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Metal composition of fine particulate air pollution and acute changes in cardiorespiratory physiology

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ABSTRACT

Background: Studying the physiologic effects of components of fine particulate mass ($PM_{2.5}$) could contribute to a better understanding of the nature of toxicity of air pollution.
Objectives: We examined the relation between acute changes in cardiovascular and respiratory function, and $PM_{2.5}$-associated-metals.
Methods: Using generalized linear mixed models, daily changes in ambient $PM_{2.5}$-associated metals were compared to daily changes in physiologic measures in 59 healthy subjects who spent 5-days near a steel plant and 5-days on a college campus.
Results: Interquartile increases in calcium, cadmium, lead, strontium, tin, vanadium and zinc were associated with statistically significant increases in heart rate of 1–3 beats per minute, increases of 1–3 mmHg in blood pressure and/or lung function decreases of up to 4% for total lung capacity.
Conclusion: Metals contained in $PM_{2.5}$ were found to be associated with acute changes in cardiovascular and respiratory physiology.

1. Introduction

Numerous cohort studies have identified consistent associations between ambient $PM_{2.5}$ and cardiorespiratory morbidity and mortality (Beelen et al., 2008; Pope et al., 2004, 2002; Chen et al., 2005; Crouse et al., 2012; Dockery and Pope, 1993; Katanoda et al., 2011; Laden et al., 2006; Lepeule et al., 2012; Miller et al., 2007; Ostro et al., 2010; Puett et al., 2011, 2009), but little is known about the specific components of $PM_{2.5}$ that may be responsible for toxicity. Oxidative stress is thought to be an important mechanism through which particulate air pollution contributes to adverse health effects. The metal content of $PM_{2.5}$ is a logical target in exploring specific components that contribute to cardiorespiratory morbidity, as transition metals such as iron are known to participate in reactions that generate oxidative stress (Araujo and Nel, 2009; Ayres et al., 2008; Ghio et al., 2012; Li et al., 2003). While few studies have examined the specific health effects of $PM_{2.5}$ metals, some evidence suggests that this fraction may contribute to respiratory hospital admission in children (Ostro et al., 2009) as well as cardiovascular mortality (Zhou et al., 2011) and heart rate changes (Hsu et al., 2011) in adults. Chen and Lippmann (2009) recently conducted a comprehensive review of the potential health effects of PM-metals and highlighted the need for studies with exposure information beyond typical fixed-site regional monitors.

To better understand the toxicity of fine particulate air pollution, we examined the association between daily changes in ambient $PM_{2.5}$-associated metals and daily changes in measures of

Abbreviations: FEV_1/FVC, Forced expiratory volume in 1-s/forced vital capacity; FEF_{50}, Maximum mid-expiratory flow; TLC, Total lung capacity; FRC, Functional residual capacity; RV, Residual volume; $PM_{2.5}$, Particulate matter with a mean aerodynamic diameter less than 2.5 microns; CI, Confidence interval; DL_{CO}, Diffusion capacity; SO_2, Sulphur dioxide; O_3, Ozone; NO_2, Nitrogen dioxide; AR_1, Autoregressive model; Al, Aluminium; As, Arsenic; B, Boron; Ca, Calcium; Cd, Cadmium; K, Potassium; Fe, Iron; Li, Lithium; Mg, Magnesium; Mn, Manganèse; Mo, Molybdène; Na, Sodium; Ni, Nickel; Pb, Lead; Sn, Tin; Sr, Strontium; V, Vanadium; Zn, Zinc.

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respiratory and cardiac physiology. Since particulate characteristics are determined by their source of origin, health effects associated with the metal composition may also be source specific. We selected metals that were present in greater ambient concentrations near a steel plant because, in a previous study, we found an association between proximity to this steel plant and physiologic differences in lung function, and questioned whether PM-associated metals might be playing a role (Dales et al., 2013).

The previous study was a randomized cross-over design where we measured differences in selected cardiorespiratory variables between two exposure scenarios; adjacent to the property line of a steel manufacturing plant, and at a college campus 5–6 few kilometres away. Study site was the exposure variable. For the present study, we combined the data from the two sites and tested the associations between day-to-day changes in physiologic measures to day-to-day changes in ambient PM-associated metals using a panel study design with time series analysis. We controlled for study site. The daily air pollution concentration is the exposure variable of interest in the present study. Particle composition differs by source. We had the opportunity to assess particles associated with a steel plant. For the present study we measured PM-associated metals at both study sites but focused on the metals that were in significantly higher concentrations near the steel plant.

2. Materials and methods

During the summer of 2010 in Sault Ste. Marie, Ontario, Canada, we recruited sixty one subjects, mostly college students on summer break, who were healthy non-smokers and not exposed to cigarette smoke at home. All subjects spent five, eight hour days outdoors study site adjacent to a steel manufacturing plant, and also spent five days outdoor on a college campus 5.5 km away to provide a range of exposures to air pollution. Subjects were sedentary for the majority of each study day with the exception of one thirty-minute exercise period of moderate exercise on an elliptical trainer during the midafternoon. The study was approved by the Health Canada Research Ethics Board and the ethics board of Algoma University, Sault Ste. Marie, Canada.

2.1. Health outcomes

Each afternoon, spirometry, lung volumes, and gas diffusion measures were collected following American Thoracic Society criteria using an Ultima PFX™ (Medical Graphics Corporation, 350 Oak Grove Parkway, St. Paul, MN 55127 U.S.A). Instruments were calibrated daily and technologists tested themselves daily to verify the reproducibility of measurements. Variables selected for analysis included the greatest one-second forced expired volume (FEV_1) and forced vital capacity (FVC) from a maximum of eight trials and the mean of at least two lung volume and diffusion capacity (DL_{CO}) measurements expressed as a percentage of predicted normal values (Gutierrez et al., 2004). Pulse oximetry was determined during the last two and a half hours of each visit using an OxiMax N65 Pulse Oximeter (Nellcor, CA, USA) (Dales et al., 2013).

Systolic and diastolic blood pressure (SBP and DBP, respectively) was measured in the afternoon in a sitting position. There was no strenuous exercise or pulmonary function testing done within 20 min of the measurement which was made using a BPTRU-200 blood pressure monitor (BpTRU Medical Devices, Coquitlam, BC, Canada). Resting heart rate and oxygen saturation were measured by an OxiMax N65 Pulse Oximeter (Covidien, Dublin, Ireland).

2.2. Exposure assessment

Daily integrated 24-h $PM_{2.5}$ concentrations were determined in close proximity, within about 20 m, to study participants at each site using Harvard-Impactors (HI) (Air Diagnostics and Engineering, Inc., Naples, ME). These samples operated at a flow rate of 10 Lpm and particles were collected on Teflon filters. The metal content of the 24-h $PM_{2.5}$ samples was determined by inductively coupled plasma mass spectrometry (ICP-MS). The Teflon filters were digested using a nitric and hydrofluoric acid mixture. NIST Standard reference material 1648 and 1633 were analysed by the lab with each batch to ensure accuracy. The laboratory detection limits for the metals were equal to three times the standard deviation of 6–8 procedural blanks.

Of the 23 metals measured, we included in our analysis only those which were statistically significantly different between the college and steel plant sites: Al, As, B, Ca, Cd, K, Fe, Li, Mg, Mn, Mo, Na, Ni, Pb, Sn, Sr, V, and Zn. In addition, Air Pointer® (Recordum Messtechnik GmbH, Mödling, Austria) instruments were used to monitor real-time concentrations of the following pollutants at each site: sulphur dioxide (SO_2), nitrogen dioxide (NO_2), nitrogen oxides (NO_x), and ozone (O_3). These instruments also recorded temperature and relative humidity as well as wind speed and direction. Ultrafine particle (UFP) concentrations were monitored using a TSI® Model 3007 Ultrafine Particle Counter with a particle size range between 0.01 and 0.1 µm. All pollutant concentrations were averaged over each 8-h exposure period and these values were used in the analysis.

2.3. Statistical analysis

Descriptive statistics were compiled for pollutant concentrations and clinical measures at each site and mean differences and 95% confidence intervals were determined to compare values between sites. Spearman's correlations were calculated to determine associations between air pollutants at each study location. Generalized linear mixed models (GLMM) were used to test the association between individual metals and acute changes in the respiratory and cardiovascular outcomes described above. Study site and participants were treated as random effects in all statistical models and all models adjusted for ambient temperature and relative humidity. Time invariant factors were controlled by design as each participant was compared to themselves in the analysis. The model can be summarized as follows:

$$E(Y/X) \sim \beta X + \delta Z + \varepsilon \quad [1]$$

Where Y represents a vector of respiratory or cardiovascular outcomes for 61 patients – each patient measured 5 days at each location – X is a matrix of predictor variables (each column corresponds to one predictor such as metal, temperature, humidity etc.) at the time when Y is measured; β is fixed effects regression coefficients linking predictor variables to clinical measures; Z is the design matrix for the random effects of the study site and participant; δ is random effects and assumed $\delta \sim N(0, G(\theta))$; G is symmetric and positive semi-definite matrix, parameterized by a variance component vector θ. ε is the residuals and assumed $\varepsilon \sim N(0, R)$. The marginal distribution of Y is $Y \sim N(X \cdot \beta, V)$, $V = ZGZ + R$. The fixed-effect coefficients β, variance components θ and ε are parameters that need to be estimated. The estimate of β and R, are given by $\hat{}\beta(\theta)$ and calculated at where profile likelihood is maximized with respect to θ.

Both single and multi-pollutant models were examined. First, individual metals were examined to explore potential associations between interquartile range (IQR) increases in ambient metal concentrations in $PM_{2.5}$ and changes in each outcome. Next, gaseous air pollutants (O_3, NO_2, SO_2) were added to the models to evaluate potential confounding by these pollutants. Finally, $PM_{2.5}$ was added to the models to examine the impact on associations for specific $PM_{2.5}$-metals. All single and adjusted associations between interquartile range (IQR) increases in ambient metal concentrations in $PM_{2.5}$ and changes in each outcome with 95% CI were generated for each metal and plotted as error bar plots. All data management and statistical modelling were completed in S-PLUS Version 6.2.

3. Results

The average age of the 61 study subjects was 24 years and most (85%) were Caucasian (Table 1). All were reported nonsmokers but a quarter had smoked in the past. At least one millimetre of rain fell on 25 of the 60 days of the study period. The average temperature during the study was 22 °C and the relative humidity was 61%.

3.1. Air pollution concentrations and $PM_{2.5}$-metal content

Mean air pollution concentrations are listed in Table 2 and $PM_{2.5}$-metal composition and detection limits are shown in Table 3. As expected, levels of most air pollutants were greater near the steel plant relative to the college site. For 10 metals (Al, Ca, Fe, K, Mg, Mn, Na, Pb, V, Zn) the mean difference between sites was larger than 1 ng/m^3 and for eight metals (Al, Ca, Fe, K, Mg, Mn, Na, Zn) the differences were larger than 10 ng/m^3. The largest difference was for Fe, which on average was 294 ng/m^3 (95% CI: 216, 373) higher at

Table 1
Baseline characteristics of the sixty one study subjects.

Characteristics	% (*n*)[a]
Age, years	24.2 (5.8)
Sex, male	46.0 (28)
Race, white	85.2 (52)
Aeroallergies (MD Confirmed)	4.9 (3)
Ever smoker	25.0 (15)

[a] Except for age which is mean and standard deviation.