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Indoor black carbon of outdoor origin and oxidative stress biomarkers in patients with chronic obstructive pulmonary disease

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ABSTRACT

Objectives: We assessed relationships between indoor black carbon (BC) exposure and urinary oxidative stress biomarkers, 8-hydroxy-2′-deoxyguanosine (8-OHdG) and malondialdehyde (MDA), in participants with chronic obstructive pulmonary disease (COPD).

Methods: Eighty-two participants completed in-home air sampling for one week prior to providing urine samples up to four times in a year. Weekly indoor and daily outdoor concentrations were used to estimate indoor daily lags and moving averages. There were no reported in-home BC sources, thus indoor levels closely represented outdoor BC infiltration. Mixed effects regression models with a random intercept for each participant were used to assess relationships between indoor BC and 8-OHdG and MDA, adjusting for age, race, BMI, diabetes, heart disease, season, time of urine collection, urine creatinine, and outdoor humidity and temperature.

Results: There were positive effects of BC on 8-OHdG and MDA, with the greatest effect the day before urine collection (6.9% increase; 95% CI 0.9–13.3%, per interquartile range: 0.22 μg/m^3) for 8-OHdG and 1 to 4 days before collection (8.3% increase; 95% CI 0.03–17.3% per IQR) for MDA. Results were similar in models adjusting for $PM_{2.5}$ not associated with BC and NO_2 (10.4% increase, 95% CI: 3.5–17.9 for 8-OHdG; 8.1% increase, 95% CI: −1.1–18.1 for MDA). Effects on 8-OHdG were greater in obese participants.

Conclusions: We found positive associations between BC exposure and 8-OHdG and MDA, in which associations with 8-OHdG were stronger in obese participants. These results suggest that exposure to low levels of traffic-related pollution results in lipid peroxidation and oxidative DNA damage in individuals with COPD.

1. Introduction

A number of studies conducted in human subjects have shown associations between acute exposures to air pollution and increases in various blood, urine, and exhaled breath biomarkers attributable to oxidative stress pathways (Barregard et al., 2008; Ceylan et al., 2006; Neophytou et al., 2014; Romieu et al., 2008; Zhang et al., 2013). Oxidative stress refers to an imbalance of the cellular redox system whereby reactive oxidative species, including free radicals, are generated due to poorly controlled oxidative reactions (Autrup et al., 1999; Betteridge, 2000; Go and Jones, 2010; Jones, 2006). It is hypothesized that oxidative stress may lead to the development of disease when free radicals react with biomolecules, such as DNA and lipids. DNA ultimately regulates numerous cellular processes, and lipids are essential components of cell membranes. Reactions between these biomolecules and free radicals result in DNA oxidation and lipid peroxidation, which then can induce cellular damage (Autrup et al., 1999; Betteridge, 2000; Jones, 2006; Kelly, 2003). There is also evidence that lipid peroxidation products may result in secondary damage to DNA (Ayala et al., 2014). The potential deleterious effects of oxidative damage to DNA and lipids are primarily studied by quantifying the concentrations of byproducts since free radicals are short-lived (Dalle-Donne et al., 2006; Zinellu

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et al., 2016).

An example of a widely studied byproduct is 8-hydroxy-2′-deoxyguanosine (8-OHdG), a biomarker of DNA oxidation that has been associated with subsequent risk of cancer and cardiovascular diseases (Chuang et al., 2014; Cooke et al., 2005; Cooke et al., 2002; Delfino et al., 2011; Tagesson et al., 1995; Tagesson et al., 1996). Malondialdehyde (MDA), a byproduct of lipid peroxidation, has also been associated with subsequent risk of cancer and atherosclerosis (Delfino et al., 2011; Lykkesfeldt, 2007; Shamberger et al., 1974; Tagesson et al., 1996). Examining the relationships of 8-OHdG and MDA with particulate air pollution can provide insight into mechanisms whereby particulate pollution results in cellular damage and potentially disease. Several studies have examined effects of ambient traffic related particulate matter (Di et al., 2017; Gong et al., 2013; Huang et al., 2012; Li et al., 2016; Ren et al., 2011; Zhang et al., 2013); however, less is known on the effects of these traffic particles that infiltrate indoors.

There are few studies assessing effects of pollution on oxidative stress in populations with clinical respiratory disease, particularly those with chronic obstructive pulmonary disease (COPD), a leading cause of mortality worldwide (Ceylan et al., 2006; Mathers and Loncar, 2006; Wang and GBD 2015 Mortality and Causes of Death Collaborators, 2016; Zanobetti et al., 2000; Zhang et al., 2017). Exposures to traffic related particles (as assessed by black carbon (BC) or elemental carbon), have been associated with hospitalization and mortality from COPD and other respiratory diseases (Bell et al., 2009; Gan et al., 2013; Peng et al., 2009; Zanobetti and Schwartz, 2006). Additionally, there is a growing body of literature indicating that biomarkers of oxidative stress increase during COPD exacerbations, which also contribute to increased hospitalizations, morbidity, and mortality (Cheng et al., 2007; Kelly, 2003; Tramuto et al., 2011). As a result, there is rationale for studying oxidative biomarkers associated with COPD severity.

2. Methods

2.1. Study sample

Participants were recruited at the VA Boston Healthcare System between November 2012 and December 2014 as part of a COPD cohort examining associations between indoor air quality and health. Potential participants were identified by medical record review of VA Boston pulmonary, primary care, and pulmonary function clinic encounters using ICD-9 codes 490–493 and 496. Identified potentially eligible participants were sent recruitment mailings. In addition, recruitment flyers were placed at VA Boston clinics and Boston area civilian hospitals. Participants who expressed interest in the study were invited to attend a clinic visit to confirm eligibility and obtain consent.

Participants were eligible if they were at least 40 years old, smoked at least 10 pack years, had physician-diagnosed COPD, and had a $FEV_1/FVC < 0.70$ on post-bronchodilator spirometry or emphysema on a CT scan reported in their medical record. Participants were ineligible if they had a history of any malignancies other than stable skin or prostate cancer at the time of entry and could not be current smokers or live with smokers, use a wood stove or fireplace, or have other major sources of in-home pollution exposure.

Participants were asked to attend four in-person visits scheduled approximately three months apart over one year. Participants who underwent therapy for a COPD exacerbation were assessed at least two weeks after completion of treatment in order to be considered clinically stable. Urine samples and questionnaires on health and home environmental features were collected at each in-person clinic visit. The study protocol was approved by Institutional Review Boards at VA Boston and Harvard Medical School and informed consent was obtained from all participants prior to study procedures.

2.2. Pollution assessment

Prior to each clinic visit, subjects were provided with an in-home micro-environmental sampler that collected data on in-home exposures for one week. Samplers were used to collect data in the room where participants reported spending the most time, excluding the kitchen. Each sampler was returned at the clinic visit or by express shipping. The in-home sampler included a pump set to a flow rate of 1.8 LPM, using a size-selective impactor to collect particles ≤ 2.5 μm in diameter ($PM_{2.5}$). An EEL M43D Smokestain Reflectometer was used to determine BC mass, using each filter as its own blank (measured before and after sampling), yielding the net weight of BC. Subsequently, BC concentrations were calculated by dividing the net measurement of each filter (μg) by the total volume of air sampled (m^3). The limit of detection for BC was 0.03 $\mu g/m^3$ based on 3 times the standard deviation of blank filters; about 10% of the samples were below the limit. All values were included to preserve the distribution of concentration levels. Nitrogen dioxide (NO_2) was measured over the same weekly sampling period using an Ogawa passive sampling badge attached to the micro-environmental sampler.

In addition to collecting measurements on weekly indoor BC, we estimated measurements of daily indoor BC. In the absence of indoor sources, the integrated indoor measurement of BC represented outdoor infiltration; therefore, we expected daily indoor levels to be proportional to outdoor levels (Gryparis et al., 2007; Suglia et al., 2008). Daily outdoor BC averages were calculated using central site data (Francis A. Countway Library, Boston, MA) measured by an aethalometer (Magee Scientific Company, model AE-16, Berkeley, CA); methods for central site data collection have been described elsewhere (Kang et al., 2010). Daily indoor BC for each home on each sampling day was estimated by further averaging the daily central site data according to the days reported by the participant and measuring in-home multi-day integrated values using the following equation, where i represents the number of days prior to urine collection (lag day 1 to day 8):

$$Indoor\ day\ BC_i = (Outdoor\ day\ BC_i / Outdoor\ week\ BC) \times Indoor\ week\ BC \quad (1)$$

We constructed daily moving averages starting the day before (lag day 1) to eight days before urine collection (lag day 8). Each of the moving averages was examined in a separate model for comparison among time periods. Since BC is a component of $PM_{2.5}$, we estimated the effects of $PM_{2.5}$ other than BC by constructing similar indoor $PM_{2.5}$ moving averages and regressing each $PM_{2.5}$ moving average on its corresponding BC moving average. We then included the residuals as an additional variable in each BC-biomarker regression model. This is a suggested approach since including directly measured $PM_{2.5}$ concentrations in the model may result in over-adjustment of BC (Mostofsky et al., 2012).

2.3. Oxidative stress assessment

Urinary concentrations of 8-OHdG were measured using a method described previously using a HPLC-ESI-MS system (Commodore et al., 2013). The limit of detection was 0.133 ng/mL, and the recovery of the sample treatment was > 80%. We measured MDA in two forms, free (protein unconjugated) and total (sum of protein unconjugated and conjugated), as there is conflicting evidence regarding the form that best reflects lipid peroxidation (De Vecchi et al., 2009; Del Rio et al., 2005). Concentrations of free MDA were measured using a HPLC system with fluorescent detection, as described previously (Gong et al., 2013). The detection limit, extraction recovery and analytical precision of this method were 1.8 nM, 75.9%, and 2.2% measured as the relative standard deviation (RSD) from 8 replicate injections, respectively. Total MDA was analyzed in a similar fashion as free MDA with the exception of an added alkaline hydrolysis step prior to sample extraction