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Domestic airborne black carbon levels and 8-isoprostane in exhaled breath condensate among children in New York City[☆]

Maria Jose Rosa^{a,*}, Beizhan Yan^b, Steven N. Chillrud^b, Luis M. Acosta^a, Adnan Divjan^a, Judith S. Jacobson^c, Rachel L. Miller^{a,d}, Inge F. Goldstein^c, and Matthew S. Perzanowski^a

^aDepartment of Environmental Health Sciences, Mailman School of Public Health, Columbia University, 722 W 168th Street, 11th floor, New York, NY 10032, United States

^bLamont-Doherty Earth Observatory, Columbia University, Comer Building, Rm 203, Palisades, NY 10964, United States

^cDepartment of Epidemiology, Mailman School of Public Health, Columbia University, 722 W 168th Street, R732, New York, NY 10032, United States

^dDivision of Pulmonary, Allergy, Critical Care Medicine, Department of Medicine, Columbia, University College of Physicians and Surgeons, 630 W 168th Street, PHE-101, New York, NY 10032, United States

Abstract

Background—Exposure to airborne black carbon (BC) has been associated with asthma development, respiratory symptoms and decrements in lung function. However, the mechanism through which BC may lead to respiratory symptoms has not been completely elucidated. Oxidative stress has been suggested as a potential mechanism through which BC might lead to adverse health outcomes. Exhaled breath condensate (EBC) allows for the non-invasive collection of airway lining fluid containing biomarkers of oxidative stress like 8-isoprostane, a stable by-product of lipid peroxidation. Therefore, we sought to characterize the association between domestic airborne BC concentrations and 8-isoprostane in EBC.

Materials and methods—Seven- and eight-year-old children participated in an asthma case-control study in New York City. During home visits, air samples and EBC were collected. Seven day averages of domestic levels of particulate matter $<2.5 \mu\text{m}$ ($\text{PM}_{2.5}$), BC and environmental tobacco smoke (ETS) were measured. Urea and 8-isoprostane were measured by liquid chromatography tandem mass spectrometry (LC/MS/MS) in EBC.

Results—In univariate models, $\text{PM}_{2.5}$ and BC, but not ETS, were significantly associated with increases in 8-isoprostane in the EBC ($\beta = 0.006$ and $\beta = 0.106$ respectively, $p < 0.05$ for both).

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*Correspondence to: Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1057, New York, NY 10029, United States. Fax: +1 212 996 0407.

Conflicts of interest

The authors report no conflicts of interest.

These associations remained statistically significant for both PM_{2.5} and BC after adjustment for covariates. In a co-pollutant model including PM_{2.5}, BC and ETS, only BC remained a statistically significant predictor of 8-isoprostane ($p < 0.05$).

Conclusions—Our findings suggest the BC fraction of PM might contain exposure relevant to increased oxidative stress in the airways.

Keywords

Air pollution; Biomarkers; Black carbon; Exhaled breath condensate; Oxidative stress

1. Introduction

Exposure to airborne particulate matter (PM), diesel exhaust particles (DEP) and combustion by-products has been implicated in asthma development and morbidity (Clark et al., 2010; Jung et al., 2012). Early life exposure to traffic-related air pollutants and living in proximity to point sources that contribute to airborne PM have been associated with elevated risk of asthma in young children (Clark et al., 2010). Proximity to roadway has been associated with increased asthma prevalence and report of wheeze in children living in southern California (McConnell et al., 2006). Indoor levels of PM were found to be associated with development of wheeze at ages 5–7 years in an inner-city cohort in New York City (NYC) (Jung et al., 2012). However the effect of these exposures on underlying biological processes in the airways that may lead to these outcomes has not been completely elucidated.

Recently, black carbon (BC) has been proposed as a more suitable surrogate for DEP exposure than PM, given its association with the volume of diesel traffic and not car traffic (Cornell et al., 2012; Lena et al., 2002). DEP are thought to be responsible for a large portion of the detrimental effects of traffic-associated PM (Sydbom et al., 2001). Truck route density was also a strong predictor of wintertime BC and domestic level BC in two different studies (Clougherty et al., 2013; Cornell et al., 2012). In addition, burning of residual fuel oil, used extensively in apartment and commercial heating in NYC, is a significant source of airborne BC (Clougherty et al., 2013; Cornell et al., 2012). Previous epidemiological studies have found associations between BC exposure and adverse respiratory outcomes. In a birth cohort in British Columbia, central site levels of BC, but not PM_{2.5}, early in life were associated with increased risk of childhood asthma diagnosis (Clark et al., 2010). Local BC levels estimated through a spatio-temporal land-use regression model were associated with decrements in lung function measures in women living in East Boston (Suglia et al., 2008). In NYC adolescents, increases in school levels of BC were associated with acute respiratory symptoms, including increased wheeze, chest tightness and shortness of breath (Patel et al., 2010).

Despite growing evidence linking BC exposure and respiratory illness, the mechanism through which BC may lead to these adverse respiratory effects has not been completely elucidated. One of the potential mechanisms is oxidative stress. 8-isoprostane, which belongs to the family of F₂-isoprostanes and is a by-product of the free radical-catalyzed peroxidation of arachidonic acid, can be measured in exhaled breath condensate (EBC). It

has been used as a surrogate marker of oxidative stress in multiple studies, and found to be elevated in the presence of asthma, cystic fibrosis and chronic obstructive pulmonary disease (Baraldi et al., 2003; Montuschi et al., 2000a,1999,2000b). Exposure to combustion fly ash particles, as a model for particulate matter exposure, also has been shown to induce generation of reactive oxygen species (ROS) in lung murine and primary human macrophages (Fritsch-Decker et al., 2011). In this particular study, murine macrophages that were incubated with a low dose of fly ash particles had a time dependent increase in 8-isoprostane concentrations (Fritsch-Decker et al., 2011).

The measurement of 8-isoprostane in the airways also can aid in the study of airborne exposures. Recently, researchers in China found positive associations between central site levels of PM_{2.5} and 8-isoprostane, measured in EBC collected from healthy young adults (Huang et al., 2012). In another recent study, 1–5 day averages of BC measured at NYC high schools were associated with increased levels of 8-isoprostane measured in EBC in adolescents enrolled at the schools (Patel et al., 2013). Spatial variability and temporality have been shown to be significant predictors of BC concentrations in NYC, stressing the importance of understanding local exposure patterns (Clougherty et al., 2013). Therefore, we sought to characterize the association between short-term domestic measures of BC, and additionally PM_{2.5} and environmental tobacco smoke (ETS), another known pollutant associated with oxidative stress (Kostikas et al., 2013; Noakes et al., 2007) and 8-isoprostane measured in EBC as a surrogate marker of oxidative stress in a cohort of children living in NYC. We hypothesized that increased levels of all three of these measures of pollutant exposure would be associated with increased levels of 8-isoprostane in EBC.

2. Materials and methods

2.1. Study cohort

Participants ($N = 350$) were enrolled in the New York City Neighborhood Asthma and Allergy Study (NYC NAAS) and enrollment has been previously described (Olmedo et al., 2011). In brief, the NYC NAAS is a case–control asthma study of 7–8 years old children living in NYC whose parents were recruited through the Health Insurance Plan of New York (HIP), a middle-income insurance provider. Neighborhoods were selected based on zip code level asthma prevalence among 5-year-old children as reported by the NYC Department of Health and Mental Hygiene (2003). Neighborhoods in the Bronx, Brooklyn, Queens and Manhattan with asthma prevalence of 3–9% were defined as lower asthma prevalence neighborhoods (LAPN) and those with asthma prevalence of 11–18% as higher asthma prevalence neighborhoods (HAPN). Cases were defined based on parental report of symptoms, including responses to the International Study of Asthma and Allergy in Childhood (ISAAC) wheeze module. Children were classified based on whether the parent reported at least one of the following for the child in the 12 months prior to administration of the questionnaire: 1) wheeze, 2) being woken at night by cough without having a cold, 3) wheeze with exercise or 4) report of asthma medication use. Children who did not meet any of these criteria were classified as controls. Demographic characteristics were obtained through questionnaires administered during home visits. Columbia University Institutional Review Board procedures for consent and assent were followed.

2.2. Domestic pollutant assessment

PM_{2.5} was collected by sampling air in the child's home at 1.5L/min for 7days. BC and ETS were quantified on the filter using a recently validated multi-wave length optical absorption technique developed for Teflon filters utilizing a modified Lawless method (Yan et al., 2011). The optical device used consisted of a balanced deuterium tungsten halogen light source (DH-2000-BAL), an integrating sphere (ISP-50-8-R), a lab-made filter holder, and an Ocean Optics USB4000-VIS-NIR miniature fiber-optic spectrometer. Children's home addresses were geocoded and linked to a previously described GIS database (Lovasi et al., 2009). The density of buildings burning residual oil and the truck route density in a 500-m Euclidean radius were examined as potential predictors due to a previously seen association between these two variables and domestic BC levels (Cornell et al., 2012). In order to examine neighborhood level exposures, annual averages of PM_{2.5} and elemental carbon (EC), which is representative of the same carbonaceous fraction as BC and are considered comparable, were obtained from the NYC Community Air Survey for 2009 and assigned to each participant based on their United Hospital Fund (UHF) ID.

2.3. Exhaled breath condensate collection and analysis

EBC was collected using the R-tube system (Respiratory Research Inc., Charlottesville, VA) during the home visit *before* the start of the 7 days air monitoring session due to logistical issues. Exhaled breath is condensed as it passes through a collection chamber within a cold (−20 °C) aluminum sleeve. Children were seated and instructed to form a complete seal around the mouth piece and breathe at a normal rate for 10 min. The breath condensate was aliquoted and stored at −80 °C until analyses. The measurement of biomarkers in EBC stems from the idea that airway lining fluid droplets become aerosolized during exhalation (Kharitonov and Barnes, 2002). However, there is extreme and variable dilution of droplets from airway lining fluid (Effros et al., 2003). Urea, which exists under homeostatic regulation in the body, has been previously used as a marker of dilution in EBC (Effros et al., 2003). Urea and 8-isoprostane were measured in 150 randomly chosen EBC samples by liquid chromatography tandem mass spectrometry (LC/MS/MS) using a Thermo Finnigan TSQ Quantum system (Thermo Fisher Scientific, Waltham, MA) at the Lamont-Doherty Earth Institute. Due to a transient problem with the assay, 8-isoprostane levels could not be measured in one batch of 14 samples. Because there was not enough EBC volume in storage, these samples could not be assayed again and were excluded from analyses. Of these 14 samples, 6 (42.9%) were from participants classified as controls while the remaining 8 (57.1%) were from participants classified as cases.

2.4. Statistical analyses

Complete data was available for 130 participants. Data were analyzed using generalized estimating equations models with an exchangeable correlation matrix and a robust estimator covariance structure (SPSS18, Chicago, IL). Children were matched by UHF ID to account for spatial correlation within neighborhoods. All three pollutants were analyzed as continuous predictors and were not logarithmically transformed in order to make the estimates more easily interpretable. 8-isoprostane and urea concentrations were natural log transformed; therefore the association between the pollutants and biomarkers is interpreted

as a percent change. Potential covariates were included in the model if their presence produced a greater than 10% change in beta. Final models were adjusted for case control status, sex, African American race, heating season (defined as October 1st–April 30th) and urea concentrations. BC, PM_{2.5} and ETS were analyzed both as separate predictors of 8-isoprostane and in a co-pollutant model.

3. Results

Selected participants did not differ significantly from participants excluded from these reported analyses (Supplemental Table E1), except that the included cohort had a significantly greater proportion of cases to controls ($p = 0.007$). Demographic characteristics for the participants and descriptive measures for each pollutant are shown in Table 1. Almost half (46.9%) of the participants were African American and 36.2% were classified as of Hispanic ethnicity. As shown in Fig. 1, domestic measures of BC and PM_{2.5} correlated moderately. BC also significantly correlated with neighborhood annual measures of EC and PM_{2.5}. In this subset of participants, we also found that both truck route density ($\beta = 0.217$, $p = 0.015$) and number of buildings burning residual oil ($\beta = 0.016$, $p = 0.001$) were significant predictors of domestic BC as previously reported in the larger cohort (Cornell et al., 2012). Domestic levels of PM_{2.5} were not significantly associated with any neighborhood pollutant measures; however there was a modest association between domestic and neighborhood PM_{2.5} during the heating season (results not shown). BC and ETS were inversely correlated, but upon further exploration, these results appeared to be driven by the samples with non-detectable levels of ETS (57/130, 44%).

PM_{2.5} ($\beta = 0.006$, 95% CI [0.000, 0.012]) and BC ($\beta = 0.106$, 95% CI [0.044, 0.167]) but not ETS exposure were associated with increased 8-isoprostane in the EBC. These associations remained significant after adjustment for case control status, sex, African American race, heating season and urea concentrations for both PM_{2.5} ($\beta = 0.008$, 95% CI [0.001, 0.014]) and BC ($\beta = 0.094$, 95% CI [0.021, 0.166]). Fig. 2 shows adjusted results expressed in terms of percent increase in 8-isoprostane per interquartile (IQR) range increase of each pollutant. An IQR increase in BC was associated with an 11% mean increase in 8-isoprostane and an IQR increase in PM_{2.5} was associated with a mean 10% increase in 8-isoprostane. As shown in Fig. 3, in a co-pollutant model including PM_{2.5}, BC and ETS, only BC ($\beta = 0.099$, 95% CI [0.012, 0.187]) remained a statistically significant predictor of 8-isoprostane. In order to determine if asthmatics were more susceptible to BC exposure, an interaction term for case/control status and BC was also included in one of the models but was found to be not significant ($p = 0.197$).

GIS variables and central site measures were also examined as potential predictors of 8-isoprostane. Truck route density and number of buildings burning residual oil were previously reported as significant predictors of domestic BC measures (Cornell et al., 2012); however, neither variable was significantly associated with 8-isoprostane (Table 2). Even though annual averages of PM_{2.5} and EC were significantly correlated with domestic BC measures (Spearman correlations 0.336 and 0.346 respectively, $p < 0.001$), these averages were not found to be predictors of 8-isoprostane (Table 2). Furthermore, none of these

variables significantly affected the associations between domestic pollutant levels and 8-isoprostane when included in multivariable models.

4. Discussion

The objective of this study was to determine the association between short-term domestic levels of airborne pollutants and 8-isoprostane, a biomarker of oxidative stress, measured in EBC. While we found that in single pollutant models, domestic levels of PM_{2.5} and BC, but not ETS, were associated with increased levels of 8-isoprostane, in a co-pollutant model including all three, only BC remained a significant predictor of increased 8-isoprostane levels. To our knowledge this is the first paper to look at these associations between 8-isoprostane and domestic levels of these airborne pollutants after adjusting for dilution by water vapor. This study provides evidence that the BC fraction of PM_{2.5} may be more important in the study of short-term oxidative stress response.

Few studies have looked at associations between airborne pollutant exposure and 8-isoprostane levels in EBC. In a study of asthmatic children in Canada, levels of PM_{2.5} obtained from central site monitoring were associated with decreased measures of pulmonary function but were not significantly associated with 8-isoprostane levels (Liu et al., 2009). Patients with stable coronary disease and healthy volunteers who underwent chamber exposure to concentrated fine and ultrafine particulate matter had significantly higher levels of 8-isoprostane after exposure (Mills et al., 2008). Recently, a study in China found that central site measurements of PM_{2.5}, but not EC, were associated with increased levels of 8-isoprostane in healthy Chinese young adults (Huang et al., 2012). In a study of NYC adolescents, higher BC levels measured at NYC high schools were associated with higher levels of 8-isoprostane, and in the same study no consistent associations were found between PM_{2.5} and 8-isoprostane (Patel et al., 2013).

There is some experimental evidence that particulate matter exposure can lead to oxidative stress. Diesel exhaust particle exposure has been shown to induce production of reactive oxygen species (ROS) in human airway epithelial cells (Marano et al., 2002). *In vitro* DEP exposure was shown to significantly induce oxidative stress as measured by glutathione synthesis genes and on total glutathione in endothelial cells and in a co-culture model of mouse macrophages and endothelial cells (Weldy et al., 2011). Incubation with combustion fly ash particles led to an increase in 8-isoprostane production in murine macrophages (Fritsch-Decker et al., 2011).

Even though tobacco smoke is a known oxidant (Howard et al., 1998; Kosecik et al., 2005), and ETS was detectable in 56% of the filters collected at the participants home, we found no significant association between domestic ETS measures and 8-isoprostane. Previous studies have not reported consistent associations between ETS exposure and oxidative stress biomarkers measured in EBC. After a 1h experimental exposure to ETS, healthy young adults had significantly higher levels of H₂O₂ in EBC (Kostikas et al., 2013). In another study, healthy children who had one or two parents who were smokers did not have significantly higher levels of H₂O₂ in EBC when compared to children who were not

exposed to ETS (Doniec et al., 2005). BC exposure might also be the more important contributor to oxidative stress, explaining the lack of any statically significant association.

Because burning of residual oil for heating and truck traffic are associated with indoor BC levels in this cohort, we also sought to determine if these variables were associated with 8-isoprostane levels. Heating season, during which burning of residual oil happens more frequently, was a significant predictor of 8-isoprostane in all models. However, the number of buildings burning residual oil and the truck route density in a 500-m Euclidean radius were not associated nor did they change the association between domestic BC and 8-isoprostane. A potential explanation for this lack of association is that these variables might reflect long term exposure while domestic measures reflect a short term exposure. These variables might not accurately reflect the local temporal variation seen in the domestic measures. This might also account for the lack of association between annual neighborhood averages of EC and 8-isoprostane levels in our cohort.

Our study had several strengths. 8-isoprostane was measured using a highly sensitive LC/MS/MS method, and was detectable in the majority of our samples. We were also able to adjust for the variable dilution of droplets from lung lining fluid, which has posed a problem in the accurate measurement of biomarkers in EBC (Effros, 2010). Urea has been used as a marker of dilution in EBC previously and shown to correlate well with other dilution markers (Effros et al., 2003). However, there are also some limitations to our study. Domestic exposure was assessed 7 days after collection of EBC. However, we previously showed a good correlation between outdoor central site BC levels measured the week prior and the week following the home visit (Cornell et al., 2012). Even though these central site measurements were only modestly correlated with our weekly domestic measures, another study in NYC found the ratio of indoor to outdoor BC measured in participants' homes to be about 1.0 across seasons (Jung et al., 2010). These results suggest a high penetration of BC generated outdoors and a lack of significant indoor sources (Jung et al., 2010), which supports our assumption that consecutive weekly indoor BC measures would be similarly correlated as consecutive weekly outdoor BC measures. BC is also a fairly stable contaminant (Kinney et al., 2002), whose variability is attributable to the distribution and production of local sources (*i.e.* increased truck traffic and burning of residual oil during the heating season) more than temporality (Clougherty et al., 2013). We would also expect that the dispersion of BC from these sources, due to weather factors such as wind speed and direction, to follow a weekly pattern (Cerveny and Balling, 1998; Wolff and Liroy, 1978) and to be similar during consecutive weeks. Another important consideration is other microenvironments besides the home in which the children might have relevant exposures to BC, like while at school or in transit (Buonanno et al., 2013). The cohort consisted of children belonging to middle-income families, limiting the generalizability to children of other socioeconomic strata. We also had a limited sample size and we did not adjust for potential indoor sources of airborne pollutants like incense burning. We cannot completely rule out BC acting as a surrogate for an unmeasured pollutant such as nickel, which is also released in significant quantities from the burning of residual fuel oil (Peltier et al., 2009). Polycyclic aromatic hydrocarbons (PAHs) may also be emitted during the combustion processes that generate BC (*i.e.* heating) and exposure to these components has been

associated with adverse respiratory outcomes (Miller et al., 2004; Rosa et al., 2011). BC may also act as a surrogate for ultrafine particulate matter, which due to its small size can deposit deeper in the lungs, and has been associated with the increased production of oxidative stress species (Alessandrini et al., 2009; Li et al., 2003).

The associations between domestic levels of BC and 8-isoprostane suggest that BC may be involved in processes that lead to increased oxidative stress in the airways. Our findings provide a better understanding of whether short-term exposure to different airborne pollutants contributes to airway oxidative stress which might contribute to downstream inflammation and respiratory symptoms. Measurement of BC levels might be more relevant than PM_{2.5} in the study of the sub-clinical effects of airborne pollutants on the airways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.envres.2014.09.003>.

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Fig. 1.

Scatter plots for domestic airborne pollutant measures. Panel A, scatter plot for domestic measures of PM_{2.5} and BC. Spearman $\rho = 0.568$. Panel B, scatter plot for domestic measures of PM_{2.5} and ETS. Spearman $\rho = 0.342$. Panel C, scatter plot for domestic measures of BC and ETS. Spearman $\rho = -0.432$. In all plots, transparency was set at 0.5 in order to avoid overplotting and visualize all points. All p -values < 0.001 .

Fig. 2.

Associations between BC, PM_{2.5} and ETS domestic measures and 8-iso-prostane in EBC (log-transformed) in a multivariable model. Data points and error bars describe the percent change in 8-isoprostane concentrations and 95% CI per an interquartile range increase in the concentrations of each pollutant, adjusted for sex, case-control status, African American race, heating season and urea concentration in EBC (log transformed).

Fig. 3.

Associations between BC, PM_{2.5} and ETS domestic measures and 8-iso-prostane in EBC (log-transformed) in a multivariable co-pollutant model. Data points and error bars describe the percent change in 8-isoprostane concentrations and 95% CI per an interquartile range increase in the concentrations of each pollutant, adjusted for sex, case-control status, African American race, heating season, urea concentration in EBC (log transformed) and with the inclusion of the three pollutants in the model.

Table 1

Demographic characteristics.

Case:control (<i>n</i>)	88:42
Male sex, <i>n</i> (%)	78/130 (60)
Ethnicity/race <i>n</i> (%)	
White	22/130 (16.9)
African American	61/130 (46.9)
Asian	15/130 (11.5)
Other/Mixed	29/130 (22.3)
Hispanic ethnicity	47/130 (36.2)
Mother completed high school, <i>n</i> (%)	119/128 (93)
Father completed high school, <i>n</i> (%)	111/121 (91.7)
Household income <25k, <i>n</i> (%)	9/130 (6.9)
Mother has asthma, <i>n</i> (%)	28/128 (21.9)
Father has asthma, <i>n</i> (%)	17/128 (13.3)
Seroatopic	65/125 (52)
PM _{2.5} median (25th–75th)	12.97 (8.21–20.22)
BC median (25th–75th)	1.30 (0.84–1.92)
ETS median (25th–75th)	0.07 (0.00–0.70)

Seroatopy defined as any specific IgE 0.35 IU/ml to ragweed, *d farinae*, cockroach, mouse urinary protein, cat, dog, tree mix or grass mix.

Table 2

Generalized estimating equations models for associations between selected GIS variables, neighborhood pollutant averages and 8-isoprostane.

Variable	Univariate β (95% CI)	Multivariable ^a β (95% CI)
Buildings burning residual oil (#)	0.001 (−0.003, 0.004)	0.000 (−0.004, 0.003)
Truck route density (km/km ²)	−0.015 (−0.110, 0.081)	−0.031 (−0.128, 0.066)
Annual PM _{2.5} average (µg/m ³)	0.030 (−0.091, 0.151)	0.011 (−0.111, 0.132)
Annual EC average (µg/m ³)	−0.177 (−0.891, 0.536)	−0.277 (−1.007, 0.453)

^a Adjusted for sex, African American race, case–control status, heating season and urea concentration (natural log).