Indoor particulate matter increases asthma morbidity in children with non-atopic and atopic asthma

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Background: Compared with atopic asthma, fewer environmental modifications are recommended for non-atopic asthma in children.

Objective: To better understand the role of indoor pollutants in provoking non-atopic asthma, we investigated the effect of in-home particulate matter on asthma symptoms among non-atopic and atopic children living in inner-city Baltimore.

Methods: A cohort of 150 children ages 2 to 6 years with asthma underwent home environmental monitoring for 3-day intervals at baseline, 3, and 6 months. Children were classified as non-atopic if they were skin test negative to a panel of 14 aeroallergens. Caregivers completed questionnaires assessing symptoms and rescue medication use. Longitudinal data analysis included regression models with generalized estimating equations.

Results: Children were primarily African American from lower socioeconomic backgrounds and spent most of their time in the home. Thirty-one percent were non-atopic, and 69% were atopic. Among non-atopic and atopic children, increased in-home fine (PM2.5) and coarse (PM2.5–10) particle concentrations were associated with significant increases in asthma symptoms and rescue medication use ranging from 7% (95% confidence interval [CI], 0–15) to 14% (95% CI, 1–27) per 10 $\mu g/m^3$ increase in particle concentration after adjustment for confounders.

Conclusions: In-home particles similarly cause increased symptoms of asthma in non-atopic and atopic children. Environmental control strategies that reduce particle concentrations may prove to be an effective means of improving asthma outcomes, especially for non-atopic asthma, for which there are few environmental control practice recommendations.

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INTRODUCTION

Asthma is influenced by a combination of host susceptibility and environmental factors, including viruses, pollutants, and allergens. Individuals with asthma often have allergic sensitization to allergens, and for these individuals, identification and avoidance of relevant allergens is an established component of asthma management. However, non-atopic asthma contributes significantly to the worldwide and US burden of disease, representing as much as 50% of the world's asthma, although atopic asthma likely predominates in children. Some evidence suggests that non-atopic asthma may confer a worse prognosis compared with atopic asthma[1–5]; however, because it is not considered an allergen-driven disease, environmental control recommendations are less well established.

Air pollutants are among the likely candidates of the possible environmental triggers for non-atopic asthma. Previous studies have suggested that air pollutants, such as sulfur dioxide, nitrogen dioxide, carbon monoxide, and benzene, have a stronger effect in non-atopic asthma than atopic asthma.[6,7] Particulate matter (PM) is a common air pollutant that has known detrimental health effects, especially for those with asthma. PM has both outdoor sources, including products of combustion and crustal materials, and indoor sources, including smoking, cooking, and cleaning activities.[8,9] Increases in ambient PM have been associated with greater morbidity in asthma and greater mortality in the general population.[10–13] However, the effect on non-atopic asthma has not been isolated.

Although Americans spend most of their time indoors (>80%), and indoor PM concentrations can exceed those measured outdoors, less is known about the health effects of

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indoor PM exposure. Previous studies of health effects of indoor PM have linked indoor PM exposure to increases in respiratory symptoms and decreases in pulmonary function but have not evaluated differential health effects of pollutants between atopic and non-atopic asthmatics.[11,14–16] To better understand the causative mechanism and to inform recommendations for improving the health of those with non-atopic asthma, we first need to provide evidence of the link between exposures and exacerbation of disease. The current study focuses on inner-city preschool-age children with asthma, a group known to have a high burden of disease and to be at risk for increased exposure to environmental pollutants. Using a cohort of well-characterized children with asthma,[14,17] we examined the response to indoor PM exposure in those with non-atopic and atopic asthma.

METHODS

Study Design

The Johns Hopkins Medical Institutional Review Board approved the study, and all participants provided written informed consent before beginning the study. Children participating in this longitudinal study[17] were evaluated at baseline and 3 and 6 months. At each interval, environmental monitoring occurred for 3 consecutive days, and health outcomes were assessed through caregiver report.

Participants

Children were recruited from health systems that provide care to most East Baltimore residents. Inclusion criteria were (1) age 2–6 years; (2) residence in 1 of 9 contiguous zip codes within East Baltimore; (3) physician diagnosis of asthma; and (4) asthma symptoms or medication use in previous 6 months.

Air Quality Assessment

Environmental monitoring methods are described elsewhere.[17] At baseline, 3 months, and 6 months, integrated air sampling was performed in the child's bedroom over 3 days using PM_{10} and $PM_{2.5}$ samples collected with personal environmental monitors (SKC, Inc, Eighty Four, Pennsylvania), which had been loaded with 37-mm Teflo filters, (Pall-Gelman, Ann Arbor, Michigan). Coarse PM fraction was calculated as PM_{10} to $PM_{2.5}$.[18] Inlet flow rates were calibrated at the beginning and end of sampling periods using primary standards (BIOS DryCal, Bios International Corporation, Butler, New Jersey). The PM gravimetric analysis was conducted on a Metler T5 microbalance. Ambient PM for the study was measured at a central site within the study area, using a $PM_{2.5}$ Partisol- Plus model 2025 FRM Sequential Air Sampler and the PM_{10} tapered element oscillating microbalance, TEOM 1400 (Rupprecht & Patashnick Co Inc, Albany, New York). When ambient values were missing ($<$10% missing), values were supplemented from the Maryland Department of Environment Station, which is within 1 mile of the central monitoring site.[19]

Clinical Evaluation

Each child underwent baseline skin prick testing (Multi-Test II, Lincoln Diagnostics, Decatur, Illinois) to a standard mix of 14 aeroallergens. Atopy was defined as at least 1 positive skin test, defined as wheal size at least 2 mm greater than the negative control, as in previous childhood asthma studies.[20–22] At baseline, 3 months, and 6 months, caregivers completed questionnaires that included closed-ended questions from the International Study of Asthma and Allergies in Childhood[23] and the Children's Health Survey for Asthma.[24] Questions included rescue medication use (short-acting beta agonist) and symptoms in the previous 2 weeks, including (1) wheezing, coughing, or chest tightness; (2) the need to slow down/stop activities; (3) wheezing so badly that the child could only speak 1 or 2 words between breaths; (4) symptoms with exercise; and (5) nocturnal symptoms. Symptoms were quantified as number of days present in the previous 2 weeks (0–14 days). Participants completed a daily activity diary during each 3-day environmental monitoring period, and this included an account of time spent in the room where monitoring occurred.

Statistical Analysis

Summary statistics, such as means or medians, were generated. Comparisons of baseline demographic characteristics were made, using the χ^2 test for proportions and Student's *t* test or Wilcoxon signed-rank test for continuous data. Negative binomial regression models were fit using generalized estimating equations[25] to model the relationship between PM and repeated measures of days of symptoms or rescue medication use. Multivariate models were constructed to account for potential confounders identified based on known relationships with asthma, atopy, or PM or statistically significant associations in bivariate models of PM and symptom outcomes. An interaction term for atopy and PM exposure was also tested. Analyses were performed with Stata statistical software, version 8.0 (Stata Corp, College Station, Texas). Statistical significance was defined as $P < .05$.

RESULTS

Participant Characteristics

The 150 preschool children enrolled in this longitudinal cohort study were predominantly African American from lower-income households (Table 1). Of the 133 who completed allergy skin testing, 31% were classified as non-atopic and 69% as atopic. Non-atopic children were slightly younger, with a mean age of 3.9 years, compared with atopic children, who had a mean age of 4.6 years ($P = .01$). No significant differences were seen between the groups with respect to race, sex, or socioeconomic status. Both the atopic and non-atopic children had evidence of active asthma, with similar measures of morbidity (Table 1). Half of the participants reported symptoms and use of rescue medications over the past 2 weeks, and approximately one third reported the need for evaluation in an acute health care setting in the previous 3 months. Children spent approximately half of each 24-hour day in their own homes, and most of this time was spent in the bedroom, where environmental monitoring was conducted (Table 1). Most of the homes were rowhomes in close proximity to the roadway, and these characteristics did not differ by atopic status.

Indoor Air Quality in Homes of Children with Atopic Versus Non-Atopic Asthma

The median interquartile range (IQR) indoor $PM_{2.5–10}$ concentrations were similar among children with non-atopic and atopic asthma, with concentrations of 13.4 (13.2) $\mu g/m^3$ and 11.6 (13.2) $\mu g/m^3$, respectively (P = .52) (Fig 1). Fine PM concentrations were elevated, with more than 75% of homes exceeding the EPA National Ambient Air Quality Standards annual limit for ambient $PM_{2.5}$ concentrations (Fig 2).[26] The indoor $PM_{2.5}$ concentrations were higher in the homes of children with non-atopic asthma compared with those with atopic asthma, 35.7 (39.4) $\mu g/m^3$ and 27.6 (30.7) $\mu g/m^3$, respectively (P = .04).

Effect of Indoor Coarse PM on Asthma Morbidity by Atopic Status

Higher concentrations of indoor coarse PM were associated with increases in asthma symptoms and the need for rescue medications for both the non-atopic and atopic groups (Tables 2, 3, Fig 3). For the non-atopic group, nearly all associations were statistically significant, with a 7% (95% confidence interval [CI] 0, 15) to 13% [95% CI 4,22]% higher incidence of symptoms per 10 $\mu g/m^3$, after adjusting for age, race, sex, socioeconomic status, season, indoor fine and ambient fine and coarse PM concentrations. The magnitude of the associations was similar among the atopic children. There was a statistically significant interaction between atopic status and the association between coarse PM and symptoms with running (P = .04 for interaction term) in the multivariate model. For children with atopic asthma, there was a 14% (95% CI 0, 27) increase in the incidence of symptoms with exercise for every 10-$\mu g/m^3$ increase in $PM_{2.5–10}$ (P = .01), after adjustment for potential confounders, but this increase was not found in non-atopic children.

Table 1. Participant Characteristics

Baseline characteristics	Non-atopic N = 41	Atopic N = 92	P value
Race (% African American)	85	92	.20
Sex (% male)	59	59	.98
Age (years) mean (SD)	3.9 (1.3)	4.6 (1.5)	.01
Household income (%)[a]			
<$15,000	62	49	.60
$15,000–30,000	24	34	
>$30,000	14	17	
Caregiver education (%)			
8th Grade/some high school	44	36	.06
High school	49	39	
Some college	7	25	
Time (h/d) mean (SD)			
Home	12.4 (6.8)	12.6 (6.2)	.88
Bedroom with monitor	7.0 (4.4)	6.5 (3.9)	.49
Parental history of asthma (%)	80	65	.11
Symptoms in previous 2 weeks (%)	52	41	.25
Rescue medications in previous 2 weeks (%)	53	53	.96
Acute health care use in previous 3 months (%)			
ED visits	27	23	.62
Hospitalizations	2	3	.80
Unscheduled doctor visits	15	18	.59

[a] For those who responded. Twenty percent of participants did not respond to this question.

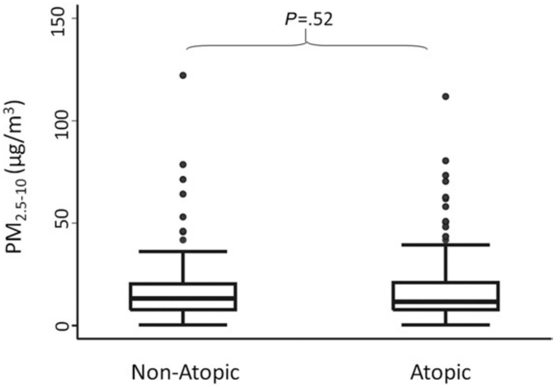

Figure 1. Indoor coarse PM concentrations in the homes of non-atopic and atopic children. *Boxes* show the interquartile range (IQR), and the *heavy dark lines* are the median values. *Whiskers* represent the closest value within 1.5 times the IQR. Indoor concentrations of coarse PM did not significantly differ between non-atopic and atopic children.

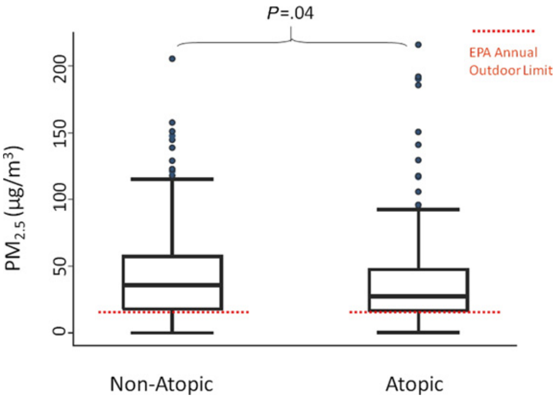

Figure 2. Indoor fine PM concentrations in the homes of non-atopic and atopic children. More than 75% of homes had indoor fine PM concentrations that exceeded the Environmental Protection Agency annual outdoor limit,[26] demonstrated by the dashed red line. Indoor concentrations of fine PM were greater in the homes of non-atopic children compared with those of atopic children.

Table 2. Indoor Coarse PM Concentrations and Asthma Morbidity by Atopic Status: Bivariate Models

	Non-atopic coarse			Atopic coarse		
	IRR	95% CI	*P* value	IRR	95% CI	*P* value
Cough, wheezing, chest tightness	1.06	(1.0, 1.13)	.06	1.02	(0.92, 1.13)	.68
Slow down	1.07	(1.0, 1.13)	.05	1.14	(1.04, 1.25)	<.01
Symptoms with running	0.73	(0.56, 0.90)	<.01	1.12	(1.01, 1.23)	.02
Nocturnal symptoms	1.08	(1.02, 1.15)	.01	1.03	(0.93, 1.14)	.55
Limited speech	1.11	(1.04, 1.18)	<.01	1.14	(0.99, 1.30)	.07
Beta-agonist use	1.07	(1.01, 1.13)	.02	1.06	(0.96, 1.15)	.24

Effect of Indoor Fine PM on Asthma Morbidity by Atopic Status

Higher concentrations of fine PM measured indoors were associated with increases in asthma symptoms and the need for rescue medications in both the non-atopic and the atopic subgroups. The magnitude of the effect was similar between groups in both the bivariate and multivariate models (Tables 4 and 5; Fig 4). No significant interaction was found between atopic status and the effect of fine PM on respiratory symptoms or rescue medication use.

DISCUSSION

We found that in-home particle concentrations were associated with asthma morbidity, including symptoms and rescue medication use, among not only atopic but also non-atopic children. Although fewer non-atopic ($n = 41$) than atopic children ($n = 92$) were in this inner-city, predominantly African American cohort, we found substantial, statistically significant relationships between in-home PM concentrations and asthma outcomes in this group. The magnitude of the response to PM was similar in non-atopic and atopic children. To our knowledge, this is the first study to focus on the relationship between atopic status and the health effects of indoor PM.

Relatively little attention has been paid to environmental triggers of non-atopic asthma. Of the few studies that have examined the effect of indoor PM on children with asthma, most have not evaluated susceptibility among non-atopic asthmatics. Studies of children in Seattle found that higher indoor and outdoor PM concentrations were associated with lower maximal midexpiratory flows among a subgroup of 11 children who were not taking anti-inflammatory medications; however, the atopic status of participants was not assessed.[15,16] In a study based in Southern California, forced expiratory volume in 1 second (FEV_1) was inversely associated with personal and indoor PM concentrations among 19 children with asthma.[11] In a subset of 12 male children in this study, an analysis of the influence of atopic status on the susceptibility to PM exposure revealed mixed results. Atopic boys showed stronger inverse associations between personal PM and FEV_1 but weaker associations between stationary-site PM and FEV_1, compared with non-atopic boys (although this latter difference was not significant). In our larger current study, we found evidence that both atopic and non-atopic children were similarly adversely impacted by indoor airborne PM exposure.

In addition to PM, several other indoor pollutants have been shown to impact those with non-atopic asthma and may even disproportionately affect non-atopic as compared with atopic asthma. For example, some studies of secondhand smoke exposure have shown a stronger effect in terms of the incidence and disease severity among non-atopic children with asthma compared with those with atopy.[27–30] Based on previous work, we have determined that penetration of outdoor air into indoor space and indoor smoking, cooking, and cleaning activities contributed to elevated in-home PM concentrations.[8] Secondhand smoke is likely to contribute to the asthmatic response that is associated with indoor PM exposure in our study. Increased levels of NO_2 were associated with increased asthma symptoms and decreased peak flows only among non-atopic asthmatic children in one study,[6] and in our

Table 3. Indoor Coarse PM Concentrations and Asthma Morbidity by Atopic Status: Multivariate Models[a]

	Non-atopic coarse			Atopic coarse		
	IRR	95% CI	*P* value	IRR	95% CI	*P* value
Cough, wheezing, chest tightness	1.08	(1.01, 1.15)	.02	1.02	(0.89, 1.15)	.73
Slow down	1.07	(1.00, 1.15)	.05	1.14	(1.01, 1.27)	.04
Symptoms with running	0.87	(0.69, 1.06)	.18	1.14	(1.00, 1.27)	.04
Nocturnal symptoms	1.08	(1.00, 1.15)	.04	1.11	(0.98, 1.24)	.11
Limited speech	1.13	(1.04, 1.22)	<.01	1.10	(0.86, 1.34)	.41
Beta agonist use	1.07	(1.02, 1.13)	.01	1.05	(0.93, 1.16)	.43

[a] Incidence rate ratios (IRR) are presented per 10 $\mu g/m^3$ increase in PM concentration. Models were adjusted for age, race, sex, parent education, season, indoor $PM_{2.5}$, outdoor $PM_{2.5}$, and outdoor $PM_{2.5\text{-}10}$.

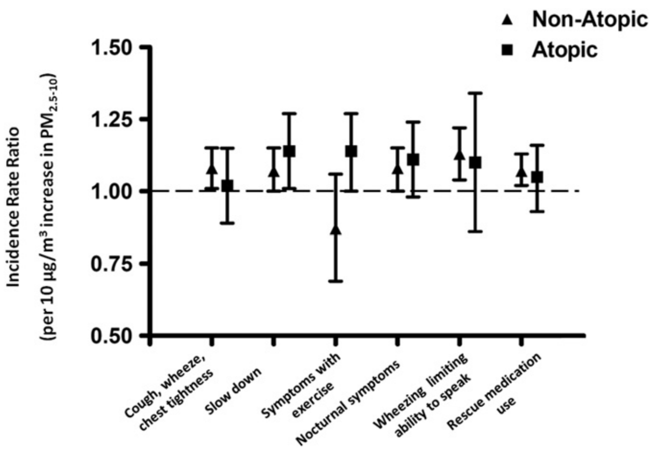

Figure 3. Multivariate analysis of the effect of indoor coarse PM on asthma morbidity. Incidence rate ratios are displayed as point estimates and 95% confidence intervals for the effect of indoor coarse $PM_{2.5-10}$ on asthma symptom outcomes and rescue medication use. Models were adjusted for age, race, sex, parent education, season, indoor $PM_{2.5}$, outdoor $PM_{2.5}$, and outdoor $PM_{2.5-10}$. With the exception of symptoms with exercise, an increase occurred in the incidence of asthma morbidity outcomes for every 10-μg/m^3 increase in $PM_{2.5-10}$ among both the non-atopic and atopic children with narrower confidence intervals for non-atopic asthma.

inner-city Baltimore cohort, indoor NO_2 levels were associated with increased asthma morbidity, independent of atopic status.[31] These findings suggest that environmental controls aimed at pollutants may be especially important to the non-atopic asthmatic.

Studies have not only suggested that pollutant exposure exacerbates existing non-atopic asthma but also that pollutant exposure may increase susceptibility to the development of non-atopic asthma, although these results have been inconsistent. In a study that investigated susceptibility to the risk of childhood asthma and wheeze with exposure to traffic, living within 75 m of a major road was associated with a more than 2-fold increased risk of lifetime asthma, prevalent asthma, or current wheeze among children without allergic symptoms, but not among those with allergic symptoms.[32] Another recent study suggested that traffic-related pollution exposure increased the risk of incident asthma and of asthma-related symptoms, and that this effect may be limited to non-atopic asthma but, according to the study authors, the small sample size limited their ability to interpret this finding.[33] However, other studies have yielded different conclusions, supporting stronger responses to traffic-related pollutant exposure among atopic children.[34,35]

Evidence suggests that the cellular response is similar between non-atopic and atopic asthma,[36–38] but that the allergens and antigens that "trigger" asthmatic responses may differ. Exposure to allergen and a subsequent allergic inflammatory response with associated bronchial hyperreactivity is associated with exacerbation of allergic asthma. For allergic asthma, pollutants may provoke asthma through various mechanisms, and hypotheses propose that particulate pollution can directly stimulate an inflammatory response or it can serve as a vehicle for carrying allergen and therefore provoke asthma through atopic pathways. Laboratory evidence supports this concept and suggests that air pollution exposure enhances the effect of allergens on asthma.[39–41] Interestingly, exposure to PM collected outdoors in Baltimore also has been shown to directly induce airway hyperresponsiveness and airway inflammation in mice in the absence of exogenous exposure to allergens in a T cell–dependent manner.[42] Although no known protein allergens have been found in these samples of outdoor Baltimore PM, possibly previously unrecognized allergens are present or PM induces cellular damage and leads to modification of self-proteins, leading to T cell activation in the absence of atopy. In support of the former hypothesis, Burney and colleagues[43] reported that in human studies exacerbations of asthma were associated with increases in the patient's immunoglobulin E binding to outdoor airborne particles collected during the weekend preceding the exacerbation as compared with control weekends in both non-atopic and atopic asthmatics.[43] Taken together, studies suggest that non-atopic patients can respond to previously unrecognized airborne antigens in a manner similar to atopic asthmatics but in the absence of atopy.

Our study has limitations, including that we do not have biological measures to investigate mechanistic differences between atopic and non-atopic responses to indoor pollutant exposure. A study currently underway[44,45] is examining potential differences in the inflammatory and oxidative stress responses between non-atopic and atopic asthmatics.

Table 4. Indoor Fine PM Concentrations and Asthma Morbidity by Atopic Status: Bivariate Models

	Non-atopic fine			Atopic fine		
	IRR	95% CI	*P* value	IRR	95% CI	*P* value
Cough, wheezing, chest tightness	1.03	(0.97, 1.09)	.31	1.02	(0.97, 1.07)	.36
Slow down	0.99	(0.92, 1.05)	.73	1.03	(0.98, 1.07)	.28
Symptoms with running	1.05	(0.99, 1.11)	.12	1.04	(1.0, 1.08)	.11
Nocturnal symptoms	0.98	(0.91, 1.05)	.59	1.04	(0.99, 1.08)	.12
Limited speech	1.05	(0.97, 1.13)	.26	0.97	(0.88, 1.06)	.52
Beta agonist use	1.08	(1.02, 1.14)	<.01	1.02	(0.97, 1.06)	.43

Table 5. Indoor Fine PM Concentrations and Asthma Morbidity by Atopic Status: Multivariate Models[a]

	Non-atopic fine			Atopic fine		
	IRR	95% CI	*P* value	IRR	95% CI	*P* value
Cough, wheezing, chest tightness	1.04	(0.96, 1.11)	.34	1.04	(0.99, 1.10)	.14
Slow down	0.98	(0.91, 1.06)	.70	1.07	(1.02, 1.13)	.01
Symptoms with running	1.06	(0.99, 1.14)	.12	1.07	(1.02, 1.13)	.01
Nocturnal symptoms	1.02	(0.94, 1.09)	.66	1.09	(1.03, 1.14)	<.01
Limited speech	1.12	(1.02, 1.22)	.02	1.02	(0.92, 1.12)	.70
Beta agonist use	1.09	(1.02, 1.15)	.01	1.03	(0.98, 1.09)	.21

[a] Incidence rate ratios (IRR) are presented per 10-$\mu g/m^3$ increase in PM concentration. Models were adjusted for age, race, sex, parent education, season, indoor $PM_{2.5}$, outdoor $PM_{2.5}$, and outdoor $PM_{2.5-10}$. Models were adjusted for age, race, sex, parent education, season, indoor $PM_{2.5-10}$, outdoor $PM_{2.5}$, and outdoor $PM_{2.5-10}$.

Although assessing exposure in all microenvironments is challenging, our measurement of indoor PM was performed in the home where children spent approximately half of their time (average of 12 hours), and most of this time was spent in the bedroom, where the environmental equipment was placed. We also were able to adjust for ambient PM concentrations in our models. Although we were not able to account for additional potential co-pollutants, we were able to adjust for ambient PM concentrations in our models. The classification of atopic status represents a single point in time during preschool age, and we acknowledge that atopic status may change in these children over time. However, we were able to perform skin testing, using a comprehensive panel of allergens that represent common environmental exposures in this community. The size of the current study is a strength, providing an evaluation of atopic status in a large, well-characterized cohort of patients with extensive environmental monitoring, overcoming some limitations of previous studies of indoor PM that included sample sizes of less than 20 subjects.[11,12,15,16]

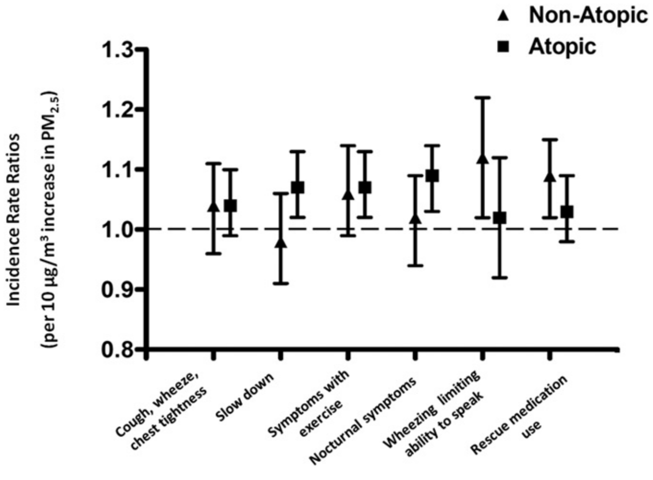

Figure 4. Multivariate analysis of the effect of indoor fine PM on asthma morbidity. Incidence rate ratios are displayed as point estimates and 95% confidence intervals for the effect of indoor $PM_{2.5}$ on asthma symptom outcomes and rescue medication use. Models were adjusted for age, race, sex, parent education, season, indoor $PM_{2.5-10}$, outdoor $PM_{2.5}$, and outdoor $PM_{2.5-10}$. There was an increase in the incidence of asthma morbidity outcomes for every 10-$\mu g/m^3$ increase in $PM_{2.5}$ for most symptom outcomes and for rescue medication use among both non-atopic and atopic children.

Guideline recommendations for the management of asthma include environmental control practices that focus largely on allergen avoidance for those with atopic asthma.[46,47] Very few environmental control practice recommendations address airborne pollutants, mainly because of the lack of strong evidence supporting a beneficial health effect of pollutant reduction. The current study demonstrates that exposure to indoor PM is associated with increased asthma morbidity among both atopic and non-atopic children. Because relatively fewer competing causes exist for exacerbations of non-atopic asthma, environmental control practices that decrease exposure to pollutants may confer an even greater health benefit for this group. In the few major asthma intervention trials,[48,49] non-atopic children have sometimes been excluded from participation.[49] The inclusion of non-atopic children should be emphasized in future studies, and comparison of responses to environmental control practices between non-atopic and atopic should be reported.

CONCLUSIONS

In-home PM concentrations were associated with increased asthma symptoms and the need for rescue medication among both non-atopic and atopic preschool children living in inner-city Baltimore. This finding may be especially important for non-atopic asthmatics, because there are fewer alternative triggers compared with those with atopy. Future studies investigating the impact of interventions to reduce indoor PM and other indoor pollutants may be critical to better understanding the causative mechanism of non-atopic asthma and to providing evidence to support environmental modification recommendations for future iterations of current national and international asthma guidelines. In the meantime, strategies to reduce and eliminate sources of indoor particulate matter pollution should be considered a priority in the management of non-atopic asthma.

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