

Prenatal and early-life exposure to indoor air-polluting factors and allergic sensitization at 2 years of age



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ABSTRACT

Background: Previous studies have suggested that exposures to indoor air-polluting factors during pregnancy and early life can influence childhood allergy development. These exposures have been investigated in singularity; however, the effect of simultaneous exposure to multiple factors remains unclear.

Objective: To evaluate the effect of prenatal and early-life exposure to 7 air-polluting factors on allergic sensitization at 2 years of age.

Methods: Mother-child pairs (n = 108) enrolled in the Kingston Allergy Birth Cohort were followed up from birth to 2 years of age. Exposure to air fresheners, candles, mold, cats, dogs, carpet, and environmental tobacco smoke (ETS) during the prenatal, 6-month, 1-year, and 2-year time points were obtained. A skin prick test (SPT) was performed on both the mother and the 2-year-old child.

Results: Exposure to candles during the prenatal window, cats during the 6-month window, and ETS at 2 years significantly increased the odds ratio (OR) of a positive SPT result (candles: OR, 5.096; 95% CI, 1.69–13.86; *P* = .006; cat: OR, 4.267; 95% CI, 1.096–15.68; *P* = .048; and ETS: OR, 3.78; 95% CI, 1.189–11.18; *P* = .04). Children with a positive SPT result had significantly more exposures than SPT-negative children (prenatal *P* = .005, 1-year *P* = .03, and 2-year *P* = .008). As the total number of exposures increased, the percentage of SPT-positive children increased (prenatal *P* = .005, 1-year *P* = .03, and 2-year *P* = .01).

Conclusion: We have provided evidence supporting the role of the indoor environment on atopic disease development. The combined effect of multiple exposures may be more influential to allergy development than a single exposure.

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Introduction

Atopic diseases, such as allergic rhinitis and asthma, have increased in prevalence during the past several decades.¹ The reason for this increase cannot be explained by genetics alone, and the environment during pregnancy and early life has been

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speculated to play a role.^{2,3} The role of indoor air pollutants on allergic disease progression has recently become a focus of research because of links between exposure to these compounds and an increased risk of allergic or respiratory outcomes.^{4–6} For example, postnatal second-hand environmental tobacco smoke (ETS) exposure during infancy was associated with an elevated risk of rhinitis, asthma, and eczema in children and teens.⁷ In addition, exposure to furry pets, such as cats and dogs, has been implicated in atopic disease development in that both cat and dog exposure has been shown to reduce the risk of asthma diagnosis.^{8,9} This observation is not conclusive because conflicting findings have been reported in the literature, with both dog and cat exposure reportedly increasing the risk of allergic sensitization in childhood.¹⁰ Moreover, dust mite exposure during early life and its implication on allergy and asthma development have been examined, and children with allergic sensitizations have significantly more dust mite exposure in the first 3 years of life compared with those without sensitizations.¹¹

Table 1
SPT Outcomes

Group	No. of study participants	
	SPT negative	SPT positive
Mother (n = 60)	24	36
Child (n = 108)	88	20
Male (n = 57)	49	8
Female (n = 51)	39	12

Abbreviation: SPT, skin prick test

Given the increase in the mean amount of time spent indoors, there is an increased risk of adverse health outcomes related to long-term low-level exposure to indoor air pollutants.¹² In addition, children have higher ventilation rates than adults and primarily breathe through the mouth. These differences could allow for air pollutants to penetrate deeper into the lungs and at higher concentrations; making children more vulnerable to air-polluting factors.¹³

Although several of these environmental exposures have been studied in relation to their role in atopic disease development, the effect of simultaneous exposure to multiple air pollutants has not been extensively evaluated. We have established the Kingston Allergy Birth Cohort (KABC) to study some of these environment-disease interactions.⁴ Thus, the aim of this project was to assess the role of prenatal and early-life exposure to indoor air-polluting factors on allergic sensitization at 2 years of age in a subset of the KABC. We hypothesized that exposure to these factors would increase the odds ratio (OR) of a positive skin prick test (SPT) result at 2 years of age and that children with a positive SPT result would have more of these exposures than children with a negative SPT result.

Methods

Cohort Design

The KABC is a prospective birth cohort that received ethical clearance from the Queen's University Health Sciences Research Ethics Board and was established in 2011. Healthy pregnant women 18 years or older in the second or third trimester of their pregnancy were recruited into the study via posters in Kingston Health Sciences Centre–Kingston General Hospital site. If participants responded positively to a query regarding the KABC from a health care professional, they completed an informed consent session with a study coordinator. After written informed consent was obtained but before delivery, mothers completed a prenatal survey, which captured information on the maternal home environment during pregnancy.

Participants and Exposure Assessment

A subset of 92 women (108 mother-child pairs) from the KABC were included in this analysis and completed a prenatal survey that

captured information about their home environment during pregnancy. These women completed additional surveys when their child was 6 months (n = 76), 1 year (n = 72), and 2 years (n = 81) of age. Prenatal and postnatal exposure to dogs, cats, mold, carpet, air fresheners, candles and incense, and ETS was captured for each time point. If the mother reported any of these exposures for herself during pregnancy or her child at the 6-month, 1-year, or 2-year time points, the child was classified as exposed. Self-report of maternal and paternal allergic disease as well as number of siblings was obtained; however, this information was not incorporated in this analysis.

Skin Prick Testing

At 2 years of age, children returned to the research site for SPTs. The SPT was completed by a trained physician or nurse. A panel of 14 common food and environmental allergens were included in the SPT panel, in addition to a positive control (histamine) and a negative control (glycerinated phenol-saline). The allergens tested on the panel were as follows: dog hair, ragweed mix, cat pelt, grass mix, dust mite mix, mold mix, tree mix, peanut, soy, tree nut mix, sesame, cow's milk, wheat, and egg white. The SPT results were read 15 minutes after application, and a positive SPT result was defined as a wheal size 3 mm larger than the negative control.

Maternal allergic status was confirmed for 60 mothers via a SPT 6 or more months after the delivery of their child. The panel of allergens for the mother's SPT included the positive (histamine) and negative (glycerinated phenol-saline) controls in addition to the following environmental allergens: ragweed (short), *Derma-topogoides pteronyssinus*, *Dermatophagoides farinae* (dust mite species), cat pelt, dog hair, grass mix, tree mix, Russian thistle, and *Alternaria* mold. The SPT was performed as outlined for the child's SPT.

Statistical Analysis

Baptista-Pike and Fisher exact tests were used to determine the ORs associated with each exposure and any positive SPT result at 2 years of age. Mann-Whitney tests and χ^2 tests for trend were conducted to assess the associations between the number of different exposures with any SPT-positive result and the effect of multiple exposures at each time point on positive SPT outcomes. All statistical analyses were conducted using GraphPad Prism 8.0 (GraphPad Software Inc). No corrections for multiple comparisons were made because of sample size limitations.

Results

Participant Demographics

At the 2-year time point, 88 and 20 children had a negative and positive SPT result, respectively. Of the mothers who completed a SPT, 24 had a negative SPT result and 36 had a positive SPT result

Table 2
Characteristics of Prenatal and Postnatal Exposure to Indoor Air Pollutants

Exposure	No. (%) of study participants							
	Prenatal (n = 92)		6 Months (n = 76)		1 Year (n = 72)		2 Years (n = 81)	
	Yes	No	Yes	No	Yes	No	Yes	No
Dogs	32 (35)	60 (65)	30 (39)	46 (61)	29 (40)	43 (60)	29 (36)	52 (64)
Cats	43 (47)	49 (53)	33 (43)	43 (57)	32 (44)	40 (56)	30 (37)	51 (63)
Air fresheners	38 (41)	54 (59)	19 (25)	57 (75)	22 (31)	50 (69)	27 (33)	54 (67)
Candles	38 (41)	54 (59)	16 (21)	60 (79)	18 (25)	54 (75)	25 (31)	56 (69)
Mold	27 (29)	65 (71)	23 (30)	53 (70)	17 (24)	55 (76)	18 (22)	63 (78)
ETS	16 (17)	76 (83)	11 (14)	65 (86)	12 (17)	60 (83)	17 (21)	64 (79)
Carpet	58 (63)	34 (37)	33 (43)	43 (57)	29 (40)	43 (60)	36 (44)	45 (56)

Abbreviation: ETS, environmental tobacco smoke

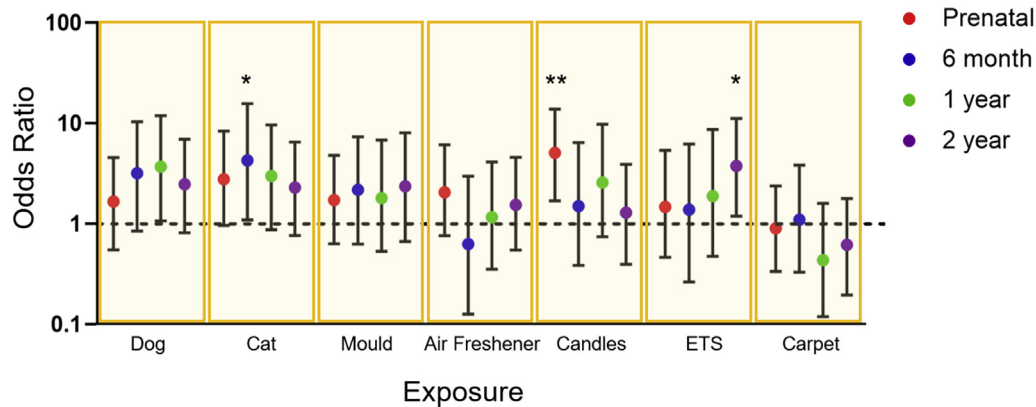


Figure 1. Odds ratio of a positive skin prick test result at 2 years of age with prenatal (n = 92), 6-month (n = 76), 1-year (n = 72), and 2-year (n = 81) exposure to indoor air pollution. * $P \leq .05$, ** $P \leq .01$. ETS, environmental tobacco smoke.

(OR, 0.76; 95% CI, 0.22–2.68; $P = .74$). Demographics of the participants and percentages of parental report for each exposure are summarized in Table 1 and Table 2. Of the 108 children who completed SPTs, 57 were male and 51 were female. Sex of the child did not significantly alter the OR of a positive SPT result (female: OR, 1.88; 95% CI, 0.70–5.06; $P = .22$).

Increased Odds of a Positive SPT Result at 2 Years With Exposure to Cats, Candles, and ETS

To assess the association between a positive SPT result at 2 years of age with prenatal and postnatal exposure to dogs, cats, air fresheners, candles, mold, ETS, and carpet, the ORs of a positive SPT at 2 years was calculated for each exposure at each time point using Fisher exact tests (Fig 1 and Table 3). Exposure to cats during the 6-month period, candles during the prenatal window, and ETS at 2 years of age significantly increased this OR (cat: OR, 4.267; 95% CI, 1.096–15.68; $P = .048$; candles: OR, 5.096; 95% CI, 1.697–13.86; $P = .006$; ETS: OR, 3.78; 95% CI, 1.189–11.18; $P = .04$). There were no statistically significant differences in the ORs of the remaining exposures for each time point.

Comparison of Prenatal and Early-Life Exposures in Children With Positive vs Negative SPT Results

To identify whether children with positive SPT results have a higher number of different exposures than children with negative SPT results at 2 years, the total number of exposures (dogs, cats, mold, air fresheners, candles, ETS, or carpet) for each child at each time point was determined and compared using Mann-Whitney tests (Fig 2). Prenatal exposure data were obtained for all participants included in this analysis (n = 92, SPT-negative n = 74, SPT-positive n = 18). The SPT-positive children had a higher total number of different exposures during the prenatal period compared with the SPT-negative children, with median exposure

numbers of 4 and 2, respectively ($P = .005$). Exposure data at the 6-month time point included fewer participants (n = 76, SPT-negative n = 65, SPT-positive n = 11); however, a similar trend of more exposures at this time point for SPT-positive children compared with SPT-negative children was observed, with median total exposure numbers of 3 and 2, respectively ($P = .06$). At the 1-year (n = 72, SPT-negative n = 60, SPT-positive n = 12) and 2-year (n = 81, SPT-negative n = 64, SPT-positive n = 17) time points, SPT-negative children had fewer total exposures than SPT-positive children, with a SPT-negative median exposure value of 2 and a SPT-positive median exposure value of 3 (1-year $P = .03$ and 2-year $P = .008$).

Comparison of the Total Number of Different Exposures in SPT-Positive vs SPT-Negative Children

Because it is rare for a child to be exposed to only 1 potentially negative exposure, we assessed the association between multiple exposures and SPT outcomes at 2 years of age. Children were grouped based on their number of different exposures, and the percentages of SPT-positive and SPT-negative children in each group were measured at each time point (Fig 3 and Table 4). The χ^2 tests for trend were completed at each time point. A positive trend between number of exposures and positive SPT results was observed for all time points. This trend was statistically significant for exposures at the prenatal ($P = .005$), 1-year ($P = .03$), and 2-year ($P = .01$) time points but not significant at the 6-month time point ($P = .07$).

Discussion

In this study, we evaluated the association of prenatal and early-life exposure with common indoor air pollutants on allergic sensitization at 2 years of age. We examined exposure to dogs, cats, air fresheners, candles, mold, ETS, and carpet, all of which have

Table 3
ORs of Positive SPT Results at 2 Years of Age

Exposure	Prenatal		6 Months		1 Year		2 Years	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Dog	1.67 (0.55–4.55)	.41	3.2 (0.86–10.41)	.10	3.72 (1.07–11.9)	.06	2.475 (0.81–6.9)	.15
Cat	2.77 (0.96–8.41)	.07	4.27 (1.096–15.7)	.048	3.00 (0.87–9.61)	.12	2.30 (0.76–6.52)	.15
Air freshener	2.05 (0.78–6.12)	.19	0.63 (0.13–2.97)	.72	1.167 (1.1–11.9)	>.99	1.54 (0.55–4.6)	.56
Candle	5.09 (1.7–13.9)	.006	1.5 (0.39–6.4)	.69	2.58 (0.74–9.8)	.16	1.292 (0.39–3.9)	.77
Mold	1.72 (0.63–4.8)	.39	2.18 (0.62–7.35)	.29	1.81 (0.53–6.82)	.46	2.36 (0.67–8.08)	.19
ETS	1.48 (0.46–5.38)	.51	1.38 (0.26–6.2)	.66	1.89 (0.47–8.7)	.41	3.78 (1.19–11.2)	.04
Carpet	0.902 (0.34–2.4)	>.99	1.1 (0.33–3.84)	>.99	0.43 (0.12–1.6)	.34	0.618 (0.2–1.8)	.43

Abbreviations: ETS, environmental tobacco smoke; OR, odds ratio; SPT, skin prick test.

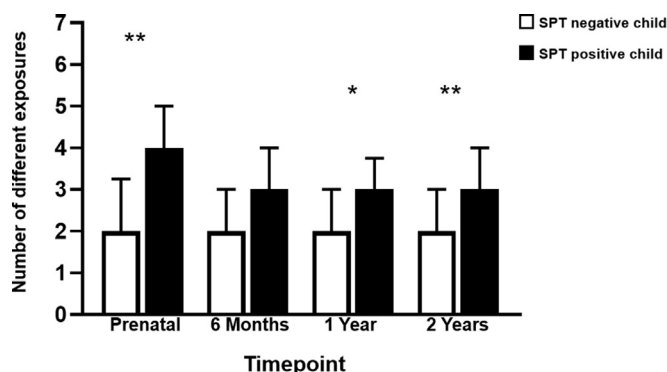


Figure 2. The total number of different exposures (0 to 7 of cat, dog, mold, air fresheners, candles, environmental tobacco smoke, and carpet) at the prenatal (skin prick test [SPT]–negative $n = 74$, SPT-positive $n = 18$), 6-month (SPT-negative $n = 65$, SPT-positive $n = 11$), 1-year (SPT-negative $n = 65$, SPT-positive $n = 11$), and 2-year (SPT-negative $n = 64$, SPT-positive $n = 17$) time points were determined and compared between SPT-negative and SPT-positive children. * $P \leq .05$, ** $P \leq .01$.

been associated with childhood allergies and atopy.^{4,14–16} Of the exposures we measured, prenatal exposure to candles, 6-month exposure to cats, and 2-year exposure to ETS significantly increased the OR of a positive SPT result at 2 years of age.

Exposure to furry pets, such as cats and dogs, during the prenatal and early-life windows have been previously investigated through epidemiologic models. Several findings suggest dog exposure in the first years of life decreases the risk of allergic sensitization, atopic dermatitis, and wheeze in childhood.¹⁷ It has been proposed that this observation is a result of an increase in the diversity in the house microbiome.⁸ This diversity has been associated with dogs but not with cats.¹⁸ In addition, cat exposure in early life reduces the risk of childhood asthma and atopic dermatitis⁹ but in a manner that proposes that very low levels or very high levels of cat exposure provides the greatest protection from allergic sensitization.¹⁹ Our findings suggest an increased risk of

allergic outcomes with cat exposure, which may be attributable to differences in age of the children included in this analysis because these children are 2 years old and could potentially grow out of their sensitizations. In addition, it is possible the cat exposure levels of the children in our cohort are in the middle of the exposure range, an area that could potentially confer the greatest risk.¹⁹ Lastly, it is important to consider that findings that suggest pet exposure is protective could be a result of bias because families without pets may not have pets because of family members with preexisting animal allergies.

Air freshener and candle exposure are of great interest regarding their association with childhood allergy and asthma. These compounds contain phthalates, which on their own have been associated with allergic and respiratory disease in children.²⁰ In previous work with the KABC, we have established that indoor air freshener exposure is associated with respiratory symptoms at 2 years of age.⁴ Our findings from this current study provide additional evidence to support the effect of these compounds on allergic sensitization.

ETS exposure increased the OR of a positive SPT result at 2 years. This finding has been continuously reported in the literature, with studies indicating that smoking during pregnancy and exposure to second-hand smoke in early life are associated with an increased risk of childhood atopy.^{21,22}

In our analysis, carpet exposure neither increased nor decreased the OR of a positive SPT result at 2 years of age. Carpet is a major source of dust mites and in our analysis was used as a proxy for dust mite exposure. In an analysis of in-home allergen exposure and allergic sensitization, a positive association between dust mite exposure and the probability of sensitization was observed.²³ The lack of an association between carpet exposure and allergic outcomes at 2 years of age in our study may be attributable to our sampling method. We obtained carpet exposure via survey, which may not be the most accurate method; visiting the homes to determine the square footage of carpet or obtaining dust samples from the home would have provided more accurate exposure data.

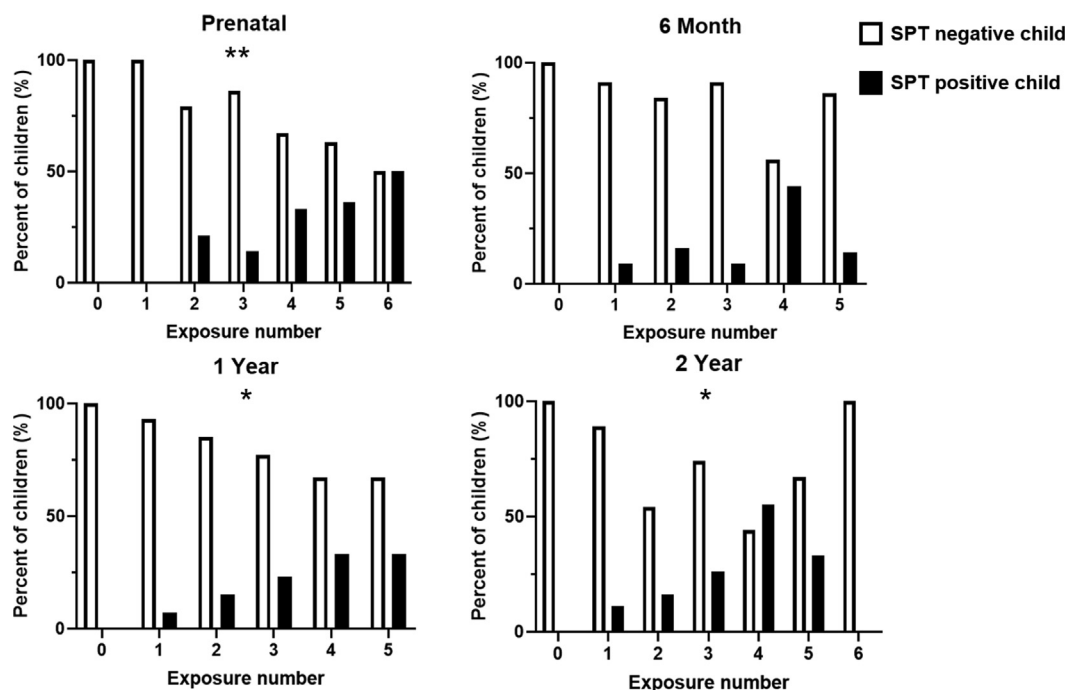


Figure 3. Children were grouped by the number of different exposures they had at each time point. The percentage of skin prick test (SPT)–positive and SPT-negative children in each exposure group is displayed, and a χ^2 test for trend was conducted. * $P \leq .05$, ** $P \leq .01$.

Table 4
Summary of Exposure Number and SPT Status for Each Time Point

No. of exposures	Prenatal (n = 92)		6 Months (n = 76)		1 Year (n = 72)		2 Years (n = 81)	
	SPT negative	SPT positive	SPT negative	SPT positive	SPT negative	SPT positive	SPT negative	SPT positive
0	5	0	7	0	7	0	6	0
1	14	0	21	2	13	1	16	2
2	19	5	16	3	17	3	21	4
3	18	3	10	1	17	5	14	5
4	10	5	5	4	4	2	4	5
5	7	4	6	1	2	1	2	1
6	1	1	0	0	0	0	1	0
7	0	0	0	0	0	0	0	0
Total	74	18	65	11	60	12	64	17

Abbreviation: SPT, skin prick test.

A secondary aim of this study was to evaluate the association of multiple exposures with allergic outcomes at 2 years of age. Children with a positive SPT result at 2 years of age had significantly more exposures prenatally, at the 1-year time point, and at the 2-year time point compared with children with a negative SPT result. Moreover, a dose-response trend was observed in that as the number of indoor air-polluting exposures increased, the percentage of children with a positive SPT result increased. When considered together, these findings suggest that the effect of multiple exposures may contribute more to allergy development than a single exposure. In the literature, ORs have been evaluated for several of the exposures we examined and are often adjusted for confounding exposures that can affect the OR. This modeling paints an accurate picture of the risk associated with one exposure; however, this does not depict everyday life because exposures rarely exist in singularity. We believe by considering the effect of simultaneous exposure to multiple factors on allergy outcomes, we can better portray real-life scenarios.

A major limitation of this work is our small sample size, which prevented any correction for multiple comparisons or confounding variables. In addition, each exposure at each time point was evaluated in a univariate approach. Assessing repeat exposures or the changing of exposure levels within children would have provided more information on how these exposures work in combination to influence atopic disease.

We have visited the homes of several children who participated in this 2-year follow-up visit, and we have obtained dust samples of their homes. Connecting these samples with home exposure data and the SPT outcomes at 2 years would enhance this study. This approach would also allow the confirmation of these exposures via concentrations of chemical and/or allergen in the dust samples. In addition, increasing our sample size for this study would enhance the OR analysis by allowing correction of multiple comparisons and confounding variables.

In conclusion, we report that findings from this study support the role of the environment in atopic disease progression and suggest that the cumulative effect of multiple exposures may have a greater influence on allergic disease outcomes than single exposures.

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References

- Thomsen SF. Epidemiology and natural history of atopic diseases. *Eur Clin Respir J*. 2015;2(1):24642.
- Jackson DJ, Gern JE, Lemanske RF. Lessons learned from birth cohort studies conducted in diverse environments. *J Allergy Clin Immunol*. 2017;139(2):379–386.
- Gallant MJ, Ellis AK. What can we learn about predictors of atopy from birth cohorts and cord blood biomarkers? *Ann Allergy, Asthma Immunol*. 2018;120(2):138–144.
- North ML, Brook JR, Lee EY, et al. The Kingston Allergy Birth Cohort: Exploring parentally reported respiratory outcomes through the lens of the exposome. *Ann Allergy, Asthma Immunol*. 2017;118(4):465–473.
- Ahn K. The role of air pollutants in atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(5):993–999.
- Sasso F, Izard M, Beneteau T, et al. 18-Year evolution of asthma and allergic diseases in French urban schoolchildren in relation to indoor air pollutant levels. *Respir Med*. 2019;148:31–36.
- Thacher JD, Gruzdeva O, Pershagen G, et al. Pre- and postnatal exposure to parental smoking and allergic disease through adolescence. *Pediatrics*. 2014;134:428–434.
- Fall T, Lundholm C, Örtqvist AK, et al. Early exposure to dogs and farm animals and the risk of childhood asthma. *JAMA Pediatr*. 2015;169(11):e153219.
- Gaffin JM, Spergel JM, Boguniewicz M, et al. Effect of cat and daycare exposures on the risk of asthma in children with atopic dermatitis. *Allergy Asthma Proc*. 2012;33(3):282.
- Pyrhönen K, Näyhä S, Läärä E. Dog and cat exposure and respective pet allergy in early childhood. *Pediatr Allergy Immunol*. 2015;26(3):247–255.
- Wahn U, Lau S, Bergmann R, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol*. 1997;99(6):763–769.
- Bernstein JA, Alexis N, Bacchus H, et al. The health effects of nonindustrial indoor air pollution. *J Allergy Clin Immunol*. 2008;121(3):585–591.
- Bateson TF, Schwartz J. Children's response to air pollutants. *J Toxicol Environ Heal Part A*. 2007;71(3):238–243.
- Svendsen ER, Gonzales M, Comodore A. The role of the indoor environment: Residential determinants of allergy, asthma and pulmonary function in children from a US-Mexico border community. *Sci Total Environ*. 2018;616:1513–1523.
- Schmitz R, Atzpodien K, Schlaud M. Prevalence and risk factors of atopic diseases in German children and adolescents. *Pediatr Allergy Immunol*. 2012;23(8):716–723.
- Herr CEW, Ghosh R, Dostal M, et al. Exposure to air pollution in critical prenatal time windows and IgE levels in newborns. *Pediatr Allergy Immunol*. 2011;22:75–84.
- Bufford JD, Reardon CL, Li Z, et al. Effects of dog ownership in early childhood on immune development and atopic diseases. *Clin Exp Allergy*. 2008;38(10):1635–1643.
- Dharmage SC, Lodge CL, Matheson MC, Campbell B, Lowe AJ. Exposure to cats: Update on risks for sensitization and allergic diseases. *Curr Allergy Asthma Rep*. 2012;12(5):413–423.
- Custovic A, Hallam CL, Simpson BM, Craven M, Simpson A, Woodcock A. Decreased prevalence of sensitization to cats with high exposure to cat allergen. *J Allergy Clin Immunol*. 2001;108(4):537–539.
- Wang LJ, Lin CC, Lin YJ, Hsieh WS, Chen PC. Early life phthalate exposure and atopic disorders in children: a prospective birth cohort study. *Environ Int*. 2014;62:48–54.
- Neuman A, Hohmann C, Orsini N, et al. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. *Am J Respir Crit Care Med*. 2012;186(10):1037–1043.
- Kantor R, Kim A, Thyssen JP, Silverberg JI. Association of atopic dermatitis with smoking: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2016;75(6):1119–1125.e1.
- Olmedo O, Goldstein IF, Acosta L, et al. Neighborhood differences in exposure and sensitization to cockroach, mouse, dust mite, cat, and dog allergens in New York City. *J Allergy Clin Immunol*. 2011;128(2):284–292.e7.