Indoor black carbon and biomarkers of systemic inflammation and endothelial activation in COPD patients

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Abstract

Rationale—Evidence linking traffic-related particle exposure to systemic effects in chronic obstructive lung disease (COPD) patients is limited.

Objectives—Assess relationships between indoor black carbon (BC), a tracer of traffic-related particles, and plasma biomarkers of systemic inflammation and endothelial activation.

Methods—BC was measured by reflectance in fine particle samples over a mean of 7.6 days in homes of 85 COPD patients up to 4 times seasonally over a year. After the completion of sampling, plasma C-reactive protein (CRP), interleukin-6 (IL-6), and soluble vascular adhesion molecule-1 (sVCAM-1) were measured. Current smokers and homes with major sources of BC were excluded; therefore, indoor BC was primarily a measure of infiltrated outdoor BC. Mixed effects regression models with a random intercept for each participant were used to assess BC effects at different times (1–9 days before phlebotomy) and in the multi-day sample.

Results—Measured median BC was 0.19 μg/m^3 (interquartile range, IQR=0.22 μg/m^3). Adjusting for season, race, age, BMI, heart disease, diabetes, ambient temperature, relative humidity, a recent cold or similar illness, and blood draw time, there was a positive relationship between BC and CRP. The largest effect size was for BC averaged over the previous seven days (11.8% increase in CRP per IQR; 95%CI = 1.8–22.9). Effects were greatest among non-statin users and persons with diabetes. There were positive effects of BC on IL-6 only in non-statin users. There were no associations with sVCAM-1.
Conclusions—These results demonstrate exposure-response relationships between indoor BC with biomarkers of systemic inflammation in COPD patients, with stronger relationships in persons not using statins and with diabetes.

Keywords
Air pollution; Inflammation; COPD; Black carbon; Biomarkers

1. Introduction

Particles emitted from vehicles are a significant source of ambient particulate matter (PM) in the U.S. and in the world (Health Effects Institute Panel on the Health Effects of Traffic-Related Air Pollution, 2010). In urban areas, elemental (EC) or black carbon (BC) in PM is primarily a tracer of exposure to PM from traffic (Grahame et al., 2014). Recent studies have demonstrated associations between greater exposures to EC or BC with a greater risk of hospital admissions for chronic obstructive pulmonary disease (COPD) (Gan et al., 2013), increases in hospital admissions for respiratory causes (Bell et al., 2009), daily hospital admissions for pneumonia (Zanobetti and Schwartz, 2006), daily cardiovascular hospital admissions and mortality (Luben et al., 2017), and all-cause daily mortality (Atkinson et al., 2014).

Based on animal and in-vitro studies, the biological pathway responsible for these adverse effects has been attributed to effects of traffic-related particles promoting systemic inflammation and vascular endothelium activation (Ghio et al., 2000; Quay et al., 1998; Ramage et al., 2004; Salvi et al., 1999, 2000; Schmid et al., 2009; Vogel et al., 2005). There is growing evidence from studies in human populations supporting an association between ambient BC exposures and systemic effects that can be measured in the blood (Alexeeff et al., 2011; Bind et al., 2012; Delfino et al., 2008, 2009; Dubowsky et al., 2006; Fang et al., 2012; Li et al., 2017; Madrigano et al., 2010; O’Neill et al., 2007; Zeka et al., 2006). The clinical implications are particularly relevant for patients with COPD since a higher level of systemic inflammation is a marker of more severe disease, greater exacerbation risk, lower functional status, and worse clinical outcomes, including increased mortality (Agusti et al., 2012; Brightling, 2013; Fabbri and Rabe, 2007; Ferrari et al., 2013; Jing et al., 2016; Man et al., 2006; Moy et al., 2014a, 2014b; Thomsen et al., 2013). However, there is only one previous study in a small number of COPD patients that suggested that EC exposure may promote systemic inflammation (Hildebrandt et al., 2009).

Other than studies conducted by Delfino and coworkers that included indoor measurements but did not assess COPD patients (Delfino et al., 2008, 2009), previous investigators have used central site measurements of EC or BC (Bind et al., 2012; Dubowsky et al., 2006; Hildebrandt et al., 2009; Li et al., 2017; Madrigano et al., 2010; O’Neill et al., 2007; Zeka et al., 2006) or land-use exposure models (Alexeeff et al., 2011; Fang et al., 2012) to assess effects of outdoor exposures. In this study we investigated the effects of BC exposures collected in each participant’s home since that is where COPD patients spend the majority of their time. We assessed associations with plasma biomarkers of systemic inflammation, i.e., C-reactive protein (CRP) and interleukin-6 (IL-6), and a biomarker of vascular endothelial
activation, soluble vascular adhesion molecule-1 (sVCAM-1). Some of the results of these studies have been previously reported in the form of an abstract (Garshick et al., 2016).

2. Methods

2.1. Population

Between November 2012 and December 2014 we recruited 88 COPD patients from Eastern Massachusetts. Potential subjects were identified by review of VA Boston pulmonary and primary care clinics and pulmonary function laboratory encounters based on ICD-9 codes 490–493 and 496. Invitation letters were sent with telephone follow-up, and flyers were placed at VA Boston. Persons were eligible if they were age 40 or greater, were former smokers who had smoked at least 10 pack years, and had a FEV₁/FVC < 0.70 on post-bronchodilator spirometry or emphysema on CT scan reports in the medical record. Persons with malignancies other than local skin or stable prostate cancer, or with a systemic inflammatory disease such as rheumatoid arthritis, were excluded. At recruitment persons were also excluded if they reported exposure at home to one or more indoor BC source such as smoking, wood stove burning or fireplace use, and regular candle or incense burning. Eligibility was confirmed at an in-person visit. Eligible participants returned for up to four additional clinic visits (1 per season). All visits were scheduled a minimum of two weeks after completion of antibiotics or steroids for a COPD exacerbation and participants were clinically stable when assessed. The protocol was approved by the Institutional Review Boards of VA Boston and Harvard Medical School, and all participants provided informed consent.

2.2. Exposure assessment

Prior to each clinic visit, subjects were provided with an in-home micro-environmental sampler to collect BC data for one week in the room where they spent most time, excluding the kitchen. Samplers were picked up and returned in-person or by express shipping. The in-home sampler included a pump (VP0140, Medo USA, Roselle, IL) set to a flow rate of 1.8 LPM, using a size-selective impactor to collect particles with aerodynamic diameter ≤2.5 μm (PM$_{2.5}$). Filters were weighed before and after sampling using a Mettler MT-5 electronic microbalance equilibrated in a temperature and humidity controlled room. An EEL M43D Smokestain Reflectometer was used to determine BC, with reflectance measured before and after sampling, yielding the net measurement of BC mass. BC concentrations were calculated by dividing the net BC mass of each filter (μg) by the total volume of air sampled (m$^3$). The limit of detection for BC was 0.03 μg/m$^3$, however all values were included to preserve the distribution of exposure. This method provided one multi-day integrated sample of BC for each sampling session. Nitrogen dioxide (NO$_2$) was measured over the same weekly sampling period using an Ogawa passive sampling badge attached to the micro-environmental sampler.

Outdoor BC daily averages were measured at a central site (Francis A. Countway Library, Boston, MA) using an aethalometer (Magee Scientific Company, model AE-16, Berkeley, CA) (Kang et al, 2010). Previously, we reported a linear relationship between BC
concentrations determined by aethalometer and reflectance ($R^2 = 0.72$, Slope = 0.95) (Gaffin et al., 2017).

Daily indoor BC for each home on each sampling day was estimated using the daily central site data on the days sampling was conducted by the participant and the in-home (weekly) integrated value using the following equation (Grady et al., 2018):

$$\text{Indoor daily} = \frac{\text{Outdoor measured daily}}{\text{Outdoor measured weekly}} \times \text{Indoor measured weekly}.$$  

In the absence of indoor sources, indoor BC represents outdoor infiltration; therefore, we expect daily indoor levels to be proportional to outdoor levels. In previous work, we found that daily variability of BC at the central site reflects that in Eastern Massachusetts (Gryparis et al., 2007; Suglia et al., 2008; Tang et al., 2018). We also demonstrated that the daily home infiltration rate of fine particles from outdoors to indoors varies little within a short period (i.e., over a week) (Brown et al., 2009). We constructed indoor BC daily moving averages starting the day before (day 1) to nine days before phlebotomy (day 9). Since BC is a component of PM$_{2.5}$, we estimated PM$_{2.5}$ effects other than BC by regressing each PM$_{2.5}$ moving average on the corresponding BC moving average and obtaining the residuals. The use of PM$_{2.5}$ residuals as an exposure variable avoids over-adjustment if the PM$_{2.5}$ concentrations were included in BC exposure models (Mostofsky et al., 2012).

### 2.3. Biomarkers of systemic inflammation and endothelial activation

At each clinic visit after sampling, blood was drawn into EDTA tubes, stored in an insulated container with an icepack, and immediately transported to the research core blood laboratory at VA Boston where samples were centrifuged for 15 min at 2600 rpm at 4 °C and stored at −80 °C. Biomarker analyses were performed by the Clinical & Epidemiologic Research Laboratory, Department of Laboratory Medicine at Children’s Hospital in Boston. High sensitivity CRP was determined using an immunoturbidimetric assay with a sensitivity of 0.03 mg/L. IL-6 was measured by an ultra-sensitive ELISA assay with a sensitivity of 0.094 pg/mL, and sVCAM-1 was measured by an ELISA assay with a sensitivity of 2.0 ng/mL.

### 2.4. Potential confounders and effect modifiers

Variables were chosen a priori as confounders or effect modifiers from known predictors of the biomarkers or BC exposure. Weight and height were obtained at each visit and body mass index (BMI) was calculated. Information on medication use, including statins and inhaled steroids, heart disease requiring treatment in the past 10 years, and doctor diagnosis of diabetes were obtained from questionnaires. Pulmonary function was available by spirometry conducted before and after 180 μg of albuterol (2 puffs) at each visit (Miller et al., 2005). At each visit each participant was asked if he/she experienced a cold or other respiratory illness in the past two weeks. Daily outdoor temperature at each person’s home was estimated using an exposure model based on satellite remote sensing, land use, and ground level temperature data (Kloog et al., 2014). Relative humidity was obtained from measurements at the Boston Logan International Airport weather station. Season was categorized based on visit month as spring (March, April, May); summer (June, July, August); winter (December, January, February); and fall (September, October, November).
2.5. Statistical Methods

Linear mixed effects regression models were used with a random intercept for each subject (PROC MIXED, SAS version 9.4). BMI, age, race, heart disease, diabetes, time of blood collection, report of a cold or other respiratory illness in the past 2 weeks, season, and temperature and relative humidity with the same moving averages as BC were included a priori in regression models. Each biomarker was natural log-transformed to meet model assumptions. There were no deviations from linearity as determined using penalized splines (R mgcv package, R, version 3.1.2) and validity of model assumptions was confirmed by examination of residuals. Effect modification by statin use, inhaled steroid use, diabetes, heart disease, obesity (BMI ≥ 30), and COPD severity (%-predicted (Hankinson et al., 1999) FEV$_1$ ≥ median) were explored using multiplicative interaction terms and stratum specific effect estimates. We conducted a sensitivity analysis to consider possible confounding by NO$_2$ and PM$_{2.5}$ residuals. Beta and 95% CI values were calculated based on a 0.22 μg/m$^3$ increase in BC (integrated sample interquartile range; IQR).

3. Results

3.1. Subject characteristics

Three subjects were excluded due to smoking, and the remaining 85 participants provided 287 measurements of BC and biomarkers (54 patients with 4 measurements; 16 with 3 measurements; 8 with 2 measurements; 7 with 1 measurement). The sampler ran indoors for a mean of 7.6 days (range 4–10) and in 94% of visits, the sampler was returned within 2 days of phlebotomy. The number of observations that contributed to each moving average varied from 259 to 287 (Supplemental Tables 1–3). Following the screening visit, the median (25–75th percentile) time between the first and last study visit was 279 (273–290) days. Mean age (sd) at study entry was 72.7 (8.4) years and most had GOLD severity 1 or 2 COPD, with mean (sd) %-predicted post-bronchodilator FEV$_1$ of 68.1 (20.6)% (Table 1). Sixty-six persons (76.5%) reported statin use, 65 persons (76.5%) reported inhaled steroid use, 21 persons (24.7%) were diabetics, and 39 persons (45.8%) were obese. Indoor BC levels were considerably lower than outdoor levels, as the median (25–75 percentile) central site outdoor values were approximately 2–4 times indoor levels (Table 2). On average, persons spent approximately 17 h inside their homes daily with little variation by season. A mild cold or other respiratory illness (not an exacerbation requiring treatment) was reported before 46 (16%) of the visits.

3.2. Main effects of BC

In a regression model that assessed the effects of indoor BC using the directly measured multi-day integrated filter sample, there was a 10.9% increase in CRP (95%CI = 0.7–22.2) for each IQR increase in BC. Assessing effects from the day prior to phlebotomy (day 1) and with BC moving averages from days 1–2 through 1–9, there was a positive relationship between BC exposure and CRP that was greater with longer moving averages (Fig. 1 and Supplemental Table 1). Effects were statistically significant with indoor BC averaged over days 1–5 through days 1–9, with the greatest effect on days 1–7 (11.8% increase in CRP; 95%CI = 1.8–22.9). BC exposures were not associated with IL-6 or sVCAM-1 (Fig. 1, Supplemental Tables 2 and 3).
3.3. Effect modification

Effect estimates for CRP were larger among non-statin users compared to statin users for all BC exposures (Fig. 2A). For example, there was a 22.3% increase (95% CI = 0.5–48.8) in CRP among non-statin users and a 9.5% increase (95% CI = −1.4 to 21.4) in CRP among statin users per IQR increase in BC averaged over days 1–7. However, the interaction between BC and statin use was only statistically significant with BC exposure on day 1 (p = 0.036). Participants with diabetes also had a greater increase in CRP for all BC exposures compared to participants without diabetes (Fig. 3A). For example, for each IQR increase in exposure averaged over days 1–5, participants with and without diabetes had a 23.5% increase in CRP (95% CI = 5.7–44.3) and 3.1% increase in CRP (95% CI = −9.1 to 16.8), respectively. However, the p-interaction for all BC moving averages and the multi-day directly measured sample was not statistically significant (p = 0.07–0.72).

There were also differences in the effects of BC exposure on IL-6 due to statin use. Non-statin users had a greater increase in IL-6 compared to statin users (Fig. 2B). The interaction between statin users and nonusers was statistically significant for exposures averaged over days 1–3 through 1–8 (p-interaction = 0.026–0.039) and for the integrated multi-day sample (p = 0.044). Although the effects in participants with diabetes effects on IL-6 were slightly greater for all moving averages of BC (Fig. 3B), these differences were not significant compared to participants without diabetes (p = 0.26–0.69). There was no effect modification by statin use or diabetes of the association between BC and sVCAM-1 (Figs. 2C and 3C).

Due to a limited sample-size in some subgroups, it was not possible to further divide the cohort by statin use and diabetes. However, it was unlikely that diabetes influenced the effects of BC in non-statin users, since most non-statin users (89%) did not have diabetes. In addition, most diabetics (90%) were taking statins, yet a greater effect of BC was noted on CRP in diabetics. There was no suggestion of effect modification between inhaled steroid use, heart disease, or %-predicted FEV\textsubscript{1} with any measure of BC exposure on CRP, IL-6, or sVCAM-1 (data not shown). It was not possible to meaningfully assess effect modification by obesity since most (87%) of the obese participants were also taking statins.

3.4. Adjustment for other pollutants

We explored whether components of PM\textsubscript{2.5} other than BC and NO\textsubscript{2} were confounders of the associations between each biomarker and BC. Fewer observations were available due to smaller numbers of corresponding NO\textsubscript{2} and PM\textsubscript{2.5} measurements (243–272 observations depending on model). In the multipollutant models, the effects of BC on each biomarker were similar to single pollutant models (Supplemental Fig. 1). For example, effects on CRP were still greater with longer moving averages and slightly wider confidence limits. For days 1–7, there was 12.2% increase in CRP (95% CI = 1.1–24.5). There were no significant effects of PM\textsubscript{2.5} residuals or NO\textsubscript{2} on BC in any model.

3.5. Other covariates

The effects of other covariates on each biomarker varied based on the specific model and biomarker. For CRP, the most important variables (i.e., significant in at least one model examining the main effects of BC) were a cold or other respiratory illness in the past two weeks, time of blood collection, season, and BMI. For IL-6, the most important variables
were a cold or other respiratory illness in the past two weeks, time of blood collection, season, and heart disease. For sVCAM-1, the most important variables were diabetes, BMI, and age.

4. Discussion

In patients with COPD we report a positive association between CRP, a biomarker of systemic inflammation, and short-term in-home exposure to BC, a marker of exposure to particles derived from traffic. Effects of BC on CRP appeared to be greater in non-statin users and in persons with diabetes. For IL-6, the positive effects of BC also appeared greater in non-statin users. There were no effects of BC on sVCAM-1, a circulating biomarker that reflects endothelial activation.

To the best of our knowledge, we are the first to report a significant association between short-term effects of BC exposure on systemic inflammation in COPD patients. A previous study included 38 COPD patients with 208 repeated measurements of EC made over 8 months at an outdoor central site 5 days before measurement of several plasma inflammatory biomarkers (Hildebrandt et al., 2009). Although there were no effects on CRP, there were suggestive effects of EC on fibrinogen and E-selectin. The reasons for not detecting associations with CRP or stronger associations with these other inflammatory biomarkers are uncertain but may relate to the small sample size and shorter time-frame for repeated measures assessment. This would reduce variation in exposure and biomarker response, making it harder to detect an effect.

Our suggestive findings regarding greater effects of BC on CRP and IL-6 in non-statin users are consistent with the anti-inflammatory effects of statins and their ability to reduce levels of circulating CRP and IL-6 (Bajpai et al., 2010; Berthold et al., 2013). However, there has been limited assessment of the effect of statins mitigating the effects of BC or EC exposures in other cohorts. For example, Delfino and coworkers described positive effects of EC exposure on CRP and IL-6 in the elderly (Delfino et al., 2008, 2009) but noted greater effects in non-statin users in only a subset of the cohort (Delfino et al., 2008). In 3996 participants from the Framingham Offspring and Third Generation Study cohort, effects of BC based on central site data were observed for exposures up to 7 days on CRP and IL-6 (Li et al., 2017). However, there was no effect modification by statin use.

A more common finding has been greater effects of BC or EC exposures on CRP and IL-6 in persons with diabetes as compared to persons without diabetes (Dubowsky et al., 2006), including in the Framingham Offspring and Third Generation Study cohort (Li et al., 2017). The VA Normative Aging Study included elderly men with and without diabetes and used a BC land use regression model to predict exposure outside each subject’s residence; positive effects of BC on IL-6 4 days before blood draw were noted in persons with diabetes but not in persons without diabetes (Fang et al., 2012). Although O’Neill et al. reported positive effects of BC on sVCAM-1 in a cohort of 92 persons with diabetes in the 6 days before phlebotomy (O’Neill et al., 2007), we did not note any effects on sVCAM-1, in persons with diabetes nor in the overall sample. In the VA Normative Aging study, positive effects of BC
were found on sVCAM-1, with the greatest effects at 4–12 weeks prior to the clinical visit in participants with diabetes (Alexeeff et al., 2011; Bind et al., 2012; Madrigano et al., 2010).

Although both CRP and IL-6 are plasma biomarkers associated with systemic inflammation, associations between BC and CRP were stronger and more consistent than those with IL-6. IL-6 is expressed in many types of cells, including endothelial cells and neutrophils, and is a primary determinant of hepatic production of CRP. However, compared to CRP, which has a plasma half-life of 19 h (Pepys and Hirschfield, 2003), IL-6 has a relatively short half-life (< 6 h) (Ridker et al., 2000). Due to its longer half-life, it is possible that CRP better reflects effects of single- or multi-day BC exposures as it will remain elevated longer in response to exposures as compared to IL-6. Vascular endothelial cell activation is characterized by the endothelial expression of cell-surface adhesion molecules such as VCAM-1 (Cook-Mills et al., 2011). It is possible that the circulating levels of sVCAM-1 in our subjects do not sufficiently reflect expression of membrane-bound VCAM-1 at the exposures measured.

Many of the previous studies of the effects of BC or EC on inflammation and endothelial dysfunction were conducted using Boston-area based cohorts (Alexeeff et al., 2011; Bind et al., 2012; Fang et al., 2012; Li et al., 2017; Madrigano et al., 2010; O’Neill et al., 2007; Zeka et al., 2006) and reflect outdoor BC measurements when ambient BC exposure levels were higher in Boston (Kang et al., 2010). In the Framingham cohort, subjects were included from 1998 on (Li et al., 2017) and in the Normative Aging Study from 1999 to 2000 (Bind et al., 2012; Fang et al., 2012; Madrigano et al., 2010; Zeka et al., 2006). Ambient levels of BC between 1998 and 2002, at the central site were considerably higher (i.e., 75%ile = 5.8 μg/m³) as compared to those measured during our study at the same location (75%ile = 0.78 μg/m³ with a maximal value of 1.53 μg/m³)(O’Neill et al., 2007). As noted, indoor levels in the current study were even lower. The very low levels of BC measured in the current study reflect the continued reduction in traffic-related particulate matter over the past 30 years (Davis et al., 2011). Nevertheless, we were still able to detect effects on CRP and IL-6 in non-statin users.

In addition to associations with cardiovascular disease, systemic inflammation in patients with COPD is associated with more severe disease, poorer functional status, and greater mortality (Agusti et al., 2012; Brightling, 2013; Fabbri and Rabe, 2007; Ferrari et al., 2013; Jing et al., 2016; Man et al., 2006; Moy et al., 2014a, 2014b; Thomsen et al., 2013; Zagaceta et al., 2017). Therefore, our findings suggest that BC-associated systemic inflammation may contribute to more severe disease and worse clinical outcomes in COPD patients. This is consistent with the associations noted in previous epidemiologic studies between greater exposures to BC or EC with adverse health outcomes related to respiratory health (Bell et al., 2009; Zanobetti and Schwartz, 2006), including hospital admissions for COPD (Gan et al., 2013) and mortality (Atkinson et al., 2014; Luben et al., 2017).

Our study design had a number of notable strengths. We recruited patients with well-documented COPD, and we confirmed their COPD diagnosis by medical record review and spirometry. We also had detailed time-varying information about other medical conditions, and medication use. Unlike previous studies, we directly measured BC exposure in the home, the location where COPD patients spend most of their time. By limiting the cohort to
persons living in homes without major indoor BC sources, we were able to measure indoor BC as a reasonable surrogate of exposure to traffic-related particulate matter infiltrating the home.

There are a number of limitations to our study. We studied persons well enough to participate by traveling to VA Boston for a study visit and able to receive and ship a sampler back to us. Therefore, we may have excluded individuals with very severe COPD who may have had a greater systemic response to BC. Our sample included only men, most of whom were Caucasian, reflecting the demographics of Veterans with COPD receiving care at VA Boston. Furthermore, we did not directly measure daily exposures, but estimated them using the multi-day indoor sample data and the respective daily outdoor concentrations. Our approach assumes that over each sampling period there is little variation in local sources of BC (dominated by local traffic) and that the indoor concentrations reflects variation in the regional contribution determined at the central site. Although we recruited persons without known in-home BC sources, it is also possible that some of the BC came from indoor sources such as cooking, or occasional candle or in-home second-hand smoke. A significant contribution from these sources seems unlikely. We asked participants to report home characteristics during sampling. During only 15 (5.2%) of the sampling periods participants reported using a candle (despite screening at recruitment), typically on one or two days, and in 11 (3.8%) a visitor briefly smoked in the home. Assessment of active smoking was done by self-report, and it is possible that some subjects smoked during sampling. Monitoring of exhaled CO as a measure of active smoking was started in 2014. Data were collected at 31 visits in the current cohort, and all values were 6 ppm or less, indicating no active smoking (Sato et al., 2003). We also recognize that the indoor exposures measured did not represent the effects of all personal BC exposures since subjects also spent time outside their home. Lastly, our assessment of effect modification should be considered exploratory due to limited sample sizes.

5. Conclusions

To summarize, in this study of patients with COPD we observed statistically significant positive associations between exposure to indoor BC on circulating CRP with a suggestion of greater effects in persons not taking statins and among those with diabetes. There was a suggestion of positive effects of BC exposure on IL-6 in non-statin users. As there were limited indoor BC sources, the only other source of BC is from the in-filtration of outdoor BC predominantly from traffic-related sources. Our findings demonstrate that even low-level exposures to BC are associated with systemic inflammatory effects in COPD patients. We recognize that the biomarkers studied are not clinical outcomes but nevertheless provide insight into underlying biological mechanisms responsible for the adverse effects of air pollution in COPD patients. Our findings also provide rationale to support efforts to reduce ambient exposures to traffic-related PM despite the considerable progress made to date.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.
Acknowledgments

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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.2018.05.010.

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Fig. 1.
Percent increase and 95% confidence limits in CRP, IL-6, and sVCAM-1 per 0.22 μg/m³ BC for moving BC averages starting at day 1 before phlebotomy through day 9 and for the integrated multi-day filter sample.
Fig. 2.
Percent increase and 95% confidence limits in CRP, IL-6, and sVCAM-1 per 0.22 μg/m³ BC in statin users and non-users for moving BC averages starting at day 1 before phlebotomy through day 9 and for the integrated multi-day filter sample.
Fig. 3.
Percent increase and 95% confidence limits in CRP, IL-6, and sVCAM-1 per 0.22 μg/m³ BC in participants with diabetes and without diabetes for moving BC averages starting at day 1 before through day 9 and for the integrated multi-day filter sample.
Table 1

Characteristics of 85 men with COPD at entry.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>72.7 (8.4)</td>
<td>46.6–89.9</td>
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<tr>
<td>Education, yrs</td>
<td>12.9 (2.1)</td>
<td>8–20</td>
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<tr>
<td>BMI, kg/m²</td>
<td>29.8 (5.6)</td>
<td>19.6–51.4</td>
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<td>Pack years</td>
<td>64.0 (41.0)</td>
<td>10–212</td>
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<tr>
<td>Post bronchodilator %-predicted FEV₁</td>
<td>68.1 (20.6)</td>
<td>16.7–122.3</td>
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<tr>
<td>Post bronchodilator %-predicted FVC</td>
<td>88.5 (18.5)</td>
<td>53.1–143.3</td>
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<tr>
<td>COPD Classification</td>
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<tr>
<td>GOLD severity</td>
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<tr>
<td>1</td>
<td>18 (21.2%)</td>
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<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>6 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5 (5.9%)</td>
<td></td>
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<tr>
<td>Normal spirometry&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (7.0%)</td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁/FVC, reduced FEV₁&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (3.5%)</td>
<td></td>
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<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>76 (89.4%)</td>
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<td>Non-White&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Asthma</td>
<td>18 (21.2%)</td>
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<tr>
<td>Diabetes</td>
<td>21 (24.7%)</td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>44 (51.8%)</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>39 (45.8%)</td>
<td></td>
</tr>
<tr>
<td>Statin use</td>
<td>66 (77.6%)</td>
<td></td>
</tr>
<tr>
<td>Inhaled steroid use</td>
<td>65 (76.5%)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Emphysema on clinical CT report.

<sup>b</sup> Includes 8 Black/African American participants. Predicted values for FVC and FEV₁ based on NHANES.
### Table 2

Environmental Exposures and biomarkers (n = 287)

<table>
<thead>
<tr>
<th></th>
<th>Median (25%ile – 75%ile)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indoor black carbon, μg/m³</td>
<td>0.19 (0.10–0.32)</td>
<td>– 0.42–1.39</td>
</tr>
<tr>
<td>Central site black carbon, μg/m³</td>
<td>0.54 (0.41–0.78)</td>
<td>0.27–1.53</td>
</tr>
<tr>
<td>Relative humidity, %</td>
<td>64.1 (7.5)</td>
<td>42.47–79.15</td>
</tr>
<tr>
<td>Outdoor temperature, °C</td>
<td>10.2 (8.8)</td>
<td>– 8.8–26.2</td>
</tr>
<tr>
<td>Distance from central site, km</td>
<td>26.4 (18.8)</td>
<td>1.06–79.9</td>
</tr>
<tr>
<td>Biomarker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>2.87 (1.22 – 6.32)</td>
<td>0.24–46.90</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>3.13 (2.11 – 5.42)</td>
<td>0.53–49.87</td>
</tr>
<tr>
<td>sVCAM-1, ng/mL</td>
<td>895.8 (750.1 – 1070.0)</td>
<td>371.1–2177.6</td>
</tr>
<tr>
<td>Hours/day inside home during sampling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All observations</td>
<td>17.0 (4.1)</td>
<td>17.1 (4.9)</td>
</tr>
<tr>
<td>Winter</td>
<td>18.0 (3.8)</td>
<td>18.9 (4.0)</td>
</tr>
<tr>
<td>Spring</td>
<td>17.3 (3.8)</td>
<td>17.5 (4.1)</td>
</tr>
<tr>
<td>Summer</td>
<td>16.5 (4.2)</td>
<td>15.1 (5.7)</td>
</tr>
<tr>
<td>Fall</td>
<td>16.4 (4.3)</td>
<td>16.9 (4.7)</td>
</tr>
</tbody>
</table>

*BC over a mean of 7.6 days (range 4–10); outdoor BC, humidity, and temperature averaged over the same period; 10% of indoor BC samples were below the limit of detection.*