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Associations between ambient wood smoke and other particulate pollutants and biomarkers of systemic inflammation, coagulation and thrombosis in cardiac patients

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ABSTRACT

Background: Increased particulate air pollution has been associated with both an increased risk of myocardial infarction (MI) and adverse changes in cardiac biomarkers. Up to 30% of ambient wintertime fine particles ($PM_{2.5}$) in Rochester, NY are from wood burning. Our study examined associations between ambient levels of a marker of wood smoke (Delta-C) and other particulate air pollutants and biomarkers of inflammation, coagulation and thrombosis.

Methods: We measured blood concentrations of C-reactive protein (CRP), D-dimer, fibrinogen, P-selectin, platelet factor 4 (PF-4), von Willebrand factor (vWF), and myeloperoxidase (MPO) of 135 patients undergoing cardiac catheterization during the winters of 2011–2013. We coupled these data with hourly ambient concentrations of Delta-C, black carbon (BC; marker of traffic pollution), and ultrafine (10–100 nm; UFP), accumulation mode (100–500 nm; AMP), and fine particles (< 2.5 μm; $PM_{2.5}$). Using linear regression models, we estimated the change in each biomarker associated with increased pollutant concentrations at intervals between 1 and 96 h preceding blood collection.

Results: Each 0.13 $\mu g/m^3$ increase in Delta-C concentration in the prior 12 h was associated with a 0.91% increase in fibrinogen levels (95% CI=0.23%, 1.59%), but unexpectedly in the prior 48 h, each 0.17 $\mu g/m^3$ increase in Delta-C concentration was associated with a 2.75% decrease in MPO levels (95% CI=−5.13%,−0.37%). We did not see associations between Delta-C concentrations and any other biomarkers. Interquartile range (IQR) increases in $PM_{2.5}$, BC, UFP, and AMP concentrations were generally associated with increased CRP and fibrinogen, but not PF4, D-dimer, vWF, or P-selectin.

Conclusions: In a population of cardiac patients, we noted adverse changes in fibrinogen associated with increased concentrations of a marker of wood smoke. Increases in $PM_{2.5}$, BC, AMP, and UFP concentrations in the previous 96 h were also associated with adverse changes in markers of systemic inflammation and coagulation, but not with markers of endothelial cell dysfunction or platelet activation.

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1. Introduction

Increased ambient concentrations of $PM_{2.5}$ (particulate matter air pollution < 2.5 μm in diameter) and other air pollutants have previously been associated with adverse changes in biomarkers of inflammation and coagulation, as well as the triggering of myocardial infarction (MI) (Brook et al., 2010; Evans et al., 2016; Gardner et al., 2014; Rich et al., 2012a). However, assessments of acute cardiovascular responses to source specific particles (e.g. those from traffic or wood burning) are needed.

We previously found that up to 30% of ambient wintertime fine particles ($PM_{2.5}$) in Rochester, NY are from wood burning (Wang et al., 2012), while global estimates reach higher than 70% in Sweden and New Zealand (Stockfelt et al., 2012). Particulate matter (PM) pollution from wood smoke and biomass fuels has historically been estimated through measurements of black carbon (BC), though BC is also produced by motor vehicle exhaust, including diesel exhaust (Naeher et al., 2007). A more specific estimate of wood smoke pollution is Delta-C, obtained by calculating the difference between ultraviolet BC (UVBC), measured at 370 nm and BC measured at 880 nm with a 2-wavelength aethalometer (Wang et al., 2012). The concept of Delta-C as a marker of wood smoke was originally described by Allen et al. (2004). Our prior study on Delta-C elevations in the context of a forest fire exposure (Wang et al., 2010) studied its independence from vehicle emissions, its ability to detect residential wood combustion (Wang et al., 2011a) and its overall measurement characteristics in two cities (Wang et al., 2011b). Delta-C has proven useful in providing improved resolution of wood smoke and traffic in source apportionment studies (Wang et al., 2012).

Wood smoke has been linked to significant respiratory morbidity and mortality (Boman et al., 2003; Naeher et al., 2007) and recent studies have suggested a link to cardiovascular morbidity through systemic inflammation (Hejl et al., 2013; Swiston et al., 2008) and other physiologic changes (Unosson et al., 2013). However, a recent review concluded that the evidence base for the cardiovascular effects of wood smoke is weak and that wood smoke exposures are highly variable due to the multifactorial nature of wood smoke creation (Adetona et al., 2016). Furthermore, the association between a specific marker of wood smoke (Delta-C) and serum biomarkers of systemic inflammation, coagulation or platelet activity has not been studied.

The relationship between air pollution exposure and cardiovascular disease involves multiple pathophysiologic pathways including systemic inflammation and coagulation (Brook et al., 2010). In response to vessel injury or inflammation, the human body relies on the coagulation factors to strengthen and complete thrombus formation initiated by platelet activity, with fibrinogen being central to this process. C-reactive protein (CRP) and myeloperoxidase (MPO) are markers of systemic inflammation, while D-Dimer is both a marker of inflammation and coagulation. P-selectin is involved in platelet adhesion to endothelial cells, and platelet factor 4 (PF-4) is a marker of platelet activation. Von Willebrand factor (vWF) is stored in endothelial cell and platelet granules and is a nonspecific marker of inflammation, coagulation and thrombosis. Based on our prior studies showing an association between ST elevation myocardial infarction (STEMI) and increased ambient $PM_{2.5}$ concentrations in the previous 1–24 h (Evans et al., 2016; Gardner et al., 2014), we used blood samples obtained from patients undergoing cardiac catheterization due to underlying stable ischemic heart disease (SIHD) or a myocardial infarction, and studied whether increased $PM_{2.5}$, Delta-C, and other particulate air pollutant concentrations were associated with adverse changes in these biomarkers within a similar time frame. We hypothesized that adverse changes in biomarkers of inflammation, coagulation and thrombosis would be associated with increased ambient levels of Delta-C, BC, $PM_{2.5}$, ultrafine particles (UFP), and accumulation mode particles (AMP) in the previous 96 h.

2. Methods

2.1. Study population

We included participants who were patients over 18 years of age treated at the Cardiac Catheterization Laboratory (Cath Lab) at the University of Rochester Medical Center (URMC) in Rochester, New York in the winter months (November 1 to April 30th) from November 1, 2011 to December 31, 2013. These patients (N=135) presented with either acute coronary syndrome (ACS), including STEMI (n=25) and non-ST elevation myocardial infarction (NSTEMI; n=32), or a non-emergent cardiac catheterization for stable SIHD (n=78). Patients with unstable angina were not included in this study due to variability in their timing to seek medical care. All patients in this database consented to the use of their blood samples and all study activities were approved by the University of Rochester Research Subjects Review Board (RSRB #00034098).

Blood samples were generally drawn at the time of the cardiac catheterization for consented patients. Patients with SIHD were scheduled for intervention in the Cath Lab from the outpatient setting on a non-emergent basis. However, patients with NSTEMI and STEMI presented to the hospital acutely with those presenting with STEMI requiring emergent cardiac catheterization. In the case of NSTEMI, medical management is typically employed prior to cardiac catheterization, which generally occurs in the subsequent 72 h. Given the lead time prior to cardiac catheterization in both the SIHD and NSTEMI groups, consent could typically be obtained prior to the procedure. Therefore, the biomarkers in the SIHD and NSTEMI group were drawn close to the time of entry into the cardiac catheterization lab (time 0). However, patients with STEMI were sometimes unable to provide consent to enroll in the study prior to their emergent procedure due to their severe illness. This resulted in variability in the time of the blood draws for the STEMI group with blood being drawn up to 72 h following the procedure.

Multiple biomarkers were used in this study that represented inflammation, coagulation and thrombosis. Plasma concentrations of D-dimer (ng/ml), fibrinogen (μg/ml), and high sensitivity C-reactive protein (ng/ml) were measured using ELISA by AssayGate, Inc (Ijamsville, MD). Serum von Willebrand factor (ng/ml) concentrations were measured using an ELISA by Sekisui Diagnostics, and plasma concentration of soluble P-selectin (ng/ml), myeloperoxidase (pg/ml), and platelet factor 4 (pg/ml) were assessed by sandwich ELISA, all at Strong Memorial Hospital Clinical Laboratories at the URMC.

2.2. Air pollution and weather data

Pollution measurements were collected at the New York State Department of Environmental Conservation (DEC) site in Rochester, NY, at the intersection of two major highways (I-490 and I-590) and state route 96 on the east side of Rochester, NY. Black carbon was measured using a two-wavelength (370 and 880 nm) aethalometer (Magee Scientific, Inc, Berkeley, CA). Delta-C was reported as the difference between BC measured at 370 and 880 nm (Wang et al., 2012). $PM_{2.5}$ mass was measured on a semi-continuous basis with a tapered element oscillating microbalance (TEOM, model 1400ab; Thermo Fisher Scientific, Inc., Waltham, MA). AMP (100–500 nm diameter) and UFP (10–100 nm diameter) were both measured using a 3071 Electrostatic Classifier with a 3010 Condensation Particle Counter (TSI Inc., St. Paul, MN). Ambient temperature and relative humidity were continuously measured at the same DEC site. All of the measured variables were averaged to 1 h values. Since this study used a central site monitor for all patients, we calculated the farthest patient was located 88 miles from the monitor, with an average distance of 24 miles.

2.3. Statistical analysis

Using linear regression models, we estimated the difference in the concentrations of CRP, D-dimer, fibrinogen, p-selectin, PF-4, vWF, and MPO associated with interquartile range (IQR) increases in AMP, $PM_{2.5}$, Delta-C, BC and UFP concentrations in the previous 1, 12, 24, 48, 72 and 96 h among patients with ACS or SIHD. Time 0 was defined as the arrival time at the cardiac catheterization laboratory. Also included in these models were age (< 50, 50–59, 60–69, 70–79, > 79 years old), dyslipidemia, prior MI, smoking (current or not), year (2011 and 2012 or 2013), weekday (weekday or weekend), hour of the day (0400–1159 or 1200-0359), temperature (degrees Fahrenheit), and relative humidity (%). To control for diurnal variation in both air pollution and biomarkers (Rudnicka et al., 2007; Zhao et al., 2009), we included the arrival time in the cardiac catheterization lab (04:00–11:59 vs. 12:00–03:59). To determine what functional form of the weather variables should be included in the models, separate models were fitted with temperature and relative humidity modeled either as continuous variables or using a natural spline with 2–4 degrees of freedom (df). Natural splines of temperature and relative humidity, each with 3 degrees of freedom, had the lowest Akaike's Information Criterion value and were thus included in the model. To reduce skewness, we log-transformed CRP, D-dimer, fibrinogen, p-selectin, PF-4, and myeloperoxidase. vWF was the lone biomarker not requiring log-transformation. One subject with an implausibly high fibrinogen level but normal levels of other inflammatory markers was excluded from the analyses, and was not included in the 135 subjects available for analysis. From this model, we estimated the percent change in each outcome associated with each interquartile range increase in pollutant concentration at each lag time.

To examine if we observed similar results across all groups, we ran the same linear regression model described above in all subsets of patients (STEMI, NSTEMI and SIHD), along with a combination of NSTEMI and SIHD (excluding STEMI due to the aforementioned variability in timing of blood collection). Second, we ran two pollutant models, for all pairs of pollutants at the specific lag times which showed the largest effect sizes to determine whether the association between a single pollutant and a change in CRP, fibrinogen and MPO was independent of a second pollutant during the same lag time. CRP, fibrinogen and MPO were chosen for the two pollutant model based on these biomarkers showing the most consistent effect estimates. We then compared the percent change in biomarkers from the single and two pollutant models. Descriptive statistics and database management were performed in SAS version 9.4 (SAS Institute Inc, Cary, NC). All multivariable regression analyses were performed in R (version 3.2.2R Foundation for Statistical Computing, Vienna, Austria) with statistical significance defined as $p < 0.05$.

3. Results

The majority of the 135 patients in the study were admitted to the cardiac catheterization lab for stable ischemic heart disease (SIHD) (n=78), with fewer for non-ST-elevation myocardial infarction (NSTEMI) (n=32) or ST-elevation myocardial infarction (STEMI) (n=25) (Table 1). The majority of the 135 patients were non-Hispanic white (96%), male (73%) and were overweight or obese (83%). Compared with the NSTEMI and SIHD groups, patients in the STEMI group were generally younger (64% under the age of 60), had the lowest percentage with hypertension (52%), dyslipidemia (60%), and diabetes (16%), and had the lowest proportion of obese patients (36%). However, a higher percentage of STEMI patients were smokers (44%) compared with the SIHD (18%) and NSTEMI (38%).

Descriptive statistics for each pollutant are shown in Tables 2a and 2b. Twenty-four-hour average concentrations of Delta C were positively correlated with $PM_{2.5}$ (r=0.49), BC (r=0.60), UFP (r=0.53) and AMP (r=0.66) (Table A1). $PM_{2.5}$ was positively correlated with BC (r=0.65), UFP (r=0.44) and AMP (r=0.65). BC was also positively associated with UFP (r=0.46) and AMP (r=0.62). UFP was positively associated with AMP (r=0.76). Pollutants were weakly correlated with temperature (r=−0.34 to 0.13) and relative humidity (r's=−0.04 to 0.21). The distributions of each biomarker included in the study are shown in Table A2.

Table 1
Characteristics of study subjects, by diagnosis.[a]

	SIHD (N=78)		NSTEMI (N=32)		STEMI (N=25)	
	N	(%)	N	(%)	N	(%)
Age						
30–59 years	18	(23)	17	(54)	16	(64)
60–69 years	29	(37)	8	(25)	7	(28)
70–89 years	31	(39)	7	(22)	2	(8)
Male	58	(74)	22	(69)	18	(72)
Race/ethnicity						
Non-Hispanic White	74	(95)	32	(100)	23	(92)
Non-Hispanic Black, Hispanic, Other	4	(5)	0	0	2	(8)
Prior cardiovascular disease	26	(33)	10	(31)	6	(24)
Prior myocardial infarction	2	(3)	8	(25)	2	(8)
Prior percutaneous intervention	18	(23)	4	(13)	5	(20)
Prior coronary artery bypass	11	(14)	3	(9)	0	0
Prior peripheral artery disease	5	(6)	4	(13)	1	(4)
Prior heart failure	7	(9)	3	(9)	0	0
Smoker	14[b]	(18)	12	(38)	11	(44)
Hypertension	67	(86)	23	(72)	13	(52)
Dyslipidemia	54	(69)	21	(66)	15	(60)
Diabetes	21	(27)	9	(28)	4	(16)
Body mass index (BMI: kg/m^2)						
Normal (BMI 18.5–25)	10	(13)	7	(22)	6	(24)
Overweight (BMI 25.0–29.9)	24	(31)	10	(31)	10	(40)
Obesity: class I (BMI 30.0–34.9)	27	(35)	9	(28)	4	(16)
Obesity: class II (BMI 35.0–39.9)	9	(12)	3	(9)	2	(8)
Obesity: class III (BMI > 40)	8	(10)	3	(9)	3	(12)

[a] Categories may not sum to 100% due to rounding.
[b] 1 subject with SIHD had missing data on Smoking.

Percent changes in each biomarker associated with IQR increases in lagged (1, 12, 24, 48, 72, and 96 h) pollutant concentrations are shown in Tables 3A and 3B. Increased Delta-C concentrations were generally associated with increases in fibrinogen, with the largest being a 0.91% increase (95% CI=0.23%, 1.59%), associated with each 0.13 μg/m^3 increase in Delta-C concentration in the prior 12 h (Fig. 1). Increased fibrinogen was also associated with increases in concentrations of $PM_{2.5}$ (e.g. Prior 1 h: IQR=5.6 μg/m^3; 2.11%; 95% CI =0.71%, 3.51%), BC (e.g. Prior 24 h: IQR=0.29 μg/m^3; 1.85%; 95% CI=0.84%, 2.85%), and UFP (e.g. Prior 48 h: IQR=1595 n/cm^3; 2.69%; 95% CI=1.34%, 4.04% [Fig. 1]). Each 5.6 μg/m^3 increase in $PM_{2.5}$ concentration in the prior 1 h was associated with a 5.33% increase in CRP (95% CI =0.45%, 10.2%), while each 0.29 μg/m^3 increase in BC concentration in the prior 24 h was associated with a 4.0% increase in CRP (95% CI=0.44%, 7.56%)(Fig. 2). IQR increases in Delta-C, UFP, and AMP were also associated with −0.64% to 3.17% changes in CRP, but these changes were not statistically significant in the adjusted model (Tables 3A and 3B).

Inconsistent with our a priori hypothesis, IQR increases in Delta-C concentrations were associated with significant decreases in plasma MPO levels at multiple lag times (Fig. 3). For example, in the prior 48 h, each 0.17 μg/m^3 increase in Delta-C concentration was associated with a decreased MPO level (−2.75%; 95% CI=−5.13%, −0.37%). Increases in concentrations of BC at lag times from 1 to 48 h, AMP in the previous 12 h and UFP in the previous 12–96 h were also associated with significant decreases in MPO (Fig. 3 and Tables 3A and 3B). Increases in each pollutant were not associated with significant changes in P-selectin, vWF, PF4, or D-dimer, with the exceptions being

Table 2a
Distribution of 24 h mean pollutant concentrations and weather characteristics in the winters of 2011–2013.

Pollutant or weather parameter	N	Mean	Standard deviation	Min.	Percentile					Max.	IQR
					5th	25th	50th	75th	95th		
AMP (n/cm^3)	135	525	321	62	158	297	439	696	1100	1665	399
Black Carbon (μg/m^3)	135	0.37	0.23	−0.17	0.11	0.20	0.29	0.49	1.00	1.11	0.29
Delta-C (μg/m^3)	135	0.14	0.18	−0.19	0.01	0.04	0.09	0.17	0.47	1.57	0.13
$PM_{2.5}$ (μg/m^3)	127	6.9	3.1	−0.3	1.8	5.0	6.8	9.0	11.9	15.3	4.0
UFP (n/cm^3)	135	2905	1477	248	1025	1771	2684	3514	5693	8836	1743
Temperature (°F)	135	35.9	12.1	10.7	17.7	27.6	34.8	42.0	57.8	70.4	14.4
Relative humidity (%)	135	65.7	13.0	28.7	44.0	57.5	67.5	73.4	90.5	93.4	15.9

a 6.38% decrease (95% CI =−11.7%, −1.05%) in PF4 associated with each 1743 n/cm^3 increase in UFP concentration in the previous 24 h and increases in PF4 at 72 h for both AMP (8.08%; 95% CI=0.61%, 15.54%) and BC (4.8%; 95% CI=(0.27%, 9.33%). Further, there were no patterns of consistent increases or decreases associated with any pollutant across lag times for these outcomes (Tables 3A and 3B).

Next, we restricted our analyses to only SIHD patients and NSTEMI, where there was less variability in blood sample collection times (relative to STEMI) to evaluate if they were similar to our findings from our main analysis that included STEMI, NSTEMI, and SIHD patients. In this combined SIHD and NSTEMI subgroup, the magnitude of the associations between pollutants and either CRP or fibrinogen appeared larger than the main analysis including all 3 groups. Generally the direction of associations (increase or decrease in biomarker level associated with increased PM concentration) appeared similar to the main analysis above (Table A3 (A-B)). For example, each 0.13 μg/m^3 increase in the Delta-C concentration in the previous 12 h remained significantly associated with a 0.89% increase in fibrinogen levels (95% CI=0.28%, 1.51%).

We then stratified our analysis by STEMI, NSTEMI, and SIHD individually. In general, for fibrinogen, the NSTEMI group showed larger percent changes in biomarkers and the STEMI group showed smaller percent changes when compared to the SIHD population, (Table A5B). We generally observed increased levels of fibrinogen associated with increased concentrations of each pollutant across lag times for all patient groups (STEMI, NSTEMI, and SIHD) (Table A5B). Similarly, we generally observed decreased levels of MPO associated with increased concentrations of each pollutant across lag times for all patient groups (STEMI, NSTEMI, and SIHD) with smaller effect estimates noted in the STEMI group (Table A5C). The estimates within the STEMI and NSTEMI patient groups were less precise than in the SIHD group. However, we observed increased CRP levels associated with increased pollutant concentrations across lag times for all pollutants for only NSTEMI and SIHD patients, but not STEMI patients (Table A5A). Of note, each IQR increase in $PM_{2.5}$ concentrations across all lag times was associated with a −0.9% to −4.89% decrease in CRP in the STEMI group, but increased CRP levels in the NSTEMI and SIHD groups (Supplementary Table A5A).

To account for the variability in time 0 of STEMI patients, we performed an analysis with time 0 changed to a point 24 h in the future. The magnitude of the percent change for fibrinogen, MPO, D Dimer, and PF4 were reduced, but in the same direction as the original analysis with time 0 set as the arrival time to the Cath Lab (data not shown). For example, the original percent change of fibrinogen for a 5.6 μg/m^3 increase in $PM_{2.5}$ at the 1 h lag was reduced from 2.16% (95% CI=(−0.57%, 4.89%)) to 1.07% (95% CI=−0.19%, 2.32%). No consistent change was noted for CRP, vWF or P-selectin in this analysis compared to the main analysis.

We then evaluated whether our parameter estimates for an individual pollutant (e.g. Delta-C and fibrinogen at a 48-h lag) from the single pollutant models described above differed from the parameter estimate for that same pollutant when adjusting for a second pollutant. We included the pollutant lags with the largest changes in fibrinogen, CRP, and MPO in the two pollutant models (e.g. CRP: $PM_{2.5}$ lag 1 h, BC lag 24 h; Fibrinogen: $PM_{2.5}$ lag 1 h, Delta C lag 12 h, BC lag 24 h, UFP lag 48 h; MPO: BC lag 12 h, AMP lag 12 h, Delta C lag 48 h and UFP lag 96 h). The 5.33% change in CRP associated with each 5.6 μg/m^3 increase in $PM_{2.5}$ concentration in the previous hour, was not substantially reduced or eliminated when separately adjusting for concentrations of BC (6.84%), Delta-C (7.52%), UFP (4.49%), or AMP (5.06%) from the same lag time. Similarly, changes in other outcomes associated with increased pollutant concentrations were similarly not substantially reduced when controlling for a 2nd pollutant. However, the 0.91% increase in fibrinogen associated with each 0.13 μg/m^3 increase in Delta-C concentration in the previous 12 h was reduced when including $PM_{2.5}$, BC and UFP and was removed (0.04% change) when including AMP at the same lag time in the model (Table A4).

4. Discussion

We observed increases in fibrinogen associated with increased Delta-C, BC, UFP and $PM_{2.5}$ at multiple lag times, and increased CRP associated with increased BC lagged 12–24 h and $PM_{2.5}$ lagged 1 h. These effects were independent of age, dyslipidemia, history of prior ACS, smoking status, year, week day, hour of the day, temperature, relative humidity, and generally independent of other pollutants. We did not see consistent effects of any pollutant on D-Dimer, P-selectin, PF4 or vWF. Contrary to our *a priori* hypothesis, we observed

Table 2b
Distribution of 1 h mean pollutant concentrations and weather characteristics in the winters of 2011–2013.

Pollutant or weather parameter	N	Mean	Standard deviation	Min.	Percentile					Max.	IQR
					5th	25th	50th	75th	95th		
AMP (n/cm^3)	135	464	319	45	123	228	384	623	1049	2003	395
Black Carbon (μg/m^3)	135	0.4	0.4	0.0	0.1	0.2	0.3	0.4	1.1	1.9	0.2
Delta-C (μg/m^3)	135	0.10	0.13	−0.15	−0.01	0.02	0.05	0.13	0.35	0.80	0.11
$PM_{2.5}$ (μg/m^3)	127	6.8	3.4	−0.4	2.5	4.1	6.1	9.7	13.1	16.4	5.6
UFP (n/cm^3)	135	3221	3125	239	559	1655	2460	3857	8180	29892	2202
Temperature (°F)	134	37.9	12.8	14.5	19.0	30.4	36.7	43.8	59.8	89.1	13.4
Relative humidity (%)	134	60.8	17.5	19.0	35.0	49.0	62.0	74.0	92.0	95.0	25.0

Table 3A
Percent change[†] in CRP, fibrinogen, MPO, and D-dimer associated with IQR increases in pollutant concentrations.

Pollutant	Time lag (h)	IQR	N	CRP % change in outcome (95%CI)	N	Fibrinogen % change in outcome (95%CI)	N	MPO % change in outcome (95% CI)	N	D-dimer % change in outcome (95% CI)
Accumulation Mode Particles (n/cm^3)	1	395	125	3.17 (−0.75, 7.09)	125	2.03** (0.94, 3.13)	133	−1.85 (−3.77, 0.07)	125	1.20 (−2.20, 4.61)
	12	452	125	2.37 (−1.66, 6.40)	125	2.40** (1.30, 3.50)	133	−2.80** (−4.68, −0.92)	125	0.23 (−3.25, 3.71)
	24	399	125	2.04 (−2.06, 6.14)	125	1.99** (0.84, 3.13)	133	−1.88 (−3.83, 0.07)	125	0.19 (−3.36, 3.73)
	48	391	125	0.82 (−3.98, 5.62)	125	1.84** (0.48, 3.20)	133	−1.71 (−4.02, 0.60)	125	−3.03 (−7.12, 1.06)
	72	413	125	2.03 (−3.91, 7.96)	125	1.62 (−0.10, 3.33)	133	−1.71 (−4.57, 1.15)	125	−4.09 (−9.15, 0.96)
	96	335	125	2.28 (−2.94, 7.49)	125	0.96 (−0.56, 2.48)	133	−2.12 (−4.66, 0.42)	125	−4.18 (−8.61, 0.25)
Black Carbon ($\mu g/m^3$)	1	0.23	125	0.15 (−1.73, 2.03)	125	0.33 (−0.22, 0.87)	133	−1.37** (−2.27, −0.47)	125	−0.44 (−2.05, 1.18)
	12	0.33	125	3.65* (0.61, 6.69)	125	1.83** (0.98, 2.67)	133	−2.10** (−3.58, −0.61)	125	0.35 (−2.33, 3.03)
	24	0.29	125	4.00* (0.44, 7.56)	125	1.85** (0.84, 2.85)	133	−1.97* (−3.70, −0.23)	125	−0.59 (−3.72, 2.54)
	48	0.26	125	1.99 (−1.90, 5.87)	125	1.40* (0.29, 2.51)	133	−1.43 (−3.31, 0.44)	125	−1.51 (−4.85, 1.84)
	72	0.20	125	1.81 (−1.72, 5.33)	125	0.92 (−0.10, 1.94)	133	−0.83 (−2.55, 0.88)	125	−0.91 (−3.95, 2.13)
	96	0.19	125	2.36 (−1.72, 6.43)	125	0.80 (−0.39, 1.99)	133	−1.41 (−3.39, 0.57)	125	−1.49 (−5.01, 2.02)
Delta-C ($\mu g/m^3$)	1	0.11	125	−0.59 (−5.01, 3.83)	125	0.88 (−0.46, 2.22)	133	−1.47 (−3.64, 0.70)	125	−2.36 (−5.83, 1.11)
	12	0.13	125	0.36 (−1.97, 2.69)	125	0.91* (0.23, 1.59)	133	−1.20* (−2.33, −0.07)	125	−1.00 (−2.85, 0.84)
	24	0.13	125	0.70 (−2.02, 3.41)	125	0.85* (0.05, 1.66)	133	−1.47* (−2.77, −0.16)	125	−0.50 (−2.66, 1.66)
	48	0.17	125	0.55 (−4.41, 5.50)	125	0.65 (−0.86, 2.16)	133	−2.75* (−5.13, −0.37)	125	−2.15 (−6.06, 1.76)
	72	0.18	125	2.43 (−3.46, 8.31)	125	0.22 (−1.60, 2.03)	133	−1.03 (−3.97, 1.92)	125	−2.51 (−7.18, 2.16)
	96	0.16	125	2.68 (−3.08, 8.44)	125	−0.18 (−1.96, 1.60)	133	−0.84 (−3.73, 2.05)	125	−3.61 (−8.14, 0.91)
$PM_{2.5}$ ($\mu g/m^3$)	1	5.6	117	5.33* (0.45, 10.20)	117	2.11** (0.71, 3.51)	125	−1.97 (−4.30, 0.37)	117	0.89 (−3.35, 5.14)
	12	4.3	115	2.90 (−1.30, 7.10)	115	1.88** (0.68, 3.09)	123	−1.93 (−3.93, 0.07)	115	0.36 (−3.34, 4.06)
	24	4.0	117	1.48 (−2.70, 5.66)	117	1.36* (0.15, 2.58)	125	−1.34 (−3.35, 0.66)	117	0.17 (−3.46, 3.80)
	48	4.2	115	−0.27 (−5.06, 4.52)	115	1.23 (−0.18, 2.64)	123	−1.61 (−3.90, 0.68)	115	−1.32 (−5.47, 2.83)
	72	4.3	116	1.30 (−4.30, 6.89)	116	1.44 (−0.21, 3.09)	123	−2.00 (−4.67, 0.66)	116	−1.28 (−6.12, 3.55)
	96	4.1	112	3.12 (−2.84, 9.08)	112	1.47 (−0.28, 3.22)	119	−1.74 (−4.54, 1.06)	112	−3.09 (−8.22, 2.05)
Ultrafine particles (n/cm^3)	1	2202	125	1.25 (−0.63, 3.12)	125	0.34 (−0.21, 0.89)	133	−0.12 (−1.05, 0.81)	125	0.67 (−0.95, 2.29)
	12	2477	125	3.11 (−1.40, 7.62)	125	2.33** (1.07, 3.59)	133	−3.28** (−5.32, −1.23)	125	3.35 (−0.51, 7.22)
	24	1743	125	1.32 (−2.45, 5.08)	125	1.90** (0.86, 2.95)	133	−2.47** (−4.22, −0.71)	125	−0.02 (−3.26, 3.22)
	48	1595	125	0.38 (−4.54, 5.31)	125	2.69** (1.34, 4.04)	133	−3.59** (−5.90, −1.29)	125	−3.15 (−7.34, 1.04)
	72	1562	125	0 (−6.22, 6.22)	125	2.48** (0.72, 4.24)	133	−4.87** (−7.79, −1.96)	125	−4.09 (−9.39, 1.20)
	96	1434	125	−0.64 (−7.05, 5.78)	125	1.99* (0.15, 3.83)	133	−5.55** (−8.51, −2.59)	125	−5.43 (−10.86, −0.01)

* $p < 0.05$.
** $p < 0.01$.
[†] Adjusted for age (< 50, 50–59, 60–69, 70–79, > 79 years old), dyslipidemia, prior MI, smoking (current or not), year (2011 and 2012 or 2013), weekday (weekday or weekend), hour of the day (0400-1159 or 1200-0359), temperature (degrees Fahrenheit), and relative humidity.

significant decreases in MPO associated with increased concentrations of Delta-C, AMP, UFP and BC. Pollutant effects on fibrinogen and MPO were similar for STEMI, NSTEMI, and SIHD patients, but unexpectedly, increased pollutant concentrations were associated with decreases in CRP.

The adverse respiratory effects of wood smoke exposure, including COPD, asthma and lung cancer, are well known (Boman et al., 2003; Ekici et al., 2005; Naeher et al., 2007), while the link between wood smoke exposure and cardiovascular disease is an area of active research. Cardiovascular disease, which manifests as acute coronary syndrome (ACS) or SIHD, involves a multifactorial pathophysiology including inflammation, endothelial dysfunction, coagulation and thrombosis (Brook et al., 2010). Several studies in the wood smoke literature have found no clear pattern of association between wood smoke exposure and biomarkers of inflammation and coagulation (Bønløkke et al., 2014; Hunter et al., 2014; Jensen et al., 2014). While our prior work did not find significant associations between Delta-C exposure and myocardial infarction (Evans et al., 2016), two controlled exposure studies reported increased biomarkers of inflammation and coagulation associated with wood-smoke particles (Barregard et al., 2006; Huang et al., 2003), while another reported decreased levels (Stockfelt et al., 2012).

Our findings of increases in fibrinogen (0.22% to 2.69%) associated with IQR increases in pollutants are consistent with past epidemiologic studies showing similarly sized effects (Bind et al., 2012; Rich et al., 2012a, 2012b; Rückerl et al., 2007). However, others reported no clear association between air pollution and fibrinogen (Delfino et al., 2008; Rückerl et al., 2006). Our observation of increased fibrinogen asso-

Table 3B
Percent change[†] in vWF, PF4, and P-selectin associated with IQR increases in pollutant concentrations.

Pollutant	Time lag (hr)	IQR	N	vWF % change in outcome (95% CI)	N	PF4 % change in outcome (95% CI)	N	P-selectin % change in outcome (95% CI)
Accumulation Mode Particles (n/cm^3)	1	395	133	−2.91 (−11.89, 6.06)	119	−4.05 (−9.33, 1.22)	132	−1.82 (−8.13, 4.48)
	12	452	133	−0.61 (−9.59, 8.37)	119	−2.19 (−8.08, 3.69)	132	−0.65 (−7.00, 5.70)
	24	399	133	2.09 (−7.05, 11.22)	119	0.20 (−5.89, 6.3)	132	1.42 (−5.00, 7.85)
	48	391	133	3.80 (−6.95, 14.54)	119	5.10 (−1.24, 11.44)	132	2.48 (−5.06, 10.02)
	72	413	133	5.87 (−7.36, 19.11)	119	8.08* (0.61, 15.54)	132	4.27 (−5.01, 13.56)
	96	335	133	2.38 (−9.47, 14.24)	119	4.47 (−2.27, 11.22)	132	2.32 (−5.96, 10.61)
Black Carbon ($\mu g/m^3$)	1	0.23	133	−3.53 (−7.79, 0.73)	119	−0.86 (−3.45, 1.73)	132	−1.22 (−4.24, 1.81)
	12	0.33	133	−1.06 (−8.12, 6.00)	119	−1.17 (−5.38, 3.03)	132	−2.07 (−7.04, 2.90)
	24	0.29	133	0.53 (−7.66, 8.72)	119	0.70 (−4.25, 5.64)	132	0.20 (−5.56, 5.95)
	48	0.26	133	1.83 (−6.89, 10.55)	119	4.48 (−0.51, 9.46)	132	1.82 (−4.39, 8.02)
	72	0.20	133	2.76 (−5.16, 10.67)	119	4.80* (0.27, 9.33)	132	1.92 (−3.76, 7.61)
	96	0.19	133	1.62 (−7.59, 10.83)	119	3.12 (−2.21, 8.44)	132	0.03 (−6.55, 6.61)
Delta-C ($\mu g/m^3$)	1	0.11	133	−6.94 (−16.31, 2.44)	119	−1.79 (−8.13, 4.54)	132	−2.75 (−10.45, 4.95)
	12	0.13	133	−2.65 (−7.66, 2.35)	119	−2.11 (−6.08, 1.85)	132	0.73 (−3.36, 4.82)
	24	0.13	133	−1.06 (−6.93, 4.82)	119	−3.95 (−10.09, 2.19)	132	0.87 (−3.89, 5.64)
	48	0.17	133	−4.03 (−14.69, 6.63)	119	0.53 (−6.46, 7.51)	132	0.59 (−8.08, 9.26)
	72	0.18	133	1.69 (−11.10, 14.48)	119	7.08 (−0.44, 14.61)	132	7.44 (−2.76, 17.64)
	96	0.16	133	3.41 (−9.10, 15.92)	119	3.46 (−4.03, 10.95)	132	4.34 (−5.77, 14.44)
$PM_{2.5}$ ($\mu g/m^3$)	1	5.6	125	−5.75 (−16.81, 5.30)	112	−5.05 (−11.69, 1.59)	125	−6.34 (−14.13, 1.45)
	12	4.3	123	−0.13 (−9.50, 9.23)	109	−0.21 (−6.13, 5.71)	123	−1.7 (−8.45, 5.05)
	24	4.0	125	0.26 (−9.00, 9.52)	111	2.63 (−3.13, 8.39)	125	1.85 (−4.90, 8.59)
	48	4.2	123	−1.02 (−11.60, 9.57)	109	2.36 (−4.01, 8.73)	123	1.31 (−6.42, 9.03)
	72	4.3	123	1.55 (−10.90, 13.99)	110	2.00 (−5.35, 9.34)	123	−0.19 (−9.19, 8.82)
	96	4.1	119	−2.05 (−15.46, 11.35)	106	1.28 (−5.98, 8.54)	119	−2.08 (−11.65, 7.48)
Ultrafine particles (n/cm^3)	1	2202	133	−2.08 (−6.35, 2.20)	119	−1.38 (−3.81, 1.06)	132	−0.23 (−3.25, 2.79)
	12	2477	133	−3.48 (−13.28, 6.32)	119	−5.19 (−11.18, 0.79)	132	−1.79 (−8.71, 5.12)
	24	1743	133	−1.73 (−10.07, 6.62)	119	−6.38* (−11.70, −1.05)	132	−0.33 (−6.23, 5.56)
	48	1595	133	3.40 (−7.64, 14.44)	119	−4.29 (−11.27, 2.70)	132	−2.43 (−10.22, 5.36)
	72	1562	133	5.92 (−8.08, 19.93)	119	1.23 (−6.95, 9.42)	132	−2.17 (−12.03, 7.68)
	96	1434	133	0.81 (−13.6, 15.23)	125	1.02 (−7.45, 9.49)	132	−0.33 (−10.46, 9.80)

* $p < 0.05$.
[†] Adjusted for age (< 50, 50–59, 60–69, 70–79, > 79 years old), dyslipidemia, prior MI, smoking (current or not), year (2011 and 2012 or 2013), weekday (weekday or weekend), hour of the day (0400-1159 or 1200-0359), temperature (degrees Fahrenheit), and relative humidity.

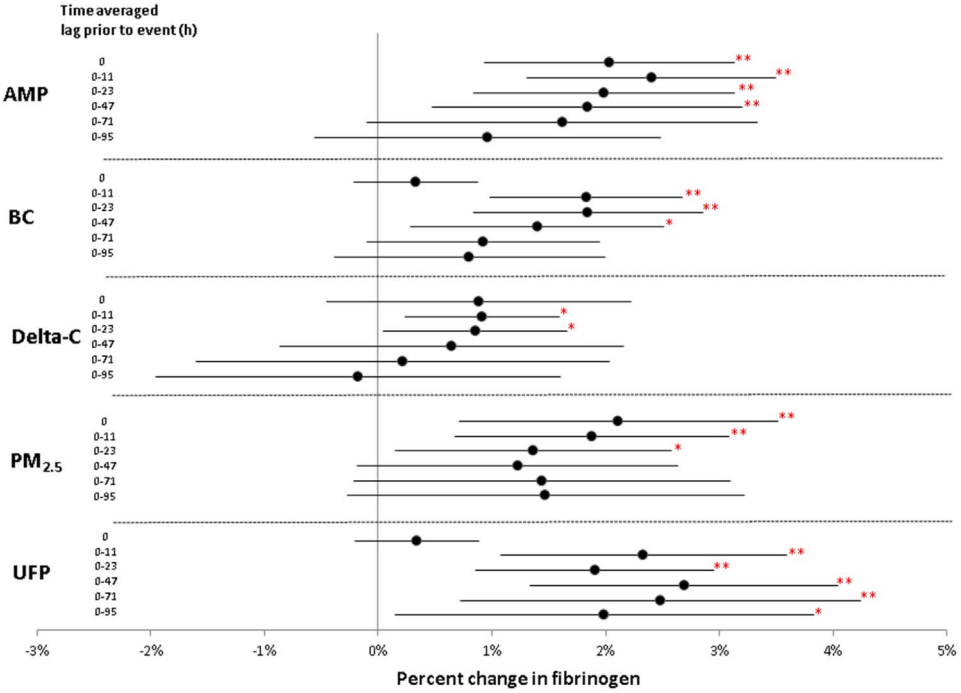

Fig. 1. Percent change in fibrinogen per interquartile range increase in pollutant concentration. *p < 0.05, **p < 0.01.

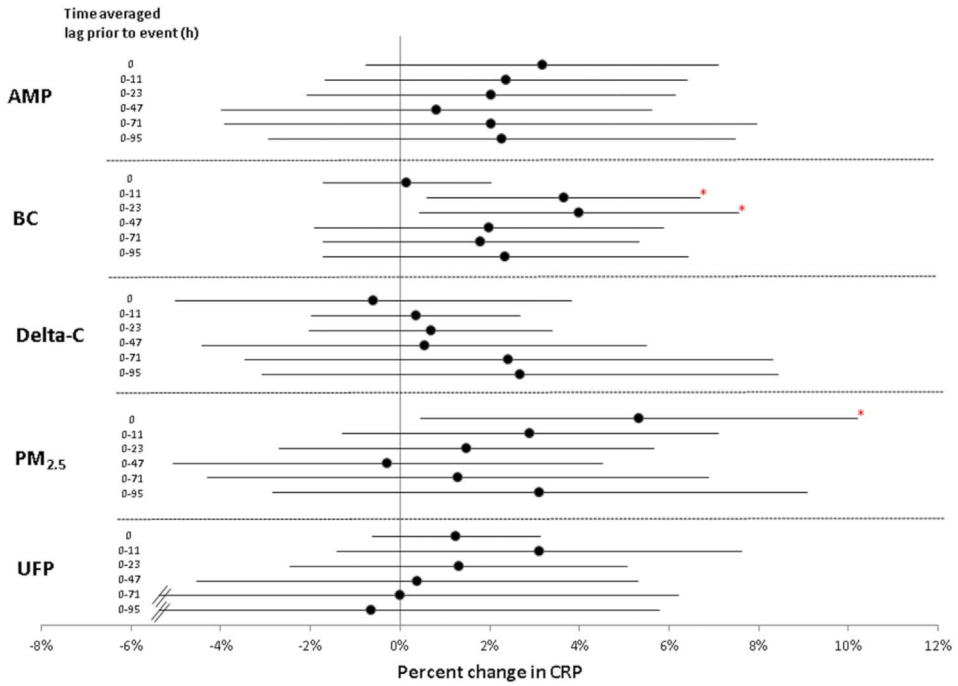

Fig. 2. Percent change in C-reactive protein (CRP) per interquartile range increase in pollutant concentration. *p < 0.05, **p < 0.01.

ciated with increased BC levels in the previous 24 h (1.85%; 95% CI of 0.84–2.85%) is consistent with a 1.32% increase (95% CI: 0.46–2.19%) observed by Bind et al. (2012), both scaled to a 0.29 μg/m^3 increase in BC. Our results were also consistent with two studies that measured D-Dimer (a breakdown product of fibrin that increases with coagulation) and found no association with particulate air pollutants (Delfino et al., 2008; Rückerl et al., 2006). Although we found no such association, increased P-selectin (indicator of both endothelial cell damage and platelet activation) has been previously associated with increased air pollutant concentrations (around 6–12% increases based on figures) in some (Delfino et al., 2008; Rich et al., 2012a), but not other studies (Bønløkke et al., 2014; Hunter et al., 2014). O'Toole et al. (2010) reported no association between increased concentrations of $PM_{2.5}$ and PF4 (marker of platelet activation and vascular inflammation) in young adults during the winter, which is consistent with our findings.

Similar to prior studies, we found acute increases in $PM_{2.5}$ concentration to be associated with increases in CRP (Bind et al., 2012; Delfino et al., 2008; Rich et al., 2012b; Rückerl et al., 2006; Siponen et al., 2014) (Fig. 2). Although the association between $PM_{2.5}$ and CRP occurred at the 1 h lag time (5.33%; 95% CI=0.45%, 10.2%; IQR =5.6 μg/m^3), it is consistent with the magnitude and direction of CRP changes associated with $PM_{2.5}$ (24–96 h) noted in previous

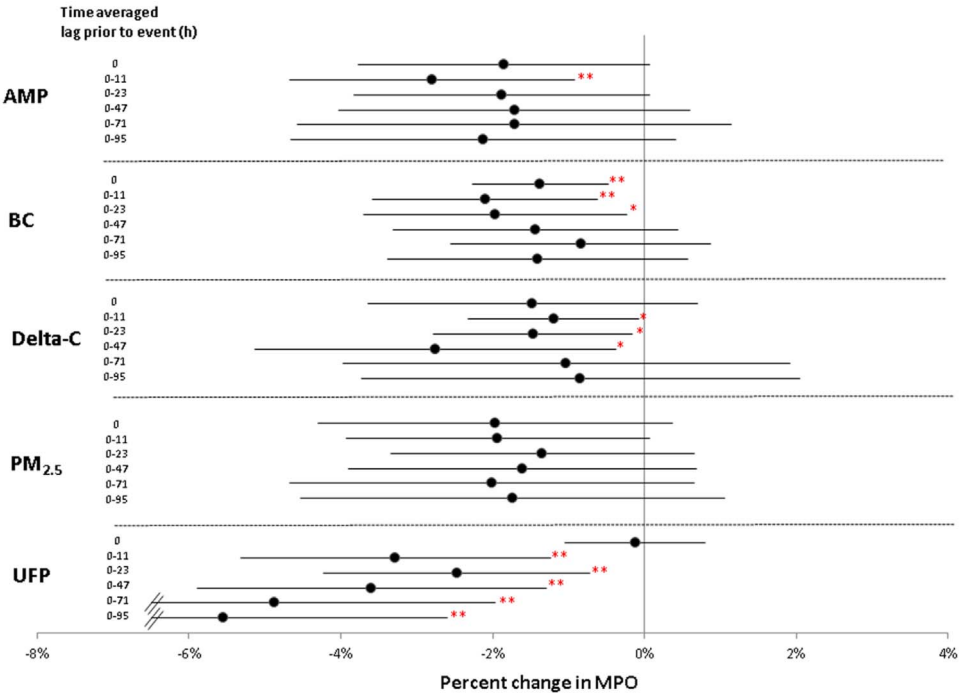

Fig. 3. Percent change in myeloperoxidase (MPO) per interquartile range increase in pollutant concentration. *p < 0.05, **p < 0.01.

studies (Delfino et al., 2008; Rückerl et al., 2006; Siponen et al., 2014). Studies on firefighters with occupational wood smoke exposures have shown increased inflammatory biomarkers including interleukin (IL)-6 and IL-8 (Hejl et al., 2013; Swiston et al., 2008). However, these findings were not replicated in a recent study following firefighters' exposures during a fire (Jensen et al., 2014). Similarly, a recent controlled wood smoke exposure study on firefighters did not show increased thrombosis or platelet activation (Hunter et al., 2014). In contrast, our marker of wood smoke, Delta-C, showed positive but not statistically significant associations with CRP.

One unexpected finding was the decrease in CRP associated with increased PM concentration in the STEMI group, but increased CRP associated with increased PM concentration in the NSTEMI and SIHD groups. This may be due to the delay in blood collection time in the STEMI group and a resultant decline in CRP levels from the time of Cath Lab arrival until blood draw in some patients due to a reduction in the level of inflammation after cardiac catheterization. Within the STEMI group, we did not see the same decrease in fibrinogen associated with increased PM concentration, which may be related to the known slower decline of fibrinogen following an inflammatory stimulus (Neto et al., 2009). The association between air pollution and MPO in the STEMI population showed a similar trend to the association between CRP and pollution, with smaller effect estimates (more negative) noted when compared to the NSTEMI and SIHD groups (Table A5C).

Myeloperoxidase (MPO) is an enzyme involved in the inflammatory response including neutrophil oxidative killing of pathologic organisms, and also has been studied as a proatherogenic mediator which adversely remodels protective, anti-inflammatory proteins in high density lipoprotein (Cameron et al., 2016; Pulli et al., 2013). Higher levels of serum MPO may be a predictor of cardiac morbidity and mortality (Nicholls and Hazen, 2005). Our finding of acutely decreased MPO associated with increased pollutant concentrations in the previous 96 h is consistent with work of Delfino et al. (2008). One possible explanation is that MPO may be protective by modifying a harmful cellular mechanism of particulate matter air pollution through a multitude of post-translational protein modifications (e.g. nitration and oxidative cross-linking) (Baldus et al., 2006; Nicholls and Hazen, 2005). Given the complexity of MPO, further investigation is needed to determine the clinical significance of a negative association between MPO and particulate matter.

Increases in vWF, which mediates platelet adhesion and aggregation in thrombosis, have been associated with acute increases in particulate air pollution previously (Rich et al., 2012a; Riediker et al., 2004; Rückerl et al., 2006). However, our findings of no association between vWF, wood smoke, or other PM is inconsistent with this work.

The heterogeneity of the existing wood smoke literature reviewed above may in part be due to differences in PM exposure type (controlled exposure vs. ambient concentrations), exposure durations investigated (single short exposure vs. repeated exposures), fuel used (wood type and condition), combustion conditions (complete vs. incomplete combustion) (Bruns et al., 2015) as well as our use of the novel marker Delta-C as a measure of wood smoke exposure. Often exposure is estimated based on less specific indicators of wood smoke such as water soluble potassium, PAHs or BC (Molnar et al., 2005). Other specific markers such as levoglucosan (Jordan et al., 2006) are not easily measured on a routine basis. The physiochemical properties of primary wood smoke generated in the vicinity of the combustion source and the ambient wood smoke that travels downwind of the primary source help determine the likelihood of generating a systemic response (Bølling et al., 2012). Ambient wood smoke PM has shown equivalent or greater lung deposition fractions than primary wood smoke PM (Sigsgaard et al., 2015) and has even shown a similar alveolar deposition fraction (19%) to traffic generated particles (22%) (Kristensson et al., 2013). Physiochemical aging chemically alters ambient wood smoke PM through reactions with ozone and other reactive molecules (Bruns et al., 2015; Sigsgaard et al., 2015), which may increase its toxicity (Nordin et al., 2015). However, the low temperatures and short intervals of sunlight during the winter months studied likely minimized the physiochemical aging of the ambient wood smoke PM. Therefore the associations noted between ambient wood smoke PM and the biomarkers of inflammation and coagulation may be independent of physiochemical aging.

There are several limitations to our study that should be considered when making inference. First, our study had a limited sample size which reduced our statistical power. Second, the STEMI patients were emergently taken to the cardiac catheterization lab so as to minimize time to revascularization. Thus, for some STEMI patients, this may have led to their biomarker data being collected up to 24–72 h after arrival at the catheterization lab once consent was obtained. Since we matched ambient PM concentrations from the few hours and days before the time of arrival at the Cath Lab, and not the exact hour of blood collection for STEMI patients after cardiac catheterization, this may have led to exposure error (i.e. wrong air pollution values matched to the patient's fibrinogen concentration for analysis). However, since the degree of error is likely unrelated to the actual biomarker level, this should only result in a bias towards the null and underestimates of effect. Further, the biomarker level in these patients measured up to 72 h after arrival at the catheterization laboratory may result in outcome misclassification as well, resulting in a loss of statistical power. Despite these limitations, the inclusion of the STEMI group with the NSTEMI and SIHD groups in the main analysis appeared to only slightly reduce the magnitude of our effect estimates, with no difference in the inference made from both analyses.

Third, since our STEMI and NSTEMI patients received the anticoagulant heparin prior to their cardiac catheterization as part of the routine medical management of ACS, the level of fibrinogen may have theoretically been lower than expected (Prisco et al., 1998) and the level of MPO higher than expected (Baldus et al., 2006). The similar results noted in the SIHD only population suggest that heparin administration was not a significant issue and at worst, the effects reported may be underestimated in the STEMI and NSTEMI groups. Fourth, we used ambient air pollution data from one monitoring station for each subject, regardless of how far they lived, worked, and spent time relative to the monitoring site. This exposure misclassification is likely not different for subjects with high versus low biomarker levels, and thus should also result in underestimates of effect. Lastly, because of the multiple models run in the manuscript, the p value defined for statistical significance could theoretically be lowered by conducting a Bonferroni multiple comparison correction. We elected to keep our p value for significance at 0.05 as the inference for this study should primarily be made on the pattern of responses for each biomarker across lags, rather than on the statistical significance.

5. Conclusion

In our population of patients with both acute and stable, but active cardiovascular disease, increases in particulate air pollutants ($PM_{2.5}$, Delta-C, BC, AMP, and UFP) were generally associated with increases in biomarkers of systemic inflammation and coagulation, which can be predictive of cardiac events like ACS. However, PM pollution and wood smoke's association with endothelial dysfunction, increased platelet activity, and MPO activity remains unclear.

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Competing interests

David Q. Rich has received research funding from and has served as a consultant for the Electric Power Research Institute in the past. However, no authors had competing financial interests during the collection of data, analysis of data or manuscript preparation.

Ethics approval and consent

All patients in this database consented to the use of their blood samples and all study activities were approved by the University of Rochester Research Subjects Review Board (RSRB #00034098).

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2017.01.027.

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