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Indoor air pollution and respiratory health effects in inner city children with moderate to severe asthma

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Abstract

Indoor air pollution is increasingly recognized as a significant risk for respiratory illness, particularly in vulnerable populations. Thirty-six children aged 6–14 years with moderate/severe asthma from inner city areas in New York City were studied for 2-week periods (summer and winter) using diaries and spirometry. Seven-day integrated indoor samples of PM_{10}, $PM_{2.5}$, trace elements, elemental/organic carbon, black carbon, and criteria gases (NO_2, SO_2, and O_3) were collected in the subjects' residences. Asthma outcomes included cough and wheeze severity, albuterol use, and pulmonary function. Mixed effects regression models for longitudinal data were used to relate weekly indoor pollutant concentrations to asthma outcomes. Odds ratios (ORs) were calculated for ordinal outcomes. During winter, significant positive associations for average weekly symptom severity scores were seen for NO_2 (OR = 2.83; $p = 0.02$), calcium (OR = 3.29; $p = 0.02$), and silicon (OR = 3.64; $p = 0.04$). In summer, chlorine was associated with average weekly symptom scores (OR = 1.85; $p = 0.004$). Average albuterol puff use per day in winter was associated with NO_2 (OR = 5.89; $p = 0.009$), nickel (OR = 2.27; $p = 0.05$), and silicon (OR = 5.59; $p = 0.05$). Albuterol use was not associated with indoor pollutants in summer. Asthma severity was associated with specific indoor pollutants. Seasonal differences were observed by pollutant and by clinical index studied.

Keywords Children · Asthma · Indoor air pollution

Introduction

In the USA, asthma is the most important chronic disease in children and young adults, affecting over 5 million in ages 5 to 17 years (Wang et al. 2005). Asthmatic children are particularly susceptible to the airway effects of inhaled irritants as a result of their smaller lung volumes and unique features of their immune, endocrine, and nervous systems (Selgrade et al. 2006).

Outdoor air pollutants, notably fine particulate matter [$PM_{2.5}$] and criteria gases (ozone [O_3], nitrogen dioxide [NO_2], and sulfur dioxide [SO_2]), are well recognized as important contributors to exacerbations of asthma (Selgrade et al. 2006; Gielen et al. 1997; Iskandar et al. 2012; Larsen et al. 2002; Peters et al. 1997; Roy et al. 2011; Schachter et al. 2016; Vedal et al. 1998). Indoor air hazards, while recognized as a problem of major concern (Habre et al. 2014a), remain less well characterized. On average, children spend up to 20 h per day indoors (Franklin, 2007, Schwab et al. 1992). While infiltration of outdoor air pollution does significantly contribute to the indoor environment, our previous analysis in these inner-city data indicate that ~ 72% of $PM_{2.5}$ mass in these homes likely originated from indoor sources (Habre et al. 2014b). Of note, concentrations of indoor pollutants, like outdoor pollutants, are subject to seasonal variation and their effects may also vary from one season to another (Bielroy and Deener, 1998).

In prior analyses of this panel, we examined outdoor pollutants, and their associations with symptoms as well as possible sources of outdoor pollutants (Schachter et al.2016; Habre et al.

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2014a; Habre et al. 2014b; Rohr et al. 2014). In this study, we examine the associations of measured indoor pollutants and their seasonal variation on measures of asthma exacerbation in children with moderate to severe asthma living in inner city New York.

Subjects and methods

Overall study design

The study was performed during the summers and winters of 2008 and 2009. Each household was monitored for two 14-day periods, one in each season. Thirty-six children with moderate to severe asthma living in East Harlem and the South Bronx were recruited over this 2-year study period. These areas were selected because of high asthma prevalence (NYC Department of Health and mental Hygiene 2008). Details of the study design may be found in prior publications (Schachter et al. 2016; Habre et al. 2014a; Habre et al. 2014b; Rohr et al. 2014) and are briefly described here. Participants were recruited (day 1) from the Mount Sinai Hospital Emergency Department (ED) and Outpatient Asthma Clinics (OAC). Of the 43 subjects screened, 39 were eligible and 36 completed at least one season's data collection. Thirty-two subjects completed both seasons.

During each season, indoor air quality was monitored and health outcomes were assessed over 14 days for each subject. On day 7, homes were revisited, equipment and diaries were checked, and subjects re-instructed in proper data collection and spirometry maneuvers. Filters in indoor samplers were switched to allow for the second week's collection of monitoring data. On day 15, the monitoring equipment and the health outcome data were collected. For each subject beginning on day 1, parents and children recorded pulmonary function twice daily (AM and PM), as well as daily symptom scores and other outcome measures. Outdoor (central site) monitoring for a subset of pollutants started 7 days before the first subject was tested.

Subjects

Subject demographics are listed in Table 1.

Inclusion criteria

Children aged 6–14 years old with moderate to severe asthma living in the studied areas were recruited. Asthma was diagnosed based on the Guidelines for the Diagnosis and Management of Asthma NAEPP Expert Panel Report (2007). Daily use of controller medication for at least 3 months in the past year, use of a beta-agonist at least 4 times per month in any one of the past 3 months, or nocturnal awakenings twice a month in the past 3 months were required for eligibility. All children were determined to be using short acting beta agonists at least once daily at time of recruitment.

Table 1 Cohort demographics and baseline lung function parameters ($n = 36$)

		Mean (SD)
Age (years)		9.8 (2.9)
Race/ethnicity		
Hispanic		23 (65%)
Black		13 (35%)
Gender		
Male		24 (65%)
Female		12 (35%)
# of days with asthma symptoms in the past 14 days		4.2 (4.3)
Oral steroid use within 2 months prior to entry into study		10 (30%)
# of households using gas stove		36 (100%)
FEV1 (L)		1.73 (0.64)
FVC (L)		2.13 (0.85)
PEF (L/s)		3.70 (1.61)
FEF 25–75 (L/s)		1.78 (1.05)
% FEV_1 predicted		0.88 (0.19)
% FVC predicted		0.94 (0.14)
% PEF predicted		1.13 (0.32)
		Median [IQR]
Summer	Symptom score (daily)	1 [0–3]
	# albuterol puffs (daily)	2 [0–4]
Winter	Symptom score (daily)	2 [1–4]
	# albuterol puffs (daily)	2 [0–4]

Exclusion criteria

We excluded children with active disease other than asthma such as hematologic, endocrine, or cardiac conditions requiring daily medications; families planning to move from their current home within the next 6 months; and families that had members who smoked at home.

Baseline visit

A baseline visit was conducted at the hospital upon recruitment, during which the objectives and requirements were explained to the child's primary caretaker and the child. A Mount Sinai Institutional Review Board approved the informed consent form (IRB Project 05-0679) and a HIPAA form was read and signed by the parent.

A respiratory history and asthma questionnaire, based on an NIH questionnaire previously used in the Inner City Asthma Study (Kattan et al. 1997), was administered. A physical examination was performed by the study physicians.

In order to determine the allergic status of our subjects, skin prick testing was conducted with 12 standard antigens and 2 controls administered with Multi-Test equipment (Alk-Abello, Horsholm, Denmark) (see Table 2).

Three reproducible spirometric tests meeting American Thoracic Society criteria (Wanger et al. 2005) were administered using the ML 3500 spirometer (Micro Medical, Lewiston, ME). Baseline measurements in the clinic included forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and peak expiratory flow (PEF). Baseline measurements were performed at least 8 h after any bronchodilator treatment had been administered. Results were expressed as their value in L or L/s and as a percent of predicted based on predicted values obtained from NHANES III (children 8–14 years) and Wang et al. (for children less than 8 years) (Hankinson et al. 1999; Wang et al. 1993).

Morbidity assessment

A daily symptom diary (cough and wheeze) with each symptom graded on a scale of 0 to 3 (none = 0, mild = 1, moderate = 2, and severe = 3) as well as medication use (albuterol puffs per day) was recorded by parent and child. The questionnaires were reviewed at the weekly visit. Unscheduled clinic or ED visits and hospitalizations were also recorded. Daily total symptom scores were obtained by adding the severity scores of both cough and wheeze. In order to analyze these data as a function of weekly indoor pollutants, we expressed symptoms in three ways: average daily scores for a given week, the maximum daily score for a given week, and the number of days during a given week with symptom scores greater than 1.

Albuterol use was quantified in two ways: the average number of albuterol inhalations (puffs) per day in a given week and the number of days in a week when the number of albuterol puffs was greater than zero.

Average values for symptom scores and albuterol usage are shown in Table 1.

Pulmonary function

Two daily lung function measurements each consisting of up to six attempts, using a Piko 1 handheld spirometer (nSpire Health Inc. Longmont, CO), were conducted at the subject's home, with PEF and FEV_1 measured morning and evening. Three successful blows (as indicated by the Piko 1 handheld spirometer) were performed at each time point and data exhibiting greater than 5% variability at any time point were discarded. Data were downloaded directly from the spirometer. Percent daily lability in PEF was calculated by dividing the absolute value of the difference between AM and PM values by the AM value as follows: 100 × [(|AM-PM|)/AM].

Table 2 Allergic status of children in CAPAS study measured by skin testing

Children with 0, 1, 2, or more positive skin tests, *N* (%)	
0	6 (18%)
1	3 (9%)
2 or more	24 (73%)
Number of children with positive skin tests to mouse allergen: 6 (18%)	
Number of children with positive skin tests to cockroach allergen: 19 (56%)	

Air pollutant measurements

The indoor sampling apparatus was placed in participants' main living area and described in detail in Habre et al. (2014b). Briefly, a multi-pollutant sampler (MPS) was used to collect 7-day integrated $PM_{2.5}$ samples on 37 mm Teflon and quartz filters (Demokritou et al. 2001; Liu et al. 2003; Sarnat et al. 2005). Teflon filters were analyzed for $PM_{2.5}$ mass concentration gravimetrically using a Mettler microbalance, and for elemental concentrations using X-ray fluorescence (XRF) analysis (detection limits provided in Supplemental Table 4). Elemental and organic carbon was measured using thermal optical reflectance (TOR) on quartz filters and black carbon using optical reflectance analysis on teflon filters.

Weekly indoor ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) gases were collected with passive diffusion using Ogawa badges (https://ogawausa.com/product-category/passive-sampler/) and analyzed using ion chromatography.

Daily outdoor O_3 concentrations were obtained from Middle School 302 (MS302) New York State Department of Environmental Conservation ambient monitoring site in the South Bronx and used to calculate weekly averages corresponding to each participant's home visit.

Data analysis

For symptoms and albuterol use data (ordinal outcomes), odds ratios (ORs) were calculated by employing regression models for longitudinal data using a cumulative logit link function to relate weekly indoor pollutant concentrations to health outcomes in that week. These models were run separately for summer and winter. The analysis was conducted in SAS using the GLIMMIX procedure which allows for the analysis of data sets with missing values. The average percentage of missing symptom data in winter was 5% and in summer 2%.

We analyzed pulmonary function (AM) FEV_1 and peak flow lability index treating pulmonary function outcomes as continuous variables in a linear mixed regression model.

Odds ratios were reported per interquartile range (IQR) change in each pollutant's concentration (Delfino et al. 2003). All ORs were calculated after adjusting for gender and Hispanic ethnicity. We also report ORs and their 95% confidence intervals (CIs) separately with adjustment for outdoor O_3.

All statistical analyses were performed using SAS Version 9.2.

Results

Indoor exposure characterization

Descriptive statistics of weekly indoor pollutant concentrations are reported in Table 3 and Supplemental Figure 2. On average, indoor NO_2 concentrations were higher in winter (33.2 ppb) than in summer (23.7 ppb), while the reverse was true for O_3 with 1.8 ppb in winter and 3.9 ppb in summer. Seasonal differences in indoor $PM_{2.5}$ and PM_{10} mass as well as organic and elemental carbon were negligible. Of the $PM_{2.5}$ elements exhibiting the largest seasonal variation, Al, Ca, Cl, Na, Ni, and Zn measurements were higher in winter than in summer, while K and S measurements were higher in summer than in winter.

Table 3 Average concentration of weekly indoor pollutants by season

Indoor weekly pollutant	Summer			Winter		
	N	Mean	SD	*N*	Mean	SD
Units: ppb						
NO_2	62	23.73	12.14	53	33.2	14.98
SO_2	62	−0.04	0.36	53	0.59	0.63
O_3	62	3.86	5.87	53	1.77	1.19
Units: μg/m^3						
$PM_{2.5}$	58	21.24	16.22	56	20.03	10.56
PM_{10}	60	29.69	19.79	56	29.27	12.14
OC	49	7.59	8.75	36	6.69	3.88
EC	49	1.03	0.55	36	1.66	2.87
TC	49	8.62	9	36	8.36	4.92
BC	57	1.04	0.38	56	1.11	0.8
Units: ng/m^3						
Al	57	20.36	17.78	56	34.05	31.55
Ca	57	63.13	45.83	56	107.34	62.95
Cl	57	157.9	344.07	56	428.76	1060.99
Cu	57	4.58	2.47	56	5.77	2.76
Fe	57	89.3	47.99	56	84.81	37.89
K	57	135.99	179.46	56	123.75	105.13
Mn	57	2.13	1.67	56	3.86	3.35
Na	57	164.98	181.45	56	396.87	536.18
Ni	57	2.79	1.66	56	11.72	13.3
Pb	57	1.57	1.13	56	2.68	2.1
Si	57	58.28	55.4	56	69.42	40.97
S	57	780.01	438.89	56	668.17	210.54
Ti	57	3.1	2.32	56	3.06	1.89
V	57	1.86	1.27	56	3.13	3.54
Zn	57	19.18	12.31	56	38.62	32.21

OC organic carbon, *EC* elemental carbon, *TC* total carbon, *BC* black carbon, *Al* aluminum, *Ca* calcium, *Cl* chlorine, *Cu* copper, *Fe* iron, *K* potassium, *Mn* manganese, *Na* sodium, *Ni* nickel, *Pb* lead, *Si* silicon, *S* sulfur, *Ti* titanium, *V* vanadium, *Zn* zinc

Asthma symptoms

Odds ratios (ORs) and their 95% CIs for the likelihood of increased average daily symptoms scores for a given week (our primary measure) by IQR change in indoor pollutants are shown in (Fig. 1a and Tables 4 and 5). NO_2, Ca, and Si were significantly associated with average symptom score during winter, with ORs of 2.83 (95% CI 1.17–6.83), 3.29 (1.26–8.55), and 3.64 (1.10–12.05), respectively. In models adjusted for outdoor O_3, ORs were 2.82 (1.10–7.24), 3.46 (1.26–9.52), and 3.73 (1.07–12.99), respectively, and maintained significance (Supplemental Table 1a).

In summer, Cl was significantly associated with average daily symptom score for a given week with OR 1.85 (1.23–2.78). The association increased slightly in O_3 adjusted models to 2.02 (1.31–3.12).

Results for other measures of asthma symptoms are shown in Table 4 (base models unadjusted for outdoor O_3) and Supplemental Tables 1b-1e (adjusted for outdoor O_3).

In winter, results for maximum daily symptom score in a given week (Table 4 and Supplemental Table 1b) were similar to our primary measure (average daily score in a given week). However, in addition to NO_2, Ca, and Si for which ORs were 3.13 (1.23–7.96), 4.00 (1.41–11.35), and 5.14 (1.35–19.51), respectively, Ni was also significantly associated with maximum symptoms with OR 1.94 (1.08–3.49). In summer, the maximum symptom score was again significantly associated with Cl (OR 1.82; 95% CI 1.26–2.63) but also negatively with elemental carbon (0.19; 0.06–0.63). For all these associations, there was little change in indoor weekly exposure models adjusted for outdoor O_3 (Table 4 and Supplemental Table 1c).

Similar season-specific results were observed when symptom severity was measured as number of days with symptom scores > 1 (or number of days with any reported symptoms) (Table 4 and Supplementary Table 1d). In winter, NO_2 and Ca were significantly associated with the number of days with symptom scores > 1 (NO_2: 2.56; 1.02–6.43 and Ca: 2.45; 1.01–5.95). In summer, Cl was significantly and positively associated with days with symptom scores > 1 (1.46; 1.01–2.10). Once again, elemental carbon was negatively associated with this index OR = 0.23 (0.06–0.82). Adjustment for outdoor O_3 did not meaningfully change these results (Supplemental Table 1f).

Albuterol use

Results for daily average albuterol use for a given week are shown in Fig. 1b and Tables 4 and 6. In winter, there were significant associations for NO_2 (5.89; 1.63–21.26), Ni (2.27; 1.02–5.07), and Si (5.59; 1.01–30.76); however, only NO_2 remained significant in the models adjusted for outdoor O_3, suggesting significant confounding of these effects by

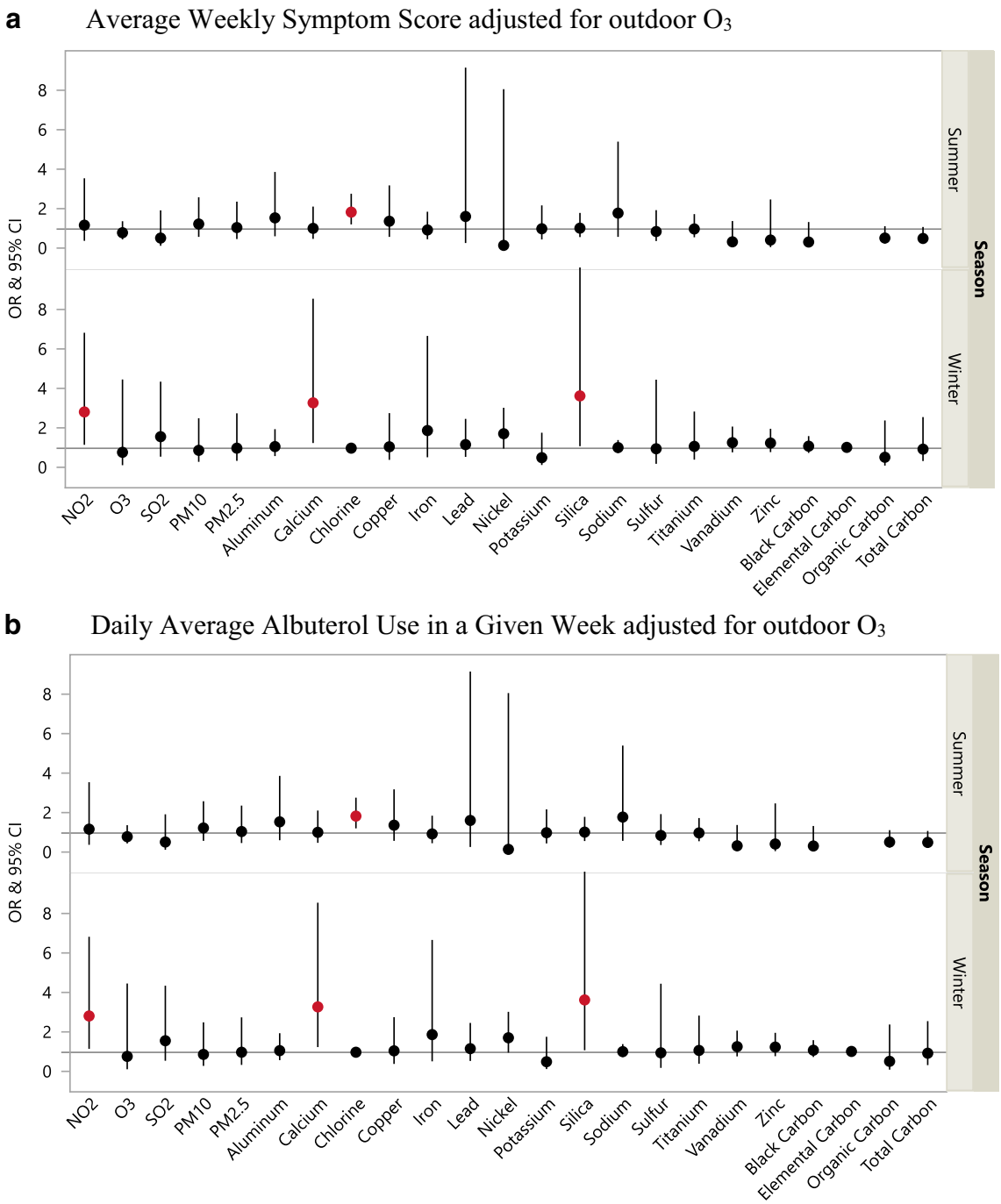

Fig. 1 Odds ratios and 95% confidence intervals for selected respiratory health outcomes adjusted for outdoor O_3. **a** Average weekly symptom score adjusted for outdoor O_3. **b** Daily average albuterol use in a given week adjusted for outdoor O_3

exposure to outdoor O_3 (Supplemental Table 2a). No significant associations were found for any pollutant in summer.

Results for our secondary measure of albuterol use defined as the number of days with number of puffs > 0 are shown in Table 4 and Supplemental Table 2b. In winter, there were significant associations for NO_2 (8.25; 2.21–30.75), $PM_{2.5}$ (3.38; 1.04–10.98), PM_{10} (3.76; 1.12–12.61), and Si (6.07; 1.32–27.83). When adjustments for outdoor O_3 were made, associations with $PM_{2.5}$ and PM_{10} were no longer significant and those with NO_2 and Si increased slightly (Supplemental Table 2c). In summer, no significant associations were noted.

Pulmonary function

No significant associations between either average morning (AM) FEV_1 or PEF lability and indoor

Table 4 Summary of pollutants with significant ORs for listed health outcomes

Health outcomes	Base model		Adjusted for outdoor ozone	
	Summer	Winter	Summer	Winter
Daily average symptom score	Cl	NO_2, Ca, Si	Cl	NO_2, Ca, Si
Maximum symptom score	Cl, (EC)	NO_2, Ca, Ni, Si	Cl, (EC)	NO_2, Ca, Ni, Si
Symptom days > 1	Cl, (EC)	NO_2, Ca	Cl, (EC)	NO_2, Ca
Average albuterol	–	NO_2, Ni, Si	–	NO_2
Albuterol days > 0	–	NO_2, Si, $PM_{2.5}$, PM_{10}	–	NO_2, Si, PM_{10}
Morning (AM) FEV_1	–	–	–	–
PEF lability	–	–	–	–

Significant ORs < 1 shown in parentheses (…). Daily average symptom score is defined as daily symptom total scores (cough + wheeze) averaged separately over week 1 and week 2. Maximum symptom score is defined as maximum daily symptom score during week 1 and week 2 measured separately. Symptoms days > 1 is defined as number of days in a given week with total symptom (cough + wheeze) score > 1. Albuterol days > 0 is defined as number of days in a given week with total albuterol use score > 1

pollutant exposures were observed in either winter or summer. Results are presented in Table 4 (base models) and Supplemental Tables 3a-d (adjusted for outdoor O_3).

Table 5 Odds ratios and 95% confidence intervals for average daily symptom scores as they relate to weekly indoor air pollutants

	Season							
	Summer				Winter			
	Odds ratio	Lower 95% CL	Upper 95% CL	*p* value	Odds ratio	Lower 95% CL	Upper 95% CL	*p* value
Indoor pollutant								
NO_2	1.19	0.40	3.56	0.7456	*2.83*	*1.17*	*6.83*	*0.0234*
SO_2	0.54	0.15	1.94	0.3413	1.58	0.57	4.36	0.3567
O_3	0.81	0.47	1.39	0.4302	0.79	0.14	4.47	0.7824
$PM_{2.5}$	1.07	0.49	2.38	0.8550	1.00	0.36	2.76	0.9957
PM_{10}	1.25	0.60	2.60	0.5465	0.89	0.31	2.51	0.8135
OC	0.54	0.26	1.14	0.1045	0.54	0.12	2.40	0.3769
EC	.	.	.	.	1.04	0.89	1.22	0.6131
TC	0.52	0.25	1.10	0.0847	0.95	0.35	2.57	0.9108
BC	0.34	0.09	1.35	0.1215	1.10	0.76	1.61	0.5998
Al	1.56	0.63	3.88	0.3286	1.08	0.60	1.96	0.7908
Ca	1.03	0.50	2.13	0.9327	*3.29*	*1.26*	*8.55*	*0.0171*
Cl	**1.85**	**1.23**	**2.78**	**0.0041**	1.00	0.91	1.11	0.9203
Cu	1.39	0.60	3.20	0.4337	1.07	0.41	2.77	0.8886
Fe	0.95	0.48	1.87	0.8682	1.89	0.54	6.67	0.3071
K	1.01	0.47	2.19	0.9803	0.52	0.15	1.78	0.2784
Na	1.80	0.60	5.41	0.2865	1.03	0.76	1.41	0.8438
Ni	0.17	0.00	8.06	0.3551	1.73	0.98	3.04	0.0565
Pb	1.63	0.29	9.15	0.5719	1.18	0.56	2.48	0.6494
Si	1.04	0.59	1.81	0.8952	*3.64*	*1.10*	*12.05*	*0.0360*
Su	0.87	0.39	1.95	0.7340	0.97	0.21	4.46	0.9703
Ti	1.00	0.58	1.75	0.9858	1.09	0.42	2.85	0.8510
V	0.35	0.09	1.40	0.1335	1.28	0.79	2.09	0.2997
Zn	0.44	0.08	2.49	0.3413	1.26	0.80	1.98	0.3097

p values less than 0.05 and 0.01 were italicized and bolded, respectively, in the table

Table 6 Odds ratios and 95% confidence intervals for average number albuterol puffs per day as they relate to weekly average pollutant concentrations

	Season							
	Summer				Winter			
	Odds ratio	Lower 95% CL	Upper 95% CL	*p* value	Odds ratio	Lower 95% CL	Upper 95% CL	*p* value
Indoor pollutant								
NO_2	2.34	0.69	7.93	0.1666	*5.89*	*1.63*	*21.26*	*0.0086*
SO_2	0.45	0.12	1.76	0.2454	1.89	0.47	7.63	0.3583
O_3	0.77	0.40	1.50	0.4333	0.58	0.06	5.52	0.6245
$PM_{2.5}$	1.86	0.76	4.54	0.1658	3.56	0.87	14.64	0.0763
PM_{10}	1.92	0.83	4.47	0.1259	2.22	0.56	8.84	0.2480
Organic carbon	0.95	0.48	1.90	0.8853	0.70	0.12	4.11	0.6778
Elemental carbon	0.96	0.33	2.75	0.9314	1.18	0.97	1.44	0.0957
Black carbon	2.50	0.59	10.55	0.2047	1.36	0.87	2.12	0.1684
Aluminum	1.12	0.43	2.88	0.8128	1.61	0.62	4.20	0.3138
Calcium	1.14	0.53	2.43	0.7309	3.97	1.00	15.75	0.0501
Chlorine	1.13	0.79	1.62	0.4878	1.09	0.92	1.29	0.2895
Copper	0.89	0.35	2.29	0.8054	1.30	0.39	4.29	0.6584
Iron	1.26	0.61	2.60	0.5191	3.44	0.62	19.19	0.1516
Potassium	0.91	0.35	2.35	0.8445	1.45	0.29	7.30	0.6417
Sodium	1.89	0.61	5.88	0.2641	1.36	0.82	2.26	0.2198
Nickel	1.59	0.03	80.67	0.8116	*2.27*	*1.02*	*5.07*	*0.0459*
Lead	2.20	0.34	14.29	0.3989	1.88	0.75	4.68	0.1688
Silicon	1.01	0.56	1.81	0.9829	*5.59*	*1.01*	*30.76*	*0.0482*
Sulfur	1.53	0.67	3.52	0.3051	1.27	0.20	8.17	0.7938
Titanium	1.13	0.63	2.02	0.6668	1.50	0.42	5.39	0.5189
Vanadium	2.13	0.58	7.84	0.2461	1.53	0.81	2.89	0.1810
Zinc	0.84	0.13	5.37	0.8458	1.70	0.94	3.08	0.0767

p values less than 0.05 and 0.01 were italicized and bolded, respectively, in the table

Discussion

We observed significant associations between weekly indoor concentrations of several pollutants and respiratory outcomes, including symptom scores and albuterol use, in inner city children with moderate to severe asthma. We found most consistent associations in the winter season with indoor NO_2, Si, and Ni for symptoms and albuterol, and in the summer with Cl for symptoms. Ca was also associated with symptoms only in the winter. We did not observe any significant associations with pulmonary function parameters. Taking into consideration our earlier analyses investigating sources of these indoor pollutants (Habre et al. 2014b, Rohr et al. 2014), the significant associations we found for indoor NO_2, Si, Ni, Ca, and Cl suggest that indoor pollutants with important contributions from both indoor and outdoor sources might be important for pediatric asthma exacerbation. Additionally, our study contributes findings to the recognized role of seasons in asthma variability and in air pollution associations with asthma (Goldstein 1980).

Multiple prior studies have pointed out the association of NO_2 with gas stoves which were present in all of the apartments we studied and were extensively used for cooking and in some cases heating. Water heaters and space heaters have also been identified as principal indoor sources of NO_2 (Dedele at al. 2016). Levels of NO_2 tend to rise in winter, with decreased ventilation in apartments, as well as the more frequent use of gas stoves for cooking and as a supplement for home heating (Uchiyama et al. 2015). In our earlier source modeling analyses of indoor pollutants in this study (Habre et al. 2014b), we found that cooking was a significant predictor of indoor NO_2 levels, followed by outdoor NO_2 levels concentrations, confirming that use of gas stoves for cooking and infiltration of outdoor NO_2 (associated with traffic and fuel combustion in our study area) contributed to indoor NO_2 levels. Recent studies of pediatric asthma severity confirm our observation of the relationship between NO_2 exposures and asthma symptom scores and the use rescue medication (Belanger et al. 2013; Lin et al., 2013; Kattan et al. 2007).

Components of indoor $PM_{2.5}$ of interest in our analysis included Ca, Si, Ni, and Cl. The majority of indoor Ca and Si concentrations were of indoor origin in our earlier analysis, likely related to the resuspension of settled crustal material and dust in these apartments (Habre et al. 2014b; Balasubramanian and Lee, 2007). These elements have also been associated with other indoor sources including cooking, particularly meat (Habre et al. 2014b; Meng et al. 2009; Sexton et al. 1986). Ca can also be emitted from humidifiers (Baxter et al. 2007; Highsmith et al. 1992). Ca is also associated with cigarette smoke (Ozkaynak et al. 1996) and although all of the families studied were composed of non-smokers some of the apartments had high levels of measured nicotine (as discussed by Schachter et al. (2011) using the method of Hammond and Leaderer (1987)). This was attributed to visitors to the apartment and smoking in the hallways or infiltration of secondhand smoke from nearby apartments.

Ni in New York City is a strong tracer of residual fuel oil combustion for building heating and shipping activity in the ports (Kim et al. 2014; Peltier et al. 2009; Peltier and Lippmann, 2010). Concentrations of this element tend to be higher in winter than in summer, specifically in New York City 2.5 times higher (Peltier and Lippmann, 2010), suggesting heating oil and major port operations (Hsu et al. 2012) are major sources. In Rohr et al. (2014), we conducted a source apportionment analysis of daily outdoor $PM_{2.5}$ pollution in our study area and identified a shipping-related source factor with high loadings of Ni and V. When we analyzed the composition of indoor $PM_{2.5}$ in our study, we also confirmed indoor Ni in these residences was almost exclusively from outdoor origin (Habre et al. 2014b). Complementing our findings, Patel (Patel and Miller, 2009) reported a significant association between a 3-month averaged inverse distance weighted concentration of ambient Ni and wheeze symptoms in children up to 2 years old in NYC.

Chlorine was the element with the second highest fraction of its concentration of indoor origin in our earlier analysis (Habre et al. 2014b). Chlorine has been associated with bleach-containing cleaning products and the aerosolization of chlorinated municipal water indoors (Zhao et al. 2006; Zhao et al. 2007). Chlorine has also been associated with cooking and environmental tobacco smoke (Habre et al. 2014b; Ozkaynak et al. 1996; Wallace, 1996). In our study, it is associated with higher summer symptom scores even when adjusting for outdoor ozone. While we also found an outdoor source factor with high loadings of Cl (as well as Na) that we labelled "salt" in our outdoor source apportionment work (Rohr et al. 2014), the highest contributions of the outdoor "salt" factor were in the winter time. Taken together, our previous indoor and outdoor source apportionment analyses suggest that the associations we are finding with indoor Cl and symptoms in the summer are related to indoor generation of Cl and not Cl of outdoor origin (related to sea salt from marine air or road salting in the winter). Table 3 shows that indoor Cl levels were lower in the summer compared to the winter in our study. This suggests that it is not the level of indoor Cl that is driving these stronger associations in the summer, but rather, the co-occurrence of other factors or pollutants in the summer that could be leading to indoor Cl having a stronger or larger effect in the summer. This warrants future investigation into possible exposures or behaviors that could be modifying the effect of indoor Cl in the summer.

The negative association between elemental carbon and symptom severity (Table 4) during summer months suggests that this component may be varying inversely with some other pollutant or environmental factor that exacerbates asthma.

Role of season

Positive associations were observed for symptoms in both winter and summer. In winter, NO_2 was associated with increased respiratory symptoms. This finding confirms observations reported by many prior studies (Deal Jr. et al., 1979, Lin et al. 2013; Breysse et al. 2010; Fuentes-Leonarte et al. 2009; Heinrich, 2011) and is consistent with the higher indoor NO_2 concentrations in winter. In our study, all homes had gas stoves which likely contributed significantly to indoor NO_2 concentrations as we described earlier. Ca, Si, and Ni appeared consistently associated with symptoms in winter. Again, this seasonal specificity may reflect higher concentrations of pollutants indoors due to reduced ventilation (closed windows), or in the case of Ca its association with humidifiers. Increased fuel oil burning for heating of residential dwellings lead to increased Ni concentrations in winter. In summer, the association between Cl and symptoms warrants further investigation as described earlier.

No associations were noted for the albuterol parameters in summer, but in winter NO_2 and to a lesser extent Ca, Si, and Ni were associated with albuterol use. This association with medication use may reflect similar sources and patterns as noted above for symptoms.

Overall, indoor NO_2, Si, and Ni were the only three pollutants associated with both more subjective (symptoms) and somewhat objective (albuterol use) asthma symptoms, despite both of these outcomes being collected via self-report in a diary. This highlights the consistency of these findings.

In a prior analysis (Grunin et al. 2010), we analyzed the potential role of allergens collected in dust samples of these homes (mouse and cockroach) on their potential modifying role for modifying the relationship between pollutant and symptom severity by season. In that study, we did not observe any significant modification.

Ozone-adjusted models

In our previous analysis of the role of outdoor pollution in asthma exacerbation (Schachter et al. 2016), outdoor O_3 concentrations were associated with increased symptom severity and albuterol use as were outdoor concentrations of PM_{10} and $PM_{2.5}$ and a number of their components. In summer adjustment for outdoor O_3 concentration resulted in loss of significance for the association of outdoor particulate matter and its components. In winter, by contrast, adjustment for outdoor O_3 had only limited effect on the association with outdoor PM. Because of the documented role played by outdoor ozone in asthma exacerbation, we controlled for outdoor O_3 in the analyses reported herein of indoor pollutants. In contrast to outdoor pollutants, adjustment for outdoor O_3 concentrations had a limited impact on the associations between indoor pollutants and effects on symptoms in either season, possibly because indoor concentrations are more representative of true personal exposures given the large amount of time children tend to spend at home. In the case of primary and secondary symptom parameters, all the associations remained statistically significant when adjustment for O_3 was made. For albuterol use on the other hand, significant associations in winter were lost for Ni and Si when the measure used was average daily albuterol use. When the measure for albuterol use was number of days when albuterol use was >0, a change was seen with only the $PM_{2.5}$ association losing significance in winter after O_3 adjustment. This limited effect is not surprising given the lower outdoor O_3 levels in winter, and our inability to find significant effect of ambient O_3 on respiratory health in this season (Schachter et al. 2016). In summer, indoor O_3 levels were not associated with health effects and outdoor O_3 had no effect on the association of chlorine with asthma symptoms.

p values and multiple comparisons

Concern in the statistical literature has been raised about the use of *p* values and the excessive emphasis placed on interpreting them. The use of an arbitrary cutoff for significance must interpreted with care in determining the presence and importance of clinical effects (Wasserstein and Lazar, 2016, Wasserstein et al. 2019). In particular, multiple comparisons increase the likelihood that some of the "significant" associations calculated in this study have occurred by chance alone (Harrington and D'Agostino Sr, 2019). Considering a more stringent *p* value significant cutoff of <0.01, only summer associations of indoor Cl with average or maximum symptoms scores are considered significant, even after adjusting for outdoor O_3, and winter associations of indoor NO_2 with average albuterol use and with days of albuterol use. However, only indoor NO_2 and days of albuterol use remains significant at *p* value <0.01 after adjusting for outdoor O_3. The plausibility of our findings is however enhanced by the similarities noted with other studies and the consistency noted in the pattern of the effects across variations of the indices of asthma severity.

Conclusions

NO_2 and $PM_{2.5}$ elements—in particular, Ca, Si, Ni, and Cl—were associated in this study with aggravated asthma symptoms and the increased use of rescue medication among inner city children with moderate to severe asthma. Indoor pollutant levels were more likely to be associated with these clinical indices in winter than in summer, a season in which asthma exacerbations tend to be more frequent, with the exception of Cl. The elements and gases associated with asthma exacerbation suggest potential indoor and outdoor sources. The associations were relatively independent of the way in which the three symptom indices and the two albuterol measures were defined.

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Compliance with ethical standards

Conflict of interest Dr. Rohr is employed by the Electric Power Research Institute (EPRI) which is primarily supported by the electric power industry in the USA and abroad. EPRI is a 501(c)(3) organization that funds external research at a number of universities and institutes worldwide. Other authors declare no conflict of interest personal, financial, or otherwise with the material presented in this manuscript.

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