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

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Green Cross Pharmaceuticals, GlaxoSmithKline, Sanofi, Sun Pharma, Merck, Novartis and Pfizer.

Keywords: Birth cohort, prenatal exposures, postnatal exposures, indoor air pollution, allergic sensitization

Abbreviations: CI: Confidence Interval, ETS: Environmental tobacco smoke, KABC: Kingston Allergy Birth Cohort, KHSC-KGH: Kingston Health Sciences Centre – Kingston General Hospital, OR: Odds ratio, SPT: Skin prick test

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Tables: Four
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 We aimed 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 (KABC) were followed from birth to 2 years of age. Exposure to air fresheners, candles, mould, cats, dogs, carpet and environmental tobacco smoke (ETS) during the prenatal, 6 month, 1 year, and 2 year timepoints 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 (candles OR 5.096 1.69–13.86, p=0.006; cat OR 4.267 1.096–15.68, p=0.048; and ETS OR 3.78 1.189–11.18, p=0.04). Children with a positive SPT had significantly more exposures than SPT negative children (prenatal p=0.005, 1 year p=0.03, and 2 year p=0.008). As total number of exposures increased the percentage of SPT positive children increased (prenatal p=0.005, 1 year p=0.031, 2 year p=0.013).

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 one single exposure.
Introduction

Atopic diseases such as allergic rhinitis and asthma have increased in prevalence over the past several decades\textsuperscript{1}. The reason for this increase cannot be explained by genetics alone and it is speculated that the environment during pregnancy and early life could play a role\textsuperscript{2,3}.

The role of indoor air pollutants on allergic disease progression has recently become a focus of research due to links between exposure to these compounds and an increased risk of allergic or respiratory outcomes\textsuperscript{4-6}. For example, postnatal second-hand ETS exposure during infancy was associated with an elevated risk of rhinitis, asthma, and eczema in children and teens\textsuperscript{7}. Additionally, 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\textsuperscript{8,9}. This observation is not conclusive, as conflicting findings have been reported in the literature, where both dog and cat exposure increases the risk of allergic sensitization in childhood\textsuperscript{10}. Moreover, dust mite exposure during early life and its implication on allergy and asthma development has been examined and children with allergic sensitizations have significantly more dust mite exposure in the first 3 years of life compared to those without sensitizations\textsuperscript{11}.

Given the increase in the average amount of time spent indoors there is an increased risk of adverse health outcomes related to chronic low level exposure to indoor air pollutants\textsuperscript{12}. Additionally, 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\textsuperscript{13}.

While 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\textsuperscript{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 hypothesize exposure to these factors will increase the odds ratio (OR) of a positive skin prick test (SPT) at 2 years of age, and that children with a positive SPT will have more of these exposures than children with a negative SPT.

**Methods**

**Cohort design**

The KABC is a prospective birth cohort that received ethical clearance from the Queen’s University Health Sciences Research Ethics Board (DMED-1161-08) 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 (KHSC-KGH). 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 prior to 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 capturing information on 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, mould, carpet, air fresheners, candles/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 timepoints, the child was classified as exposed. Self report of maternal and paternal allergic disease as well as number of siblings was obtained, however was not incorporated in this analysis.

**Skin prick testing**

At two years of age, children returned to the research site for skin prick testing. 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, mould mix, tree mix, peanut, soy, tree nut mix, sesame, cow’s milk, wheat, and egg white. The SPTs 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 skin pick testing 6 or more months following 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), *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, (dust mite species) cat pelt, dog hair, grass mix, tree mix, Russian thistle, and Alternaria mould. The SPT was performed as outlined for the child’s SPT.

**Statistical analysis**

Baptista-Pike and Fisher Exact tests were used to determine the odds ratios associated with each individual exposure and any positive SPT result at 2 years of age. Mann-Whitney tests and Chi Square tests for trend were conducted to assess the relationships 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. No corrections for multiple comparisons were made due to 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 that completed a SPT, 24 had a negative SPT result and 36 had a positive SPT result (OR 0.76 95% Confidence Interval (CI) 0.22 – 2.68, p = 0.74).

Demographics of the participants and percentages of parental report for each exposure is summarized in Table 1 and Table 2. Of the 108 children that completed skin pick testing, 57 were male and 51 were female. Sex of the child did not significantly alter the OR of a positive SPT (Female OR 1.88 95% CI 0.70 – 5.06, p = 0.22).

**Increased OR of a positive SPT at 2 years with exposure to cats, candles, and ETS**

To assess the relationship between a positive SPT at 2 years of age with prenatal and postnatal exposure to dogs, cats, air fresheners, candles, mould, ETS, and carpet, ORs of a positive SPT at 2 years was calculated for each exposure at each time point using Fisher’s exact tests (Figure 1, Table 3).

Exposure to cats during the 6 month time 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 = 0.048; candles OR 5.096, 95% CI 1.697 – 13.86, p = 0.006; ETS OR 3.78, 95% CI 1.189 – 11.18, p = 0.04). There were no statistically significant differences in the OR of the remaining exposures for each timepoint.
Children with a positive SPT have more exposures during the prenatal and early life timepoints than children with a negative SPT.

To identify if children with a positive SPT have a higher number of different exposures than children with a negative SPT at 2 years, the total number of exposures (dogs, cats, mould, air fresheners, candles, ETS, or carpet) for each child at each time point was determined and compared using Mann-Whitney tests. Prenatal exposure data was obtained for all participants included in this analysis (n = 92, SPT negative n = 74, SPT positive n = 18). SPT positive children had a higher total number of different exposures during the prenatal time period compared to SPT negative children, with median exposure numbers of 4 and 2 respectively (p = 0.0052). 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 to SPT negative children was observed with median total exposure numbers of 3 and 2 respectively (p = 0.064). 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 SPT negative median exposure values of 2 and SPT positive median exposure values of 3 (1 year p = 0.03 and 2 year p = 0.008).

As total number of different exposures increases the percentage of SPT positive children increases and the percent of SPT negative children decreases.

As it is rare for a child to be exposed to only one potentially negative exposure, we assessed the relationship 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 negative children in each group were measured at each time point.
4). Chi square tests for trend were completed at each timepoint. A positive trend between number of exposures and positive SPT result was observed for all timepoints. This trend was statistically significant for exposures at the prenatal (p = 0.005), 1 year (p = 0.031), and 2 year (p = 0.013) time points, and trending towards significance at the 6 month timepoint (p = 0.067).

Discussion

In this study we evaluated the impact of prenatal and early life exposure to common indoor air pollutants on allergic sensitization at 2 years of age. We examined exposure to dogs, cats, air fresheners, candles, mould, ETS, and carpet; all of which have been associated with childhood allergies and atopy. 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 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 epidemiological models. Several findings suggest dog exposure in the first years of life decreases the risk of allergic sensitization, atopic dermatitis, and wheeze in childhood. It has been proposed that this observation is a result of an increase in the diversity in the house microbiome. This diversity has been associated with dogs but not with cats. Additionally, cat exposure in early life has also been shown to reduce the risk of childhood asthma and atopic dermatitis; but in a manner that proposes either very low level or very high level of cat exposure provides the greatest protection from allergic sensitization. Our findings suggest an increased risk of allergic outcomes with cat exposure, which may be due to differences in age of the children included in this analysis; as these children are 2 years old and could potentially grow out of their sensitizations. Additionally, 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\textsuperscript{19}. Lastly, it is important to consider findings that suggest pet exposure are protective could be a result of bias; as families that do not have pets may do so because of family members with pre-existing animal allergies.

Air freshener and candle exposure are of great interest regarding their impact on childhood allergy and asthma. These compounds contain phthalates; which on their own have been associated with allergic and respiratory disease in children\textsuperscript{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\textsuperscript{4}. Our findings from this current study provides additional evidence to support the impact of these compounds on allergic sensitization.

ETS exposure increased the OR of a positive SPT at 2 years. This finding has been continuously reported in the literature as studies have indicated smoking during pregnancy and exposure to second hand smoke in early life is associated with an increased risk of childhood atopy\textsuperscript{21,22}.

In our analysis, carpet exposure neither increased nor deceased the OR of a positive SPT 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\textsuperscript{23}. The lack of an association between carpet exposure and allergic outcomes at 2 years of age in our study may be due 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.
A secondary aim of this study was to evaluate the effect of multiple exposures on allergic outcomes at 2 years of age. Children with a positive SPT at 2 years of age had significantly more exposures prenatally, at the 1 year, and at the 2 year time points compared to children with a negative SPT. 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 increased. When considered together these findings suggest that the effect of multiple exposures may contribute more to allergy development than one 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 impact the OR. This modeling paints an accurate picture of the risk associated with one exposure; however, this does not depict everyday life, as 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. This prevented any correction for multiple comparisons or confounding variables. Additionally, each exposure at each timepoint 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 that 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 would allow the confirmation of these exposures via concentrations of chemical and/or allergen in the dust samples. Additionally, 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.
Acknowledgements

Thank you to the CHILD study team for developing the environmental health surveys that were adapted for this study. Thank you to Dr. Michelle North, Mena Soliman, and Michelle Roddy for their assistance in data collection and performing the skin prick testing. Thank you to Jenny Thiele, Lisa Steacy, Erika Wall, Alesandra Castañón Martínez, and Carmen Li for their work in data verification and collection. Thank you to Wilma Hopman and Andrew Day for their guidance in the statistical analysis.


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Figure 1. ORs of a positive SPT at 2 years with prenatal (n=92, red), 6 months (n=76, blue), 1 year (n=72, green), and 2 year (n=81, purple), exposure to indoor air pollution *p ≤ 0.05, **p≤0.01.

Figure 2. The total number of different exposures (0 to 7 of cat, dog, mould, air fresheners, candles, ETS, and carpet) at the prenatal (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 ≤ 0.05, **p≤0.01.

Figure 3. Children were grouped by the number of different exposures they had at each time point. The percentage of SPT positive and SPT negative children in each exposure group is displayed and a Chi square test for trend was conducted, *p ≤ 0.05, **p≤0.01.
### Table 1. Skin prick test outcomes.

<table>
<thead>
<tr>
<th></th>
<th>SPT neg</th>
<th>SPT pos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mom (n=60)</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>Child (n=108)</td>
<td>88</td>
<td>20</td>
</tr>
<tr>
<td>Male (n=57)</td>
<td>49</td>
<td>8</td>
</tr>
<tr>
<td>Female (n=51)</td>
<td>39</td>
<td>12</td>
</tr>
</tbody>
</table>

Abbreviations: SPT, Skin prick test

### Table 2. Characteristics of prenatal and postnatal exposure to indoor air pollutants.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Prenatal (n=92)</th>
<th>6 Month (n=76)</th>
<th>1 Year (n=72)</th>
<th>2 Year (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (%)</td>
<td>No (%)</td>
<td>Yes (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td>Dogs</td>
<td>32 (35)</td>
<td>60 (65)</td>
<td>30 (39)</td>
<td>46 (61)</td>
</tr>
<tr>
<td>Cats</td>
<td>43 (47)</td>
<td>49 (53)</td>
<td>33 (43)</td>
<td>43 (57)</td>
</tr>
<tr>
<td>Air Fresheners</td>
<td>38 (41)</td>
<td>54 (59)</td>
<td>19 (25)</td>
<td>57 (75)</td>
</tr>
<tr>
<td>Candles</td>
<td>38 (41)</td>
<td>54 (59)</td>
<td>16 (21)</td>
<td>60 (79)</td>
</tr>
<tr>
<td>Mould</td>
<td>27 (29)</td>
<td>65 (71)</td>
<td>23 (30)</td>
<td>53 (70)</td>
</tr>
<tr>
<td>ETS</td>
<td>16 (17)</td>
<td>76 (83)</td>
<td>11 (14)</td>
<td>65 (86)</td>
</tr>
<tr>
<td>Carpet</td>
<td>58 (63)</td>
<td>34 (37)</td>
<td>33 (43)</td>
<td>43 (57)</td>
</tr>
</tbody>
</table>

Abbreviations: ETS, Environmental tobacco smoke

### Table 3. OR of positive SPT at 2 years

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Prenatal (OR 95 % CI)</th>
<th>p</th>
<th>6 Month (OR 95 % CI)</th>
<th>p</th>
<th>1 Year (OR 95 % CI)</th>
<th>p</th>
<th>2 Year (OR 95 % CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>1.67 (0.55-4.55)</td>
<td>0.410</td>
<td>3.2 (0.86-10.41)</td>
<td>0.100</td>
<td>3.72 (1.07-11.9)</td>
<td>0.055</td>
<td>2.475 (0.81-6.9)</td>
<td>0.152</td>
</tr>
<tr>
<td>Cat</td>
<td>2.77 (0.96-8.41)</td>
<td>0.069</td>
<td>4.27 (1.09-15.7)</td>
<td>0.048</td>
<td>3.00 (0.87-9.61)</td>
<td>0.117</td>
<td>2.30 (0.76-6.52)</td>
<td>0.150</td>
</tr>
<tr>
<td>Air Freshener</td>
<td>2.05 (0.78-6.12)</td>
<td>0.191</td>
<td>0.63 (0.13-2.97)</td>
<td>0.720</td>
<td>1.167 (1.1-11.9)</td>
<td>0.999</td>
<td>1.54 (0.55-4.6)</td>
<td>0.560</td>
</tr>
<tr>
<td>Candle</td>
<td>5.09 (1.7-13.9)</td>
<td>0.006</td>
<td>1.5 (0.39-6.4)</td>
<td>0.690</td>
<td>2.58 (0.74-9.8)</td>
<td>0.160</td>
<td>1.292 (0.39-3.9)</td>
<td>0.770</td>
</tr>
<tr>
<td>Mould</td>
<td>1.72 (0.63-4.8)</td>
<td>0.389</td>
<td>2.18 (0.62-7.35)</td>
<td>0.292</td>
<td>1.81 (0.53-6.82)</td>
<td>0.460</td>
<td>2.36 (0.67-8.08)</td>
<td>0.190</td>
</tr>
<tr>
<td>ETS</td>
<td>1.48 (0.46-5.38)</td>
<td>0.510</td>
<td>1.38 (0.26-6.2)</td>
<td>0.656</td>
<td>1.89 (0.47-8.7)</td>
<td>0.408</td>
<td>3.78 (1.19-11.2)</td>
<td>0.039</td>
</tr>
<tr>
<td>Carpet</td>
<td>0.902 (0.34-2.4)</td>
<td>0.999</td>
<td>1.1 (0.33-3.84)</td>
<td>0.999</td>
<td>0.43 (0.12-1.6)</td>
<td>0.340</td>
<td>0.618 (0.2-1.8)</td>
<td>0.430</td>
</tr>
</tbody>
</table>

Abbreviations: CI, Confidence interval; ETS, Environmental tobacco smoke; OR, Odds ratio; SPT, Skin prick test

### Table 4. Summary of exposure number and SPT status for each time point.

<table>
<thead>
<tr>
<th>Number of</th>
<th>Prenatal (n=92)</th>
<th>6 Month (n=76)</th>
<th>1 Year (n=72)</th>
<th>2 Year (n=81)</th>
</tr>
</thead>
</table>
### Overview

**Exposures**

<table>
<thead>
<tr>
<th>Exposures</th>
<th>SPT Negative</th>
<th>SPT Positive</th>
<th>SPT Negative</th>
<th>SPT Positive</th>
<th>SPT Negative</th>
<th>SPT Positive</th>
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<th>SPT Positive</th>
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<td>7</td>
<td>0</td>
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<td>0</td>
<td>6</td>
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<tr>
<td>1</td>
<td>14</td>
<td>0</td>
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<td>1</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
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<td>14</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
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<td><strong>18</strong></td>
<td><strong>65</strong></td>
<td><strong>11</strong></td>
<td><strong>60</strong></td>
<td><strong>12</strong></td>
<td><strong>64</strong></td>
<td><strong>17</strong></td>
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</table>

**Abbreviations:** SPT, Skin prick test
Figure 1.
Figure 2.
Figure 3.