincing results in terms of reducing atopic disease (asthma, eczema, rhinitis), though they have shown reductions in objective markers of atopic sensitization.²⁷ Therefore, these studies might merely imply that susceptible children are most probably sensitized to the allergens that are found close to the child's microenvironment. Other studies are clearly needed to clarify the pathophysiologic mechanisms suggested above.

In conclusion, we found that dog exposure in early life seems to protect against the development of childhood asthma but does not influence the development of allergic sensitization. These results, as well as those from recent observational cohort studies,^{4,28,29} challenge the assumption that families with newborns should avoid household pets to prevent asthma and allergy in their children.^{22,23,30}

Although pet avoidance could be beneficial in secondary prevention of asthma and allergic diseases, pet avoidance in early life might not be a useful population-level strategy for the primary prevention of asthma and allergy. Further studies are needed to confirm our findings and clarify the possible biological mechanisms.

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