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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.

Table 2
Descriptive data for air pollution concentrations during each study day.

Air pollutant	Site	
	Near the steel plant	On the college campus
	Mean (SD)	Mean (SD)
SO_2 (ppb)	7.76 (13.21)	1.59 (4.18)
NO_2 (ppb)	7.07 (5.13)	4.52 (3.79)
NO_x (ppb)	13.97 (10.40)	6.01 (5.40)
O_3 (ppb)	29.68 (8.58)	32.56 (9.47)
UFP (particles/cm^3)	13,054 (13,106)	5907 (3641)
$PM_{2.5}$ ($\mu g/m^3$)	12.83 (8.07)	11.55 (7.17)

the site near the steel plant relative to the college campus. Four or five fold differences between the sites were seen for magnesium, iron, calcium, nickel, cadmium, lead and vanadium.

To put these concentrations into some perspective we compared them to findings by Zhou et al. (2011) who reported mean PM component values during the warmer season for both Detroit and Seattle between 2002 and 2004. Compared to those values, the values in the present study were greater by approximately: 8 to 10 times for aluminium, 3–7 times for iron, and double for potassium. Zinc was approximately 1.3–4 times greater. Vanadium concentrations were between those of Detroit and Seattle.

Spearman's correlations for particulate mass, gases, and metal components are presented in Table 4. In general, correlations between $PM_{2.5}$-metals and other air pollutants (NO_2, NO_x, O_3, SO_2, $PM_{2.5}$) were moderate ($r < 0.56$). Four metals, Ca, Fe, Li, and V were each highly correlated ($r > 0.8$) with only one other metal. Four metals, Mg, Mn, Na, and Sr were each highly correlated with several other metals. Correlations between individual metals and $PM_{2.5}$ were not strong, ranging from 0.00 with Mo to 0.42 with B. Correlations were also assessed between gas phase pollutants and metals, with the highest correlation found between NO_2 and Li ($r = 0.51$) and the lowest between O_3 and Ba ($r = -0.19$).

3.2. Relationship between specific metals and cardiorespiratory outcomes

Effect estimates for single- and multi-pollutant models exploring the relationship between specific $PM_{2.5}$-metals and cardiovascular and respiratory outcomes are shown in Figs. 1 and 2. In total, seven metals were associated with statistically significant changes in at least one of the cardiorespiratory outcomes examined, and these were either transition metals (Cd, V, Zn), group 2 elements (Ca, Sr) or group 4 elements (Sn, Pb). Many metals were associated with an increased heart rate. Ca (2.26, 95% CI 1.59, 2.3), Sn (1.9, 95% CI 1.5, 2.1), and Sr (3.13, 95% CI 2.2, 4.1) were associated with 2–3 beat per minute increases in heart rate in models adjusted for gaseous pollutants. Cd was associated with increases in diastolic (1.16, 95% CI 1.1, 2.01) and systolic (1.16, 95% CI 1.02, 2.03) blood pressure, and Pb with increases in systolic blood pressure (3.03, 95% CI 2.1, 3.9). Adjusted for gaseous pollutants and particulates Al (0.49, 95% CI 0.08, 0.9), Ca (0.59, 95% CI 0.02, 1.16), and Mn (0.79, 95% CI 0.11, 1.47) were associated with increases in diastolic blood pressure, Cd, was associated with increased diastolic (0.16, 95% CI 0.04, 0.27) and systolic (0.15, 95% CI 0.01, 0.28) blood pressure.

Several metals were associated with small reductions in measures of respiratory function. Adjusting for gaseous pollutants and fine particulate mass, Cd was associated with decreases in FEF_{25-75}(−0.19, 95% CI −0.35, −0.03), TLC (−0.18, 95% CI −0.3, −0.05), FEV_1 (−0.13, 95% CI −0.21, −0.05) and FVC (−0.08, 95% CI −0.15, −0.01). With the exception of Mg and Pb, statistically significant inverse associations between $PM_{2.5}$-metals and respiratory outcomes were limited to transition metals (Cd, Zn, V). Results of all the association between gaseous pollutants and physiologic variables, and between metals and physiologic variables for all the metals can be found in Appendices 1, 2 and 3.

In general, effect estimates for metals tended to decrease with the inclusion of $PM_{2.5}$ mass in statistical models relative to models with gaseous pollutants only, suggesting the possibility of overcontrolling by particulate mass which also includes the metal components. We also subtracted metal components from particulate mass in an attempt to determine the influence of the former. With metals subtracted the observed effect of $PM_{2.5}$ mass on the physiologic variables became less for most variables and non-significant except for diastolic blood pressure (Table 5).

4. Discussion

Several $PM_{2.5}$ metals were associated with acute changes in cardiovascular or respiratory physiology. In particular, cadmium

Table 3
Descriptive data for $PM_{2.5}$ metal content (ng/m^3) at each study site.

$PM_{2.5}$ metal	Detection limit	IQR	Site		
			Near the steel plant	College campus	Plant–college
			Mean (SD)	Mean (SD)	Mean difference (95% CI)
Al	0.14	88.40	170 (138)	65.7 (39)	83.8 (56, 112)
As	0.01	0.54	1.20 (1.10)	0.39 (0.22)	0.81 (0.51, 1.1)
B	0.28	2.94	4.53 (2.90)	3.93 (2.00)	0.68 (0.14, 1.2)
Ca	6.94	255.90	372 (270)	72.90 (54)	288 (216, 360)
Cd	0.01	0.06	0.21 (0.33)	0.06 (0.04)	0.15 (0.05, 0.25)
Fe	1.39	269.20	394 (310)	85.20 (68)	294 (216, 373)
K	2.08	32.60	83.6 (80)	34.4 (14)	48.80 (25, 72)
Li	0.01	0.08	0.21 (0.28)	0.04 (0.03)	0.14 (0.08, 0.19)
Mg	0.02	59.90	104 (128)	20.80 (11)	82.80 (45, 121)
Mn	0.01	10.76	13.5 (9.60)	2.5 (1.80)	10.50 (8.10, 13)
Mo	0.01	0.35	0.72 (0.95)	0.24 (0.42)	0.45 (0.15, 0.74)
Na	0.56	33.20	71.60 (87)	25.70 (14)	43.10 (18, 68)
Ni	0.03	0.70	1.62 (3.00)	0.47 (0.31)	0.95 (0.24, 1.70)
Pb	0.01	2.59	5.96 (6.60)	1.31 (1.0)	4.69 (2.80, 6.60)
Sn	0.06	0.19	0.45 (0.48)	0.21 (0.17)	0.23 (0.09, 0.37)
Sr	0.07	0.40	0.60 (0.36)	0.28 (0.19)	0.31 (0.22, 0.39)
V	0.00	1.11	2.32 (4.50)	0.55 (0.43)	1.80 (0.52, 3.1)
Zn	0.06	12.29	34.30 (45)	11.10 (11)	20.90 (8.20, 33)

IQR, interquartile range.

Table 4
Spearman correlations among particulate mass and metals measured near the plant site and college campus combined.

	O_3	NO_2	SO_2	$PM_{2.5}$	Al	As	B	Ca	Cd	Fe	K	Li	Mg
O_3	1												
NO_2	−0.17	1											
SO_2	−0.15	0.70	1										
$PM_{2.5}$	0.11	0.43	0.42	1									
Al	0.13	0.33	0.22	0.18	1								
As	−0.14	0.41	0.38	0.29	0.34	1							
B	0.19	0.04	−0.05	0.42	0.28	0.33	1						
Ca	0.05	0.44	0.25	0.15	0.81	0.49	0.22	1					
Cd	−0.17	0.36	0.35	0.4	0.34	0.70	0.38	0.4	1				
Fe	−0.08	0.52	0.36	0.19	0.7	0.62	0.21	0.85	0.55	1			
K	0.09	0.43	0.29	0.33	0.71	0.65	0.51	0.74	0.61	0.74	1		
Li	0.01	0.51	0.40	0.34	0.64	0.71	0.26	0.8	0.63	0.85	0.77	1	
Mg	0.02	0.47	0.28	0.2	0.82	0.55	0.25	0.95	0.48	0.86	0.8	0.85	1
Mn	−0.04	0.5	0.31	0.21	0.73	0.6	0.26	0.89	0.52	0.95	0.75	0.85	0.89
Mo	−0.10	0.29	0.23	0	0.28	0.7	0.12	0.48	0.47	0.72	0.53	0.62	0.50
Na	0.05	0.45	0.36	0.26	0.71	0.64	0.26	0.77	0.57	0.8	0.83	0.87	0.83
Ni	0.03	0.4	0.25	0.14	0.53	0.68	0.3	0.63	0.53	0.71	0.7	0.68	0.64
Pb	−0.12	0.42	0.48	0.3	0.42	0.79	0.25	0.6	0.76	0.68	0.65	0.77	0.65
Sn	−0.06	0.32	0.37	0.35	0.43	0.71	0.32	0.47	0.68	0.65	0.66	0.71	0.53
Sr	0.18	0.4	0.31	0.2	0.83	0.52	0.28	0.85	0.44	0.76	0.79	0.81	0.87
V	0.07	0.43	0.27	0.17	0.58	0.59	0.22	0.71	0.46	0.67	0.67	0.69	0.70
Zn	−0.14	0.38	0.38	0.26	0.43	0.58	0.33	0.54	0.72	0.68	0.66	0.68	0.56

	Mn	Mo	Na	Ni	Pb	Sn	Sr	V	Zn
Mn	1								
Mo	0.64	1							
Na	0.78	0.59	1						
Ni	0.67	0.69	0.72	1					
Pb	0.69	0.61	0.69	0.62	1				
Sn	0.62	0.58	0.71	0.59	0.72	1			
Sr	0.77	0.43	0.83	0.64	0.61	0.55	1		
V	0.69	0.53	0.67	0.87	0.62	0.51	0.70	1	
Zn	0.67	0.6	0.67	0.64	0.76	0.69	0.53	0.55	1

was associated with increased blood pressure and several transition metals were associated with reductions in lung volumes, flows, and gas diffusion. However, strong correlations between a number of individual elements made it difficult to separate their individual effects. Cadmium, V, and Zn are transitional metals. The toxicity may be due to the induction of oxidative stress which predisposes the generation of reactive oxygen species that may cause inflammation and damage. Our findings that cadmium was associated

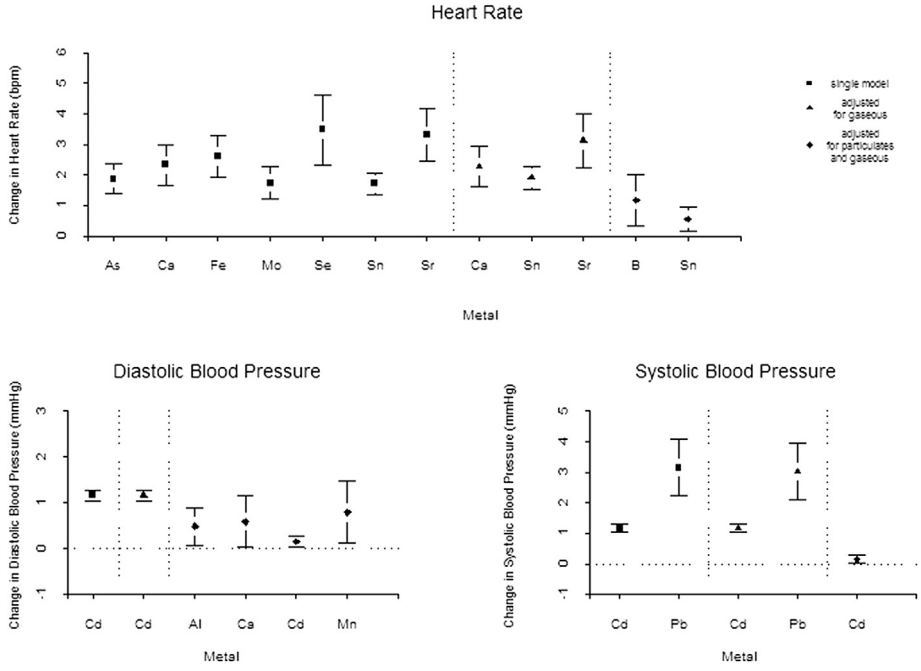

Fig. 1. The mean (95% CI) change in cardiovascular physiology associated with an interquartile range change in metal concentrations (ng/m^3). The single pollutants models are adjusted for ambient temperature and relative humidity. The multi-pollutants models are adjusted for gases, and then for gases and $PM_{2.5}$.

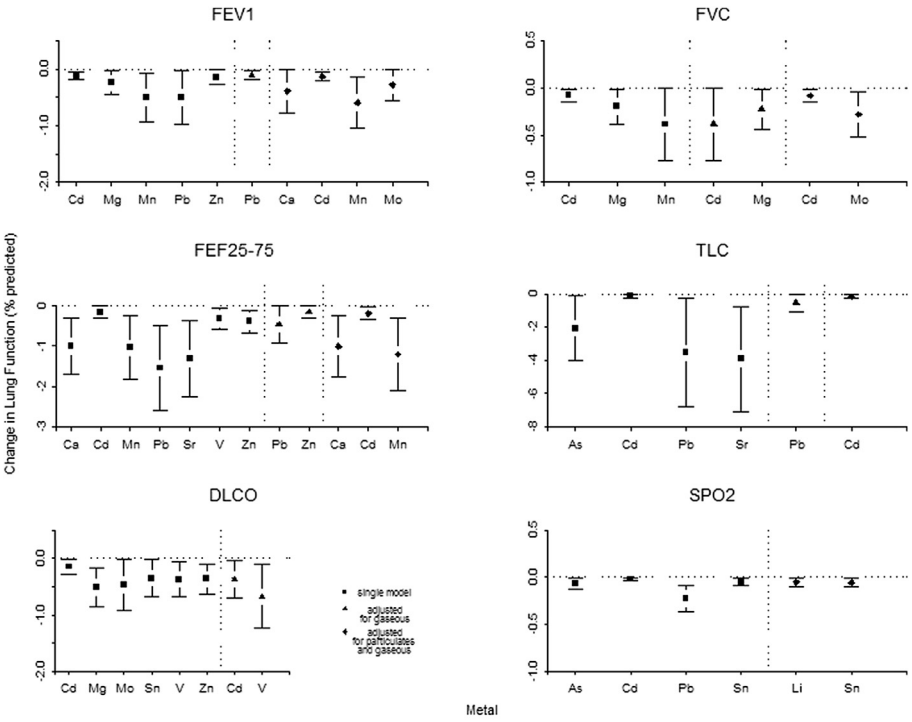

Fig. 2. The mean (95% CI) change in pulmonary physiology associated with an interquartile range change in metal concentrations (ng/m^3). The single pollutant models are adjusted for ambient temperature and relative humidity. The multi-pollutants models are adjusted for gases, and then for gases and $PM_{2.5}$.

with small but statistically significant reductions in FVC and DLCO and a 1.25 mmHg increase in diastolic blood pressure are biologically plausible given the known toxicity of this metal. Cadmium has been found to bind and deplete antioxidant defenses such as glutathione and metallothionein reducing the capacity to scavenge reactive oxygen species such as OH radicals (Liu et al., 2009).

Apart from this biochemical evidence of a plausible adverse effect of metals, animal studies also support the existence of toxicity. In a rat lung epithelial line, the rank order of metals from greatest to least toxicity was vanadium, zinc, nickel, and iron. Toxicity was measured by reduced cellular metabolism, death or cytokine secretion (Riley et al., 2003). Single intratracheal injections of vanadium and nickel increased BALF protein, a measure of pulmonary vascular leakage (Kodavanti et al., 2001). Lippmann et al. (2006) reported that increased concentrations of nickel, chromium, and iron in fine particulate air pollution acutely increased the heart rate and reduced the heart rate variability of mice.

Human studies are also suggestive of an adverse health effect from inhaled metals. In the Veterans Association's normative ageing study 24-h cadmium concentrations in urine were negatively associated with pulmonary function among 96 subjects. FEV_1, FVC, and FEV_1/FVC, were all significantly and negatively associated with increased levels of urine cadmium. However, with the small sample size it was difficult to dissect the independent effect of other constituents of cigarette smoke and isolate the effect of cadmium alone (Lampe et al., 2008). Whether this represents acute or chronic exposure cannot be determined. Although we observed acute effects associated with cadmium exposure, there is a suspicion of chronic effects associated with this metal; it has been suggested that the cadmium content of tobacco smoke may increase the risk of pulmonary and cardiovascular disease (Everett and Frithsen, 2008; Kundu et al., 2009; Mannino, 2004; Tellez-Plaza et al., 2008).

Several metals have been associated with adverse health effects. A cross-sectional study of 72 US cities between 2000 and 2005 found that interquartile increases in organic carbon, elemental carbon, sodium, and silicone were associated with a short-term increase in mortality between 0.16% and 0.39%. Single pollutant models were used. Gases and particulate mass were not adjusted for (Krall et al., 2013). A time series analysis based on data from Connecticut and Massachusetts found that calcium, black carbon, vanadium, and zinc were associated with an increased risk of cardiovascular hospitalizations. Aluminium, calcium, chlorine, HCO3, nickel, silicone, titanium, vanadium were associated with an increased risk of respiratory hospitalizations. Two pollutant models were used for adjustment but gases and particular matter were not adjusted for when looking at the constituents (Bell et al., 2014). Based on the information available to date, The Health Effects Institute National Particle Component Toxicity Initiative Review Panel could not determine which specific particulate components are accounting for the epidemiologic association between fine particulate matter and health. A lack of comprehensive data on ambient components, concentrations below detection limits, and the high correlations often seen between multiple components were considered limiting factors (Vedal et al., 2013).

Table 5
The mean change in cardiovascular and pulmonary physiology associated with an interquartile range change in concentrations of total $PM_{2.5}$ and $PM_{2.5}$ without metal components. Statistically significant changes are highlighted.

Physiologic variables	$PM_{2.5}$ (μg/m^3)	$PM_{2.5}$-metals (μg/m^3)
Heart rate	**1.13 (0.36, 1.89)**	0.55 (−0.32, 1.42)
Diastolic BP	**0.86 (0.19, 1.53)**	**0.81 (0.12, 1.50)**
Systolic BP	**0.87 (0.09, 1.65)**	0.77 (−0.05, 1.59)
FEV_1	−0.41 (−0.89, 0.06)	−0.33 (−0.86, 0.21)
FVC	−0.27 (−0.69, 0.16)	−0.47 (−0.95, 0.01)
FEF_{25-75}	−0.92 (−1.98, 0.13)	−0.17 (−1.36, 1.02)
TLC	−0.13 (−0.86, 0.60)	0.08 (−0.82, 0.97)
DLCO	0.06 (−0.98, 1.10)	−0.12 (−0.39, 0.15)
SpO_2	**−0.14 (−0.24, −0.04)**	9.06 (−109.70, 127.82)

There is evidence that fine particulate toxicity is source specific. Dominici et al. (2007) reported that all-cause mortality associated with ambient fine particulate matter was stronger in areas with higher concentrations of vanadium and nickel. Thus, the influence of particulate matter in the vicinity of a steel plant and its metal components provides relatively unique information that would not be available from the majority of studies which focus on urban air pollution which is mostly traffic-sourced.

4.1. Strengths and limitations of the study

Given the evidence of source specificity, previous studies of PM metal components related to urban air pollution cannot be readily generalized to a source influenced by steel plant emissions. Thus, our study provides novel and unique information. There were high correlations between multiple metals, making it difficult to characterize the individual effects of Mg, Mn, Na and Sr. However, we adjusted all results by $PM_{2.5}$ mass which comprises all the metals and non-metal components. There are advantages and disadvantages of adjusting for $PM_{2.5}$. The models which adjusted for $PM_{2.5}$ allowed us to control for metal and non-metal components of particulates apart from the individual metal of interest. The disadvantage of including $PM_{2.5}$ in the model is over-adjustment which biases the results towards the null. Since all of the metals are included in the $PM_{2.5}$ mass, by including it in the models we are controlling for metals and then looking for a residual effect of metals. We presented results without adjustment, with adjustment for pollutant gases and with gases and particulates, for the reader to judge the effects of different models. In addition, the finding that particulate matter-physiology associations were weaker when metals were subtracted out suggests that metal components are playing a role but the differences between particulate mass with and without metal components were not significantly different.

To minimize false positive results from multiple comparisons, we examined only metals that were significantly associated with the site near the steel plant. This issue of multiple comparisons is common in studies of $PM_{2.5}$-metals because of the many metals contained in particulate mass (Zhou et al., 2011). As discussed above, there is *a priori* evidence supporting toxicity of cadmium based on its cellular effects and on prior human studies.

The magnitude of the effect on lung function was small by clinical standards, but changes of this magnitude have been associated with air pollutants that have significant effects on morbidity and mortality (Pietropaoli et al., 2004; Timonen et al., 2002). Although the observed changes in blood pressure were small, a large meta-analysis of randomized blood pressure-lowering medications concluded that a 5 mmHg decrease in diastolic hypertension corresponded to decreases of 41% for stroke and 22% for coronary heart disease (Law et al., 2009). If we could extrapolate from this finding, perhaps the change in blood pressure we observed may be associated with a five to ten percent change in the risk of stroke and heart disease. We recognize however that we measured only acute changes in physiology and our study group would not represent those who are older and hypertensive. The magnitude of change in a physiologic measure may not be proportional to the effect on morbidity and mortality. Relatively small reductions in blood pressure may have public health benefits.

Even if the magnitude of the observed physiologic change is small, these results contribute to the literature on mechanisms of toxicity by helping to explain what components of metals may be associated with physiologic effects and what those effects may be. In addition there may be effects with longer exposures, but this being a short-term study, we cannot comment on the effects to be expected in the long-term residents of neighbourhoods adjacent to steel manufacturing plants.

5. Conclusions

Metal toxicity may be one mechanistic explanation for the previously observed associations between air pollution and cardiac and respiratory morbidity and mortality (Dockery and Pope, 1993; Ostro et al., 2009). Since the composition of particulate matter is influenced by the site of origin, future studies of the relative toxicity of different source-specific particles may be able to determine if certain individual metals consistently appear to be toxic despite co-existing within a variety of different air pollution mixtures. This would assist in teasing out the individual components of importance to health.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2014.03.004.

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