

Early environmental determinants of asthma risk in a high-risk birth cohort

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Environmental exposures during early life have been suggested to have the greatest impact on childhood asthma. Our aim was to evaluate the risk factors associated with asthma at age 7 yr in a high-risk cohort that participated in a randomized controlled study on the primary prevention of asthma. Indoor exposures were characterized before birth and at 2 weeks, 4, 8, 12, 18, and 24 months after birth and again at 7 yr. Nasal scrapings for respiratory viruses were done at the same intervals during the first 2 yr. At age 7, the children were assessed by a pediatric allergist and had allergy skin tests. Logistic regression analysis was undertaken to evaluate the effect of exposures on asthma for the entire cohort with adjustment for group allocation. In addition to the lower risk of asthma in the intervention group, we found a higher prevalence of asthma at age 7 for males, those having a positive history of asthma in mother, father, or older siblings, for children residing in Winnipeg and for atopic subjects. Upon adjustment for intervention group assignment and baseline factors, significant environmental risk factors during year 1 included dog ownership and respiratory syncytial viral infection detected at 12 months while maternal smoking was protective. Dog ownership was a significant risk factor in year 2, but highly correlated with dog ownership in year 1. Indoor environmental exposures during year 7 were not associated with asthma at age 7. Maternal smoking at year 7 was associated with a reduced risk of asthma at 7 yr. Early-life exposures were more important determinants than those in later years. A 'window of opportunity' exists for intervention measures to be applied.

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Asthma is a complex disease resulting from the interaction between environmental influences and genetic predisposition. Several environmental risk factors have been found to be associated with an increased risk of asthma, such as exposure to indoor aeroallergens (1), environmental tobacco smoke (2, 3) and viral infections (4, 5). However, these findings have been controversial. Some studies found that exposure to pets in infancy increases the risk of asthma in childhood and others found a reduced risk of sensitization or asthma (6–11). Similarly, exposure to high levels of house dust mite allergens was shown to predict the development

of asthma in some studies (12) but not in others (13).

In 1995, we conducted a prospective, randomized, controlled study to determine the effectiveness of a multi-faceted intervention program for the primary prevention of asthma in high-risk infants in two Canadian centers, Vancouver and Winnipeg (14, 15). The multi-faceted intervention program was applied during the first year of life and focused on factors believed to be associated with asthma at the time the study was initiated. This included the reduction of exposure to house dust mite and pet avoidance, avoidance of environmental tobacco smoke,

encouragement of breast feeding and delayed introduction of solids until 6 months. We found a significant reduction of 56% for pediatric allergist-diagnosed asthma in the intervention group at the age of 7 yr (15). In this report, we examined the risk factors and the timing of exposure to these risk factors associated with the development of asthma at age 7 yr in this high-risk cohort.

Methods

Study population

The birth cohort was recruited in two centers, Winnipeg and Vancouver, Canada, and has been described in previous reports (14, 15). Briefly, infants at high risk for developing asthma, defined as those with at least one first-degree relative with asthma or two first-degree relatives with other immunoglobulin E (IgE)-mediated allergic diseases, were identified during mothers' third trimester of pregnancy. Families were randomly allocated to the multi-faceted intervention group (n = 279) or to the control group (n = 266) prior to the child's birth. At 7 yr of age, 80 members (14.7%) of the cohort were lost to follow up. The number of families that dropped out was not significantly different between the two groups. Three hundred and eighty (70%) children returned for assessment by a pediatric allergist and for laboratory testing.

House-dust sampling and determination of allergen levels

Home visits were carried out at the time of recruitment and at 2 wk, 4, 8, 12, 18 and 24 months after birth and again at 7 yr of life. During each visit, dust samples were collected from six sites (parents' mattress, floor of parents' bedroom, child's mattress, floor of child's bedroom, the floor of the most commonly used room and the most commonly used upholstered furniture) using a standard protocol (14). Detailed description of house dust mite avoidance program had been described previously (14). The samples were analyzed in duplicates for house dust mite, cat and dog allergens using ELISA assays with purified monoclonal antibodies against group 1 mite allergens, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (Der p1 and Der f1) (16); cat allergen (Fel d1) (17); and dog allergen (Can f1), respectively (18) and the mean of the duplicates was used in the analysis. The total mite allergen (sum of Der p1 and Der f1) was reported as µg/g

dust. The limit of detection was 0.5 ng/ml for Der f1 and Der p1, 0.16 mg/ml for Fel d1 and 1 ng/ml for Can f1.

Nasal sampling and reverse transcription-polymerase chain reaction (RT-PCR) for asthma-associated viruses

Nasal epithelium was obtained using a Rhinoprobe curette (ASI, Arlington, TX, USA) at 2 wk, 4, 8, 12 and 24 months for viral studies. Without the knowledge of clinical information, total RNA was extracted from the specimens using the RNeasy kit (Qiagen Corp., Mississauga, Ontario, Canada) and underwent reverse transcription into complementary DNA. PCR for picornavirus (rhinovirus/enterovirus), parainfluenza virus (PIV), and respiratory syncytial virus (RSV) were carried out following a previously published protocol (19).

Follow-up assessment

At age 7 yr, the children were examined by a pediatric allergist in each center who had no knowledge of the randomization and did not participate in the care of the children or their families. The pediatric allergist conducted a structured interview with the child and parents. The diagnosis of asthma was a clinical decision made by the pediatric allergist based on symptoms of wheeze and cough, use of medications and physical findings without knowledge of the results of allergy skin tests.

Allergy skin tests were performed using the epicutaneous method with a prick lanceter (Bayer Inc., Toronto, Canada) with the following allergens (Omega Laboratories, Montreal, Quebec, Canada): house dust mite (*D. pteronyssinus* and *D. farinae*), cat, dog, cockroach, *Alternaria alternata*, *Cladosporium herbarum*, mixed tree, mixed grass and ragweed pollens, cow's milk, egg white, wheat, soy, and peanut together with a negative control of normal saline and a positive control of histamine diphosphate at 1 mg/ml. A mean wheel diameter of 3 mm or greater than the negative control was considered a positive reaction. Atopy was defined as positive skin test reactivity to one or more of these allergens.

Ethics

Ethics Committees of the University of British Columbia and the University of Manitoba approved the study. Parents signed informed consent, and at year 7, children gave verbal consent.

Data analysis

Children with pediatric-allergist diagnosed asthma (asthma) and those without were compared for personal and family characteristics (baseline characteristics) using chi-square analysis. Odds ratios (OR) and 95% confidence intervals (CI) based on univariate logistic regression analyses were calculated in relation to the following characteristics: race, sex, order of birth, maternal education (post-secondary education or not), history of asthma and history of other allergies in mother, father or older siblings, season of birth, and city of residence (Vancouver, Winnipeg).

The exposure variables were then compared between children with and without asthma using chi-square analysis and the adjusted OR and 95% CI were calculated using multiple logistic regression with the group allocation and each exposure variable forced into the model, while the baseline characteristics were entered into the model in a stepwise manner with $p < 0.1$ as the level of significance. Exposure variables for all three occasions, years 1, 2, and 7, consisted of the following: mother or father smoking any time, cat or dog ownership any time during the last 12 months for each year's assessment, levels of house dust mite allergen (as continuous variables and as categorical variables $\geq 2 \mu\text{g/g}$ and $< 2 \mu\text{g/g}$ dust). Exposure variables during years 1 and 2 included day-care attendance, exclusive breastfeeding for four or more months, and RT-PCR reactions to different respiratory viruses (picornavirus, PIV, and RSV) from nasal samples (positive or negative). Exposures to viruses were analysed in several ways: positive RT-PCR to each individual virus at different times; or as positive RT-PCR to individual viruses or to any virus at any time during the first 12 months or between 12 and 24 months, and the time from birth for the PCR to an individual virus to be positive.

A correlation matrix of these variables was used to identify multicollinearity, particularly among exposure variables obtained repeatedly at different periods. Because dog and cat ownership were highly correlated with Can f1 and Fel d1 allergen levels, respectively, they were not used in the same model.

The significance of all exposure factors at each time period (years 1, 2, and 7) on the risk of asthma at 7 yr was first assessed separately at each year of observation using multiple logistic regression when each exposure and group allocation variables were forced and all baseline characteristics entered in a stepwise manner.

The aforementioned analyses were repeated separately for the control and intervention group and also with and without the child's atopic status. To study the potential effect of atopy as an effect modifier, tests for interaction were conducted of atopy combined with each exposure variable. Other potentially relevant interaction terms between such risk factors as treatment allocation group, maternal history of asthma, city of residence and various intervention measures were also examined. A p value of < 0.05 was considered to be significant.

Statistical analysis was carried out using STATA (Stata/SE 8.0, College Station, TX, USA) and SPSS/PC Version 15 (SPSS, Chicago, IL, USA).

Results

Of the 380 children who were assessed at the age of 7 yr, 71 (18.7%) children in this high-risk cohort were diagnosed by pediatric allergists as having asthma. Children in the intervention group had a significantly lower risk for developing asthma compared with the control group (14.9% vs. 23%, adjusted OR 0.44; 95% CI 0.25–0.79) (15).

There was a significantly higher proportion of children from non-Caucasian families (Asian and others) returning for assessment than children from Caucasian families, but no significant differences in exposure between those who returned and those who did not (data not shown).

Baseline characteristics

A higher proportion of boys, children with a history of asthma in the mother, father and or older siblings, and residents in Winnipeg, developed asthma at 7 yr (Table 1). There were no significant differences in the distribution of race, birth order, season of birth and maternal education between children with asthma and children without asthma.

Individual-exposure risk factors at years 1, 2 or 7 and risk of asthma at 7 yr of age

Stepwise multiple logistic regression analysis done separately by year for each of the exposure factors showed that exclusive breastfeeding for ≥ 4 months and positive RT-PCR for RSV at 12 months but not at 24 months was associated with increased risk of asthma at 7 yr (Table 2). There was no relationship between asthma at age 7 yr and cat or dog ownership at any year and exposure to higher levels of house dust mite

Table 1. Baseline characteristics of children with and without asthma at 7 yr

	Asthma [N (%)] 71 (18.7)	No asthma [N (%)] 309 (81.3)	Univariate OR (95% CI)
Race			
Non-white	10 (14.1)	69 (22.3)	1
White	61 (85.9)	240 (77.7)	1.75 (0.85–3.6)
Gender			
Female	24 (33.8)	153 (49.5)	1
Male	47 (66.2)	156 (50.5)	1.92 (1.12–3.29)
Birth order			
Not first born	40 (56.3)	167 (54.0)	1
First born	31 (43.7)	142 (46.0)	0.91 (0.54–1.53)
History of asthma			
No asthma	8 (11.3)	77 (24.9)	1
Father and/or sibling with asthma	25 (35.2)	108 (35.0)	2.22 (0.95–5.20)
Mother with asthma	38 (53.5)	124 (40.1)	2.94 (1.31–6.65)
Maternal post-secondary education:			
No	21 (29.6)	64 (20.7)	1
Yes	50 (70.4)	245 (79.3)	0.62 (0.35–1.11)
City of residence			
Vancouver	23 (12.4)	163 (87.6)	1
Winnipeg	48 (24.7)	146 (75.3)	2.33 (1.35–4.02)
Season of birth			
Dec.–Feb.	20 (28.2)	72 (23.3)	1
March–May	23 (32.4)	110 (35.6)	0.75 (0.39–1.47)
June–Aug.	15 (21.1)	58 (18.8)	0.93 (0.44–1.98)
Sept.–Nov.	13 (18.3)	69 (22.3)	0.68 (0.31–1.47)

OR, odds ratio; CI, confidence interval.

allergen, Fel d1 and Can f1, when these variables were categorized into ≥ 2 $\mu\text{g/g}$ dust and < 2 $\mu\text{g/g}$ dust or when used as continuous variables in the analysis. Exposure to maternal smoking on all occasions was associated with a significantly reduced risk of asthma.

Positive RT-PCR to HRV and PIV at any time during the first 2 yr did not result in an increased risk of asthma at 7 yr. The time to the first positive RT-PCR to RSV also was not associated with increased asthma risk (data not shown).

Significant risk factors and timing of exposure and asthma risk at 7 yr

Stepwise multiple logistic regression analyses were carried out on risk factors associated with asthma at year 7 with and without the atopic status of the child during corresponding years. We found that positive RT-PCR for RSV at 12 months and dog ownership during year 1 were associated with increased asthma risk at 7 yr, while maternal smoking was associated with a reduced risk in both the models. We present in Table 3 the child's atopic status in the model (model 1, Table 3). The child's atopic status at 12 months was the strongest predictor of asthma risk at 7 yr (OR 6.50, 95% CI 3.26–12.9), followed by a maternal history of asthma,

Table 2. Environmental factors and atopic status of the child at varying times and risk of asthma at 7 yr (adjusted OR and 95% CI)

Exclusive breastfeeding ≥ 4 months	Asthma N (%)	No asthma N (%)	Adjusted OR (95% CI)*
	41 (57.7)	156 (50.5)	2.23 (1.22–4.09)
Attendance of day care			
During year 1	5 (7.0)	26 (8.4)	0.75 (0.27–2.14)
During year 2	7 (9.9)	28 (9.1)	0.90 (0.35–2.27)
Positive viral RT-PCR			
Picornavirus – 12 months	10 (14.9)	44 (14.9)	0.85 (0.39–1.86)
24 months	23 (34.3)	110 (37.8)	0.86 (0.48–1.56)
PIV – 12 months	12 (17.9)	33 (11.2)	1.22 (0.56–2.64)
24 months	5 (7.5)	16 (5.5)	1.68 (0.60–5.57)
RSV – 12 months	22 (32.8)	49 (16.6)	2.28 (1.20–4.31)
24 months	5 (7.5)	13 (4.5)	2.44 (0.73–8.19)
Mother smoking			
Year 1	5 (7.0)	39 (12.6)	0.23 (0.08–0.69)
Year 2	6 (8.5)	36 (11.7)	0.36 (0.14–0.96)
Year 7	7 (9.9)	47 (15.2)	0.36 (0.14–0.89)
Father smoking			
Year 1	14 (19.7)	59 (19.1)	0.90 (0.46–1.81)
Year 2	11 (15.5)	43 (13.9)	0.89 (0.42–1.91)
Year 7	14 (20.0)	52 (16.9)	0.90 (0.44–1.82)
Cat ownership			
Year 1	18 (25.4)	66 (21.4)	1.39 (0.74–2.65)
Year 2	16 (22.5)	52 (16.8)	1.56 (0.80–3.06)
Year 7	17 (23.9)	61 (19.7)	1.40 (0.73–2.70)
Dog ownership			
Year 1	18 (25.4)	42 (13.6)	1.68 (0.84–3.34)
Year 2	20 (28.2)	46 (14.9)	1.79 (0.93–3.46)
Year 7	17 (23.9)	41 (13.3)	1.54 (0.73–3.09)
HDM ≥ 2 $\mu\text{g/g}$			
Year 1	12 (16.9)	54 (17.5)	1.26 (0.59–2.68)
Year 2	12 (16.9)	52 (16.8)	1.36 (0.63–2.91)
Year 7	22 (39.3)	125 (45.0)	0.85 (0.46–1.57)
Child atopic			
Year 1	34 (47.9)	56 (18.4)	5.74 (3.10–10.6)
Year 2	30 (42.9)	35 (11.6)	7.24 (3.76–13.9)
Year 7	52 (74.3)	115 (38.7)	4.77 (2.61–8.72)

OR, odds ratio; CI, confidence interval; RT-PCR, reverse transcription-polymerase chain reaction; PIV, parainfluenza virus; RSV, respiratory syncytial virus; House dust mite (HDM).

*Each exposure and group allocation variables forced in and all baseline characteristics entered in a stepwise manner in the multiple logistic regression analysis.

paternal/sibling history of asthma, being male and resident in Winnipeg. Without atopy in the model, the other risk factors still remained statistically significant in years 1 and 7, while at year 2, dog ownership was just short of significance ($p = 0.08$). When allergen levels, Fel d1 and Can f1, were used in the model instead of cat and dog ownership, neither of the allergens were significant risk factors for asthma (data not shown).

The only exposure associated with a significantly increased risk for asthma was dog ownership at year 2 (adjusted OR 2.26, 95% CI 1.11–4.62) (model 2, Table 3). However, dog ownership in year 2 was highly correlated with

Table 3. Significant exposure factors at various times after birth and risk of asthma at 7 yr – results of multiple logistic regression analysis

	Model 1 Year 1 exposure	Model 2 Year 2 exposure	Model 3 Year 7 exposure
Baseline characteristics			
Male	2.46 (1.29–4.68)	1.82 (0.98–3.37)	–
Mother with asthma	5.08 (1.82–14.2)	3.70 (1.45–9.40)	5.02 (1.61–15.6)
Father or siblings with asthma	3.18 (1.11–9.09)	2.61 (1.00–6.83)	4.04 (1.25–13.1)
Winnipeg	2.26 (1.14–4.48)	2.51 (1.29–4.88)	2.21 (1.11–4.39)
Maternal post-secondary education	0.49 (0.24–1.01)	–	0.46 (0.22–1.00)
Intervention	0.38 (0.20–0.73)	0.51 (0.28–0.92)	0.33 (0.17–0.67)
Child's atopic status			
Child's atopic status at year 1	6.50 (3.26–12.9)	NI	NI
Child's atopic status at year 2	NI	6.92 (3.53–13.6)	NI
Child's atopic status at year 7	NI	NI	5.81 (2.79–12.1)
Exposure – year 1		NI	NI
RSV at 12 months	2.84 (1.40–5.76)		
Dog ownership – year 1	3.15 (1.43–6.97)		
Mother smoking – year 1	0.23 (0.07–0.67)		
Exposure – year 2	NI		NI
Dog ownership – year 2		2.26 (1.11–4.62)	
Exposure – year 7	NI	NI	
Mother smoking – year 7			0.22 (0.06–0.84)

Models of multiple logistic regression analysis: group allocation forced in and exposure variables all entered in a stepwise manner and p value set at 0.1.

RSV, respiratory syncytial virus.

NI, not included; –, not significant.

Model 1: Baseline characteristics, year 1 exposure variables and child's atopic status at year 1.

Model 2: Baseline characteristics, year 2 exposure variables and child's atopic status at year 2.

Model 3: Baseline characteristics, year 7 exposure variables and child's atopic status at year 7.

dog ownership in year 1 ($r = 0.77$, $p < 0.001$). Maternal smoking at year 7 was associated with a reduced risk of asthma at 7 yr (model 3, Table 3). The child's atopic status in the corresponding year was a highly significant risk factor (OR 6.92, 95% CI 3.53–13.6 and OR 5.81, 95% CI 2.79–12.1 in years 2 and 7, respectively).

There was no significant interaction between intervention status and different exposure variables, including maternal smoking and dog ownership ($p > 0.05$) with the exception of RSV and intervention status (adjusted OR 0.11, 95% CI 0.03–0.41), suggesting that the effect of RSV infection on asthma was greater in the control than the intervention group. No significant interactions were found between intervention status and baseline characteristics, such as city of residence, and family history of asthma; between maternal history of asthma and various exposure variables; between the child's atopic status at year 1 and various exposure variables.

The aforementioned analysis was repeated separately for children in the control and the intervention group. The risk factors were essentially the same with the exception that RSV infection at 12 months was a significant environmental risk factor for the control group (adjusted OR 4.61, 95% CI 1.87–11.4) but not in the intervention group; dog ownership was a signif-

icant risk factor for the intervention group (adjusted OR 5.52, 95% CI 1.8–16.9) and there was a similar trend in the control group.

Discussion

We studied the risk factors for the development of asthma at age 7 yr in a cohort of high-risk children who had participated in a randomized clinical trial for primary prevention of asthma in two Canadian centers, Vancouver and Winnipeg. At age 7 yr, we were able to assess 380 (70%) out of the original cohort of 549 children, and there were no significant differences in baseline characteristics and exposure factors between those who returned for assessment and those who did not, apart from ethnic origin. This suggests that the participants were an unbiased sample. Ethnic origin was not a risk factor for asthma in this study. The intervention measures, initiated prior to birth and applied in the first year of life, a period seen as a 'window of opportunity' in which to affect the development of immune response mechanisms, had resulted in a reduction of pediatric allergist-diagnosed asthma by 56% in the intervention group when assessed at 7 yr of age (15).

The study was designed to determine the effectiveness of a multifaceted program and not

of the individual components. Therefore, the analysis for risk factors for asthma in this high-risk group was undertaken with consideration of intervention vs. control group allocation. We found that personal and family characteristics associated with increased risk for asthma at age 7 yr in this high-risk cohort included male sex, a history of asthma in the mother and older siblings and residence in Winnipeg. The atopic status of the child, as early as age 1 yr, was the most significant risk factor for asthma at 7 yr. Environmental factors associated with a significantly increased risk for asthma at age 7 yr in our cohort included dog ownership during the first year and positive RT-PCR for RSV at 12 months; maternal smoking during the first year was found to be protective. In year 2, dog ownership was important but was highly correlated with that in year 1. Exposures during the seventh year were not associated with asthma at age 7 yr.

Respiratory syncytial virus and other severe lower respiratory tract infections may promote asthma by affecting lung development and initiating airway remodeling. In the Tucson Children's Respiratory Study, children with RSV had an OR of 4.3 (95% CI 2.2–8.7) for continued wheezing by age 6 yr, and these children continued to have an increased risk for wheezing up to age 11 (20). In a previous study of this cohort at age 2 yr, we found that positive RT-PCR for RSV and PIV (not HRV) at any time during the first 12 months was associated with recurrent wheeze (21). In this study, we found that RSV infection at 12 months of life was a significant risk factor for the development of asthma at age 7 yr more for the control group than the intervention group. Our finding also suggests that the timing of RSV infection might be important. Only positive RT-PCR at 12 months for RSV, reflecting RSV infection between 8 and 12 months was associated with an increased risk for asthma. It should be noted that we did not specifically sample for viral PCR at the time of clinical upper or lower respiratory illness in these children.

Dog ownership but not cat ownership during the first year of life was associated with increased risk for asthma at age 7 in this high-risk cohort. Dog ownership has been reported to be associated with higher endotoxin levels in house dust (22). Although high endotoxin exposure has been reported with protection against sensitization (23), it has also been shown to be associated with increased wheeze during the first year of life although the effect diminished as the children grew up (24). In this study, the compliance to pet

avoidance was poor, few families in the intervention group removed pets.

While sensitization to indoor allergens has been found to be associated with an increased risk for asthma in childhood (25), the relationship between the level of exposure to indoor allergens and development of asthma is controversial. Sporik et al. reported in 1990 that the level of exposure to house dust mite during early infancy determines the development of asthma at age 11 yr (26). The Multicentre Allergy Study in Germany demonstrated a dose-response relationship between indoor exposure to dust mite and cat allergens and the risk of sensitization, but not with the risk of asthma (15). A more recent follow-up study of the German birth cohort at 13 yr of age showed that persistence of asthma characterized by bronchial hyper-responsiveness and impairment of lung function is determined by sensitization to indoor aeroallergens during the first 3 yr of life and exposure to high levels of allergens (27). Although we were successful in reducing house dust mite allergen levels during the first 2 yr of life in the homes of children in the intervention group, we were unable to demonstrate any relationship between the level of exposure to house dust mite allergen at any time and the risk of asthma at 7 yr.

We found residence in Winnipeg to be a risk factor for asthma. Winnipeg has a drier, colder continental climate while Vancouver has a moist coastal climate. Levels of house dust mite allergen in homes in Winnipeg are lower compared with those in Vancouver, but outdoor levels of *Alternaria* and *Cladsporum* are higher (28). However, spores of *Alternaria* are also present indoors (29). Sensitization to *Alternaria* has been shown to be an important risk factor for asthma in the midwest of the United States and some other countries (29, 30). As the same pediatric allergist assessed children in each center, but differed across centers, it is possible that they might have assessed the children differently. However, a structured interview format was used during the assessment and the prevalence of atopy was higher among children in Winnipeg compared with those in Vancouver, (51.1% vs. 39.5%, respectively, for atopy, $p < 0.02$); atopy was highly correlated with the diagnosis of asthma by the pediatric allergists, who were blinded to these objective findings.

Although, most studies showed that maternal smoking is a risk factor for childhood asthma (2, 3), we found that it is a protective factor in this high-risk cohort. This is likely to be attributed to selection bias as mothers in this high-risk cohort were much less likely to smoke if their older

children had asthma or other allergic illnesses (6.7% vs. 21.6%, $p = <0.001$) as reported by other studies (31, 32).

This study showed that the effects of the inherent risk factors of asthma, such as atopic predisposition, family history of asthma, cannot be modified by our intervention measures. The finding that exposure factors, such as dog ownership and RSV infection, during the first year of life are more important than exposure during later years suggests that there is 'window of opportunity' for intervention measures to be applied for the primary prevention of asthma in high-risk children.

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