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ORIGINAL ARTICLE

Prenatal and early-life predictors of atopy and allergic disease in Canadian children: results of the Family Atherosclerosis Monitoring In earLY life (FAMILY) Study

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Prenatal and early-life environmental exposures play a key role in the development of atopy and allergic disease. The Family Atherosclerosis Monitoring In earLY life Study is a general, population-based Canadian birth cohort that prospectively evaluated prenatal and early-life traits and their association with atopy and/or allergic disease. The study population included 901 babies, 857 mothers and 530 fathers. Prenatal and postnatal risk factors were evaluated through questionnaires collected during the antenatal period and at 1 year. The end points of atopy and allergic diseases in infants were evaluated through questionnaires and skin prick testing. Key outcomes included atopy (24.5%), food allergy (17.5%), cow's milk allergy (4.8%), wheezing (18.6%) and eczema (16%). The association between infant antibiotic exposure [odds ratio (OR): 2.04, 95% confidence interval (CI): 1.45–2.88] and increased atopy was noted in the multivariate analysis, whereas prenatal maternal exposure to dogs (OR: 0.60, 95% CI: 0.42–0.84) and acetaminophen (OR: 0.68, 95% CI: 0.51–0.92) was associated with decreased atopy. This population-based birth cohort in Canada demonstrated high rates of atopy, food allergy, wheezing and eczema. Several previously reported and some novel prenatal and postnatal exposures were associated with atopy and allergic diseases at 1 year of age.

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Key words: allergy/atopy, human, newborn children, outcome/system, pregnancy

Introduction

Allergic diseases represent a global health problem of increasing prevalence and severity. In some European countries, up to 50% of children demonstrate Immunoglobulin E (IgE) sensitization ('atopy') to inhalant or food allergens.[1] Allergic diseases are complex multifactorial disorders, with both genetic and environmental components interacting during early life and probably *in utero*. Given the developed 'plasticity' of the prenatal and postnatal periods, environmental exposures, acting on genetically susceptible hosts, may have the greatest potential during these periods to influence the development of disease in early childhood.

In utero and early-life events appear to be important for the development of many chronic inflammatory-immune diseases including allergy and asthma.[2] There are a number of environmental exposures during pregnancy and early life, which pose a potential risk for, or protect against, allergic disease development in the infant; these include inhalants such as allergens and molds.[3] In addition, nutritional–metabolic, psychosocial and other lifestyle factors have been hypothesized to play key roles.[1] Epidemiological and immunological studies suggest that dietary modification in fetal life, as well as fetal under- or over-nutrition, could affect the development of allergic diseases.[4] There are, however, conflicting data regarding the role of timing of introduction of solid foods, duration of breastfeeding and exposure to pets as potential factors, which could be targets for prevention or intervention in modulating the development or maintenance of allergic diseases.

In this study, we report the effects of environmental and nutritional factors during the prenatal and postnatal periods on atopic sensitization (atopy) and the development of allergic diseases (reported diagnosis of wheezing, eczema, allergic rhinitis or food allergy) in the prospective birth cohort Family Atherosclerosis Monitoring In earLY life (FAMILY) Study.[5,6]

Methods

Study design

The FAMILY Study is a McMaster University/Population Health Research Institute-based longitudinal birth cohort established in 2005, and designed to examine early-life determinants in chronic disease development, with a primary emphasis on nutritional, metabolic and cardiovascular variables

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and their relationship with the development of childhood obesity and cardiovascular disease risk factors, as well as childhood allergy and asthma.[5,6]

The study population included 901 babies, 857 mothers and 530 fathers (Table 1). Among them, data of 825 children, 783 mothers and 493 fathers were analyzed, based on availability of questionnaires and skin prick testing. In all, 857 women and 530 fathers were recruited after obtaining informed consent during pregnancy, drawing from three hospitals in Hamilton and Burlington, ON, Canada.

Prenatal and postnatal determinants in the child and family for the development of obesity and cardiovascular disease, as well as select factors for allergic disease development, were measured as described in the following paragraph. Questionnaire data were collected from mothers during pregnancy (24–28 weeks of gestation) and at the 1-year visit.

Data were also collected on fathers (at the mother's initial pregnancy visit) and on children at 1 year of age. These questionnaire data included information on pre-existing diseases, food dairies, nutritional supplements, medications, tobacco use, socio-demographic variables, maternal pet ownership and maternal exposure to farm animals. Data were also collected on duration of breastfeeding, infant food intake, medications taken by the infant during the 1st year of life and the mother during pregnancy, maternal smoking status prenatally and postnatally, vaccination history of the infant, and signs and symptoms of allergic disease in the infant (see Tables 2 and 3).

The present study was approved by Research Ethics Boards of the participating hospitals (Hamilton Health Sciences, St Joseph's Hospital – Hamilton, Joseph Brant Memorial Hospital, Burlington, ON, Canada).

Table 1. *Description of the study cohort*

Description of family	Family groups (n = 783)	Available data
Age of the mother (baseline)	32.3 (5.0)	783
Age of the father (baseline)	34.2 (5.9)	493
Mother's European ethnicity	86.0%	783
Other children in the family	55.4%	783
Education >13 years	85.2%	782
Smoking history (mother)		
Never	63.9%	758
Quit before pregnancy	23.4%	
Smoked during pregnancy	12.8%	
Household income ⩾$50 K/year	78.1%	761
Mother employed at baseline	80.4%	782
Mother's allergies[a]	72.7%	781
Father's allergies[a]	65.2%	684

n = 783 represents the number of pregnant mothers.

[a]As defined by self-reported eczema, rhinitis, asthma (wheezing) or a positive skin test.

Skin prick testing

Skin prick testing was performed by standardized methods on fathers during the prenatal visit and on mothers and babies at the 1-year visit. A positive control (histamine), a negative control (diluent), standard series of five food allergen extracts (wheat, egg, milk, peanut and nuts) and 14 inhalant allergen extracts [cat dander, dog dander, horse, feather, cockroach, house dust mite (*Dermatophagoides farinae*), house dust mite (*Dermatophagoides pteronyssinus*), *Altenaria* mold, *Hormodendrum* mold, *Aspergillus* mold, grass, tree, ragweed, weeds] were applied to the volar surface of the forearm for adults. In infants, multi-testers (Multi-Test II; Lincoln Diagnostics) were used – a positive control (histamine), a negative control (diluent), standard series of six food allergen extracts (wheat, egg, milk, soy, peanut and mixed tree nuts) and eight inhalant allergen extracts (cat dander, dog dander, feather, cockroach, house dust mite, grass, tree, ragweed). A skin prick test was deemed positive if the greatest diameter of the wheal was at least 2 mm greater than the greatest diameter of the saline control.[7]

Primary allergic outcomes for analysis

Primary outcomes at 1 year of age included atopy, food allergy and allergic disease. We defined atopy as having at least one positive skin test. For the purposes of these analyses, we defined 'allergic disease' as the development of asthma, wheezing, allergic rhinitis or eczema as reported by the mother. We defined food allergy in the child by 1 year of age as reported by the mother or if there was a positive skin test for food allergens in the child at 1 year.

Statistical analysis

Statistical analyses were conducted using SAS version 9.2 for Unix (SAS Institute Inc., Cary, NC, USA). Frequencies and proportions were calculated for all of the prenatal and postnatal exposures potentially associated with the outcomes of interest: allergic disease, atopy and food allergy. Multivariable logistic regression modeling was used to consider the effect of prenatal and early childhood environmental exposures, maternal nutritional exposures during pregnancy, postnatal breastfeeding and child nutritional exposures, and the use of medication in children on the development of allergic disease. For exposures that were highly correlated between the prenatal and postnatal periods, the prenatal measure was included (e.g. dog in home). Exposures with a univariate P-value of >0.10 were entered into the multivariable model. The final model was determined using backward selection methods, keeping variables with a $P < 0.05$.

Results

There were 783 families with a 1-year follow-up visit. The follow-up cohort included 825 children (51% male and 90% singletons) with an average age of 13 months at follow-up and a mean gestational age of 39 weeks at birth. Of the 825, 818 had

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Table 2. *Proportion of children with prenatal exposures by allergic outcomes at the 1st year*

	Allergic disease			Atopy			Food allergy		
Exposures	Yes (%)	No (%)	*P*-value	Yes (%)	No (%)	*P*-value	Yes (%)	No (%)	*P*-value
n	360	458		141	435		143	675	
Parental allergy									
Maternal allergy history	76.1	70.2	0.06	75.2	77.9	0.50	75.5	72.2	0.42
Paternal allergy history	69.5	62.3	0.04	71.3	67.0	0.36	80.2	62.2	<0.0001
Pet exposures									
Lives on a farm	3.5	3.3	0.89	5.0	3.7	0.48	4.3	3.2	0.53
Exposed to farm animals	4.5	4.0	0.71	2.9	3.0	0.94	3.5	4.3	0.66
Cats at home	39.5	41.1	0.64	36.7	41.8	0.29	38.0	40.9	0.53
Dogs at home	33.1	41.1	0.02	34.5	40.6	0.20	33.8	38.4	0.30
Birds at home	4.7	2.6	0.11	6.4	3.0	0.07	5.6	3.1	0.14
Rodents at home	6.4	3.3	0.04	6.4	4.1	0.27	9.8	3.6	0.001
Fish at home	11.9	10.9	0.65	11.3	10.8	0.86	12.6	11.1	0.61
Reptiles at home	3.3	1.3	0.05	3.5	1.8	0.24	2.8	2.1	0.59
Tobacco exposure									
Smoking status			0.23			0.99			0.77
Never	59.9	67.0		62.6	61.4		62.0	64.3	
Quit before pregnancy	26.4	21.3		24.5	25.9		23.9	23.5	
Smoked in the first trimester	6.5	5.7		5.8	5.8		5.6	6.1	
Smoked during pregnancy	7.1	6.1		7.2	6.9		8.5	6.1	
Exposed to secondhand smoke	12.3	7.3	0.02	11.5	9.2	0.54	12.0	9.0	0.27
Antibiotic and nutritional exposures (maternal)									
Eggs	96.2	95.2	0.52	95.7	95.4	0.88	96.4	95.5	0.63
Dairy	99.1	99.0	0.92	100	98.8	0.20	100	98.9	0.21
Peanut butter/other nuts	94.2	94.8	0.71	92.8	95.2	0.29	94.3	94.5	0.90
Seeds	43.3	45.6	0.52	41.7	45.0	0.49	43.6	44.8	0.79
Tofu	18.4	20.2	0.54	18.0	19.6	0.67	17.9	19.7	0.61
Antibiotics	26.2	21.9	0.17	28.4	25.7	0.54	29.1	22.6	0.11
C-section	37.8	38.4	0.86	34.8	43.3	0.07	35.0	38.8	0.39

n is lower for atopy based on the available skin prick testing data.

allergic disease measures captured: 576 had skin prick testing, whereas 793 completed self-reported allergy measures (Table 4).

Rates of allergic disease and associated phenotypes noted in the FAMILY Study cohort were as follows: atopy 24.5%, food allergy 17.5%, cow's milk allergy 4.8%, eczema 16.0% and wheezing 18.6% (Table 4). Rates of allergy were comparable within each ethnic group.

Multivariate analyses of prenatal and postnatal exposures

Prenatal and postnatal environmental and dietary exposures, which were associated with allergic disease with $P < 0.10$ in the univariate analysis, were included in a multiple logistic regression (Table 5). Use of antibiotics in the child's 1st year [odds ratio (OR): 2.04, 95% confidence interval (CI): 1.45–2.88] had an effect in increasing the odds of allergic disease, whereas use of acetaminophen in the 1st year (OR: 0.68, 95% CI: 0.51–0.92) and prenatal maternal exposure to dogs at home (OR: 0.60, 95% CI: 0.42–0.84) were 'protective' against allergic disease. Early introduction to soymilk was not included in these analyses, as its use is likely directly related to possible allergy. Postnatal exposure to pet dogs was not included as it was strongly correlated to prenatal dog exposures at home. Combined exposure to smoking during pregnancy and prenatal period and secondhand smoke exposure did not show significance, which can partly be because of very small numbers exposed to smoking in this cohort.

Discussion

The natural history of the development of allergic diseases in childhood likely reflects a complex interplay between genetic factors and environmental exposures.[8] Despite advances in our understanding of immunological responses associated with many chronic inflammatory diseases, there is still uncertainty surrounding the timing and the precise identity of the specific environmental factors that impact the development of allergic disease in early life. The FAMILY birth cohort provides an opportunity to study early-life, including *in utero*, exposures on the development of atopy and allergic disease in a general

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Table 3. *Proportion of children with postnatal exposures by allergic outcomes in the 1st year*

	Allergic disease			Atopy			Food allergy		
Exposures	Yes (%)	No (%)	*P*-value	Yes (%)	No (%)	*P*-value	Yes (%)	No (%)	*P*-value
n	360	458		141	435		143	675	
Pet exposures									
Lives on farm	3.4	3.4	0.98	4.4	3.8	0.75	3.6	3.4	0.91
Exposed to farm animals	3.1	4.8	0.23	2.2	5.0	0.16	2.1	4.5	0.21
Cats at home	34.7	37.2	0.47	32.6	37.6	0.29	35.7	36.2	0.91
Dogs at home	29.5	38.4	0.009	32.1	37.0	0.30	30.4	35.3	0.27
Birds at home	2.5	1.5	0.32	2.8	2.3	0.72	4.2	1.5	0.03
Rodents at home	3.1	2.6	0.72	2.8	2.3	0.72	2.8	2.8	0.99
Fish at home	11.4	9.2	0.31	11.3	10.1	0.68	14.0	9.3	0.10
Reptiles at home	1.7	1.1	0.48	2.8	0.7	0.04	1.4	1.3	0.95
Child medication use									
Antibiotics	45.3	26.6	<0.0001	44.7	32.6	0.01	43.4	33.0	0.02
Acetaminophen	39.7	47.4	0.03	36.9	47.6	0.03	43.4	44.1	0.86
Nonsteroidal anti-inflammatory drugs	21.4	17.9	0.21	20.6	20.0	0.88	18.9	19.6	0.85
Vaccinated	98.0	96.8	0.30	97.0	97.6	0.71	96.4	97.5	0.45
Breastfeeding exposure									
Breastfed up to 17 weeks	35.3	45.5	0.004	35.0	39.2	0.38	42.4	40.8	0.71
Breastfed up to 26 weeks	23.9	30.5	0.04	24.8	26.1	0.76	30.9	26.9	0.33
Nutritional exposure (child)									
Cow milk/formula before 6 months	43.9	37.3	0.06	39.6	36.9	0.59	40.3	40.2	0.99
Goat milk before 6 months	0.0	0.0	0.61	0.0	0.0	0.61	0.0	0.0	0.61
Hydrolyzed formula/milk before 6 months	30.9	28.3	0.43	32.1	35.5	0.47	33.8	28.5	0.21
Soy formula/milk before 6 months	10.2	4.3	0.001	12.7	6.5	0.02	14.4	5.4	0.0002
Peanuts/butter before 9 months	1.4	2.7	0.21	3.0	1.7	0.34	1.4	2.3	0.53
Egg before 9 months	12.2	10.7	0.51	6.0	12.7	0.03	12.2	11.2	0.72
Introduction to solid food			0.20			0.42			0.99
<4 months	10.5	7.3		8.2	8.2		8.6	8.7	
4–6 months	49.9	48.9		53.0	46.8		48.9	49.4	
>6 months	39.7	43.9		38.8	45.1		42.4	41.9	
Tobacco exposure									
Mother is current smoker	10.7	8.2	0.23	10.4	9.6	0.79	10.7	9.0	0.54
Exposed to secondhand smoke	4.5	2.2	0.08	4.5	2.9	0.37	2.9	3.3	0.82

population rather than a high-risk cohort of atopy. We identified a number of exposures that were positively or negatively associated with allergy. Although some of the major findings of this study were consistent with findings from other birth cohorts (e.g. dog exposures), others such as negative associations with postnatal acetaminophen were unexpected.

Relative to the general Canadian population,[9] where self-reported food allergy is 7%, eczema is 17% and asthma in children is 13%, the children of the FAMILY Study cohort overall had high prevalence rates of allergic diseases and associated phenotypes: atopy 24.5%, food allergy 17.5%, cow's milk allergy 4.8%, eczema 16.0% and wheezing 18.6% (Table 4). The higher prevalence of food allergy in part can be due to the inclusive definition used for food allergy in our study.

The protective association between early-life exposure to dogs and development of allergic disease has been studied extensively. We have likewise found a protective effect of exposure to dog during pregnancy and the 1st year of life on the development of allergic disease. Pelucchi *et al.*[10] reviewed data on the relationship between pet exposure and occurrence of atopic dermatitis (AD). The authors found that children with regular contact with pets had a 25% reduced risk of AD. Interestingly, this finding was specific to dog, as opposed to cat, exposure. The protective factor associated with dog exposure in the prenatal and postnatal periods is still relatively unknown, but may be related to the effects of contact with dog-associated microbial agents during the 1st few years of life. In support of the 'hygiene hypothesis,' regular contact with animals, and thus increased exposure to microbial products, including endotoxins, in pregnancy or during early life, has been linked to reduce atopic sensitization and allergic disease,[10] presumably through modulation of infant immune responses[11] or alterations in the gut microbiome.[12]

We found a negative association between atopy and predominantly breastfeeding up to 17 weeks on multivariate analysis. There are several studies showing a protective effect of

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breastfeeding in the first 4–6 months of life for the development of asthma, eczema and cow's milk allergy. Kramer *et al.*[13] found a reduction in risk of Atopic Dermatitis (AD) with exclusive breastfeeding by age 3 months but did not find any clear reduction in asthma, allergic rhinitis, positive skin prick testing and food allergy.

Exposure to antibiotics during the 1st year of life was associated with the development of atopy and allergic disease. This effect has been seen in multiple other studies. Marie-Josée *et al.*[14] and Ong *et al.*[15] found an increased risk of asthma in children with antibiotic use during the first 6 months of life. Tsakok *et al.*[16] showed increased risk of eczema with exposure to antibiotics in the 1st year of life. These findings are consistent with our multivariate analyses. Recent reports have confirmed previously documented associations of antibiotic use by newborns with altered infant microbiota profiles, including long-term reduction in microbiota diversity.[17] Furthermore, antibiotic use during infancy is associated with increased risk for atopic disease later in childhood.[18] Shreiner *et al.*[19] explains this phenomenon as the 'microflora hypothesis,' in which the antibiotic-induced changes to microbiota resulted in increased susceptibility to T Helper Cells 2 (Th2) cytokine-specific responses. This has public health and policy implications, given that Persaud *et al.*[20] as part of the Canadian Healthy Infant Longitudinal Development (CHILD) Study found that neonates in Canada are routinely exposed to antibiotics in the perinatal period. In a further analysis of the CHILD study, Arrieta *et al.*[21] showed the association between gut microbiota and development of asthma. Nonetheless, caution should be exercised in interpreting our findings, as the influence of early-life antibiotic use on development of allergic disease could at least partially be explained by early respiratory infections themselves, a potential cause of asthma, and thus the requirement for increased antimicrobial medications.[22] We do not

Table 4. *Allergic outcomes in children*

	Children (n = 825)
Singletons (%)	90.2
Male children (%)	50.9
Female children (%)	49.1
Gestational age at birth [mean weeks (S.D.)]	38.9 (2.1)
Age at year 1 visit [mean months (S.D.)]	13.0 (1.6)
Allergic outcomes at year 1 visit	
Allergic disease (overall) (n = 818)	44.0%
Food allergy (n = 818)	17.5%
Cow's milk	4.8%
Soy protein	1.1%
Egg	1.5%
Other	5.1%
Atopy	16.3%
Environmental allergy (n = 793)	31.5%
Wheezing	18.6%
Asthma	2.5%
Eczema	16.0%
Rhinitis	0.1%
Atopy (n = 576)	24.5%
Food	16.3%
Pollen	3.3%
Animal	9.4%

n = 825 represents the number of children (which included twin pregnancies accounting for the difference in numbers).

Table 5. *Predictors of allergic disease* (n = *642)*

	Full model[a]			Reduced model[b]		
Exposures	Standardized estimate	P-value	Odds ratio (95% CI)	Standardized estimate	P-value	Odds ratio (95% CI)
Prenatal exposures						
Maternal allergy history	0.042	0.37	1.19 (0.82–1.74)	–		
Paternal allergy history	0.043	0.36	1.18 (0.83–1.67)	–		
Dogs at home	−0.139	0.003	0.60 (0.42–0.84)	−0.103	0.01	0.68 (0.50–0.92)
Rodents at home	0.090	0.06	2.37 (0.99–6.11)	0.089	0.03	2.24 (1.07–4.86)
Reptiles at home	0.057	0.24	2.15 (0.63–8.47)	–		
Maternal exposure to secondhand smoke	0.051	0.30	1.41 (0.74–2.70)	0.087	0.04	1.74 (1.04–2.94)
Postnatal exposures of child						
Use of antibiotics in the 1st year	0.189	<0.0001	2.04 (1.45–2.88)	0.202	<0.0001	2.15 (1.59–2.93)
Use of acetaminophen in the 1st year	−0.132	0.004	0.62 (0.44–0.86)	−0.104	0.01	0.68 (0.51–0.92)
Breastfed up to 17 weeks	−0.054	0.29	0.82 (0.56–1.19)	−0.101	0.02	0.69 (0.51–0.93)
Cow's milk before 6 months of age	0.070	0.17	1.30 (0.90–1.88)	–		
Exposed to secondhand smoke	0.067	0.20	2.09 (0.70–7.12)	–		

CI, confidence interval.

[a]Multiple logistic regression model (n = 642), including all exposures that were significant with a $P < 0.10$ in univariate models.

[b]Multiple logistic regression model (n = 787) keeping exposures significant with a $P < 0.05$ using backwards selection methods.

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have data on respiratory infections in FAMILY, and therefore cannot exclude this possibility.

Secondhand tobacco smoke exposure during pregnancy, but not direct maternal smoking, was found to be significantly associated with the development of allergic disease ($P = 0.0180$). The role of smoking, both direct and secondhand, in the development of allergic disease is well established.[23–25] A recent study by Simons *et al.*[26] demonstrated that children whose mothers smoked or were exposed to secondhand smoke at home during pregnancy were more likely to develop asthma. These studies reinforce the concept that the development of allergic disease is not entirely dependent on maternally derived tobacco smoke, and secondary sources of smoke exposure are perhaps equally important. In our study, the lack of statistical significance for the association between maternal smoking and allergy may be explained by insufficient numbers of subjects to achieve significance, as only a small number of mothers smoked during pregnancy (7%) and only a small number of babies (4.7%) were exposed to secondhand smoke.

Exposure to acetaminophen was found to have an inverse association with allergic disease and atopy in our study. The relationship of acetaminophen use has been studied previously in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort,[27] with opposing results to ours. Studies have demonstrated increased risk of infant wheezing with acetaminophen use in early[28] and late[27] pregnancy, and increased incidence of asthma and atopy upon exposure to acetaminophen during the 1st year of life.[29,30] In contrast, our study showed a negative association between atopy/allergy development and acetaminophen use in the 1st year. A possible explanation for this discrepancy is that these other studies evaluated allergic disease in children at ages 2–6[30] and 5–7 years,[29] whereas our study looked at the same parameter in 1-year-old children. Our findings suggest a temporal relationship underpinning the association of acetaminophen use with atopy and allergic disease, with a changing gradient from infancy through school age. Of course it is difficult to separate the possible role of infections, which may cause fever and trigger the use of acetaminophen in the 1st year of life.[31]

Although birth cohorts provide a unique opportunity to examine factors that may alter the development of atopy, there are limitations that must be considered. Clearly, these studies are not interventions; and observed associations do not necessarily imply causation. Reverse causation is a possibility that needs to be considered. For example, mothers may change an infant's diet or remove pets from the home if signs of atopy in the infant are noted. Although our primary end point of atopy was objective, the number and specific types of allergens tested were arbitrary. We included food allergy and allergic disease as end points. These included skin test positivity but also relied on questionnaire data for the development of eczema, asthma, allergic rhinitis or food allergy; we did not independently (i.e. by physical examination) assess for these conditions. Finally, although the associations we have found may be important for the development of atopic disease in the 1st year of life, they may not continue to be important factors at subsequent ages. As such, it would be important to further investigate the development of allergic disease in FAMILY Study children to ages 3 and 5 years to determine whether these associations remain or are altered.

Conclusions

The FAMILY Study cohort demonstrated high rates of atopy and allergic disease at 1 year of age relative to the general Canadian population. Some previously reported exposures, such as exposure to dogs in the prenatal period and exposure to antibiotics were demonstrated in our study to be significantly associated with atopy and allergic disease. Novel factors such as postnatal infant use of acetaminophen were negatively associated with our targeted outcomes.

Further research is needed to understand the role of these associations in the development of atopy and allergic disease.

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Conflicts of Interest

None.

Ethical Standards

The study was approved by the Research Ethics Boards at the participating hospitals (Hamilton Health Sciences, St Joseph's Hospital, Hamilton and Joseph Brant Memorial Hospital, Burlington, ON).

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