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Response of biomarkers of inflammation and coagulation to short-term changes in central site, local, and predicted particle number concentrations

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Abstract

Purpose—Previous studies have reported acute (hours–28 days) associations between ambient ultrafine particles (UFP; diameter <0.1) and biomarkers of cardiovascular health using central site data. We evaluated particle number concentration (a proxy measure for UFP) measured at a central site, a local near-highway site and predicted residential concentrations with response of biomarkers of inflammation and coagulation in a near-highway population.

Methods—Participants provided two blood samples for analysis of interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor- α receptor II, and fibrinogen. Mixed effect models were used to evaluate the association between PNC levels on the same day, prior 2 days, and moving averages of 3 to 28 days.

Results—Estimated effects on biomarkers of a 5000 unit increase in central site PNC generally increased with longer averaging times for IL-6, hs-CRP, and fibrinogen. Effect estimates were highest for a 28-day moving average, with 91% (95% confidence interval [CI]: 9, 230) higher IL-6 levels, 74% (95% CI: –7, 220) higher hs-CRP levels, and 59% (95% CI: –13, 130) higher fibrinogen levels. We observed no clear trend between near-highway or predicted residential PNC and any of the biomarkers.

Conclusions—Only central site PNC increased blood markers of inflammation while near-highway and predicted residential values did not. We cannot fully explain this result, although differing PNC composition is a possibility. Future studies would assist in understanding these findings.

Keywords

Particles; Highway; Cardiovascular; Inflammation; Coagulation

Introduction

Air pollution is widespread in the urban environment and there is substantial evidence of associations with cardiovascular (CV) morbidity and mortality [1–4]. Three principal pathways have been proposed to explain the adverse CV effects of inhalation of particulate matter: oxidative stress and inflammation, stimulation of the autonomic nervous system, and direct interaction between particles or their components and the CV system [1]. The first pathway, which begins with pulmonary inflammation, progresses to a systemic inflammatory state of oxidative stress, acute phase response, and endothelial dysfunction. Supporting this pathway are observations of associations between particulate matter and markers of systemic inflammation [5–9] and blood pressure [10–12].

The specific components responsible for associations between air pollution and adverse outcomes are yet to be fully defined; however, there is evidence from human, animal, and in vitro studies that ultrafine particles (UFP; diameter <0.1 μm) have causal effects [5,13–17]. UFP have the ability to deposit deep into the lungs, where large surface areas are available for the adsorption of harmful chemicals [14,18,19]. In the urban environment, regional levels of UFP are augmented by contributions from motor vehicle exhaust resulting in both substantial temporal and spatial variability, particularly near busy roadways [20–22].

Our goal was to examine the effect of short-term exposure to UFP on biomarkers of inflammation and coagulation in a predominately near-highway population. UFP can be reasonably approximated by particle number concentration (PNC) because 80% to 90% of PNC is in the ultrafine range in urban areas [23,24]. We hypothesized that short-term changes in ambient PNC would be related to increases in interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor- α receptor II (TNF-RII), and fibrinogen. In most published studies, a single metric is used for PNC exposure, typically from a central site [8,9,25–28]. However, central sites may not represent PNC variation (and therefore exposures) near highways and a neighborhood monitor or predicted residential concentrations [29]. In other studies in which residential measurements have provided the data for exposure, associations of residential PNC and quasi-UFP (diameter <0.25 μm) with blood pressure and inflammatory markers have been identified [6,30]. We evaluated potential associations of PNC measured at a central site, a near-highway monitor, and modeled values with biomarkers of inflammation and coagulation.

Methods

Study area and population

This analysis used data from the Community Assessment of Freeway Exposure and Health (CAFEH) study, a cross-sectional, community-based participatory research study of near-highway air pollution and CV health [31]. The study enrolled residents from three near-highway neighborhoods in Boston, Massachusetts (United States), metropolitan area.

We used data from the Somerville, Massachusetts subsample of CAFEH for this analysis. A detailed description of the study is provided elsewhere [32]. Somerville is a city located to the northwest of Boston whose southeast portion is split by I-93, which carries 150,000 vehicles per day (vpd) and another major roadway, Route-38 (20,000 vpd) [33]. Participants were recruited from three areas based on residential distance to the highway: less than 100 m, 100 to 400 m, and an urban background location greater than 1000 m (Fig. 1). A random sample of addresses within these distance categories was selected for recruitment, and additional participants were recruited from a convenience sample of residents in two senior housing developments. Inclusion criteria were 40 years or older, residing within the study, area and ability to answer a questionnaire in one of five languages (English, Spanish, Haitian Creole, Portuguese, or Chinese). Participants were asked to provide blood samples at two time points approximately 5 months apart. Blood and other clinical data were collected from August 2009 through September 2010. Clinics took place from approximately 6 AM to noon on scheduled days with most clinical visits being from 7 to 11 AM. The study was approved by the Tufts University School of Medicine IRB, and all participants provided informed consent.

Individual level covariates

Data on demographic variables including age, sex, race and ethnicity, employment status, income, and education were collected. Data on factors that may affect exposure to particulate matter including smoking, secondhand smoke, and employment status were also collected. The name and dosage of each participant's prescribed medications during in-home interviews were recorded. A physician categorized medications into those prescribed to manage cholesterol, hypertension, diabetes, and inflammation. The presence of prior or current health conditions including asthma, congestive heart failure, myocardial infarction, rheumatoid arthritis and stroke were identified by self-report.

Exposure measurements

Environmental monitoring used to create the exposure metrics in these analyses are detailed elsewhere [29,34,35]. Ambient measurements of PNC were measured from a rooftop monitor (six floors above street level) at the Countway Library of Medicine of

Harvard Medical School (Harvard School of Public Health [SPH]) on Huntington Avenue, in Boston approximately 7 km away from the study area. Continuous hourly measurements of PNC were collected from November 2009 through December 2010 at the SPH site using a butanol-based CPC (Model 3022A; TSI Inc., Shoreview, MN). PNC were concurrently measured near the highway on the roof of the Mystic Activity Center (MAC) in Somerville

(Fig. 1). PNC at the near-highway site was measured using a water-based condensation particle counter (Model 3781; TSI Inc., Shoreview, MN), and meteorologic variables were recorded by a Vantage Pro2 weather station (Davis Instrument Corp., Hayward, CA).

An hourly spatiotemporal model of PNC at participant residences was built using data collected with the Tufts Air Pollution Monitoring Laboratory and is described in full in Patton et al. [34]. The Tufts Air Pollution Monitoring Laboratory was driven over the same route two to six times per day on 43 days (234 total hours at different times of the day, on all days of the week, and in all seasons) [35]. A regression model was built and validated that included spatial (e.g., distance to I-93) and temporal (e.g., wind direction) variables to predict hourly ambient PNC across the study area ($R^2 = 0.43$; cross-validated $R^2 = 0.38$ – 0.47) [34]. Orthorectified coordinates for residential addresses were used to calculate predicted ambient residential PNC for every hour of the year for each study participant [36].

Blood markers

Venous blood samples were collected, fractionated into plasma, buffy coat, and red blood cells and frozen at -80° . The stored samples were analyzed in two batches for biomarkers using immunoassay kits for IL-6 (Quantikine HS; R&D Systems, Inc., Minneapolis, MN), hs-CRP (SPQ High Sensitivity CRP Reagent Set; DiaSorin, Stillwater, MN), TNF-RII (Quantikine ELISA; R&D Systems, Inc.), and fibrinogen (κ -Assay; Kamiya Biomedical, Seattle, WA). Finger-stick blood samples were analyzed for lipid profile (total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides) using a CardioChek PA device (PTS Diagnostics, Inc., Indianapolis, IN). Height was measured using a stadiometer (Model 905055, Shorr Productions LLC, Olney, MD), and weight was measured using a standard scale (Model 8761321009, SECA, Chino, CA) for the calculation of body mass index (BMI).

Analysis

We examined the relationship of the three metrics of ambient PNC with blood biomarkers using linear mixed effects models with a random intercept for each participant. We evaluated a series of exposure metrics including lags of 0, 1, and 2 days and moving averages (MAs) of 3, 7, 14, 21, and 28 days. Past studies helped inform the selection of time periods [8,30]. Because of missing data at the MAC site (approximately 15% for the study duration), all lags and the MA of 3 days were calculated only when complete data were present. MAs of 7 days or more were calculated when at least 70% of data were available. We built separate models for each exposure metric and each biomarker, including potential confounders. Age was included in all models as well as time between measurements and the harmonic mean of day of year (to adjust for seasonal variation). We evaluated the following covariates for inclusion in models: sex, race, Hispanic ethnicity, education, income, BMI, smoking, work status; health conditions including asthma, congestive heart failure, myocardial infarction, hypercholesterolemia, arthritis; medications for the control of cholesterol (statins), diabetes, hypertension, inflammation; day of week, weekday, and ambient temperature. Covariates were included based on their strength of association with the outcome and impact on effect estimates of 10% or more. The distributions for IL-6, hs-CRP, and TNF-RII were right skewed so we log transformed them for regression analyses.

Models of hs-CRP were run excluding measurements above 10 mg/L, which may be indicative of acute infection [37].

Because of missing data at the MAC site, we also conducted a complete case analysis across all exposure metrics as a sensitivity analysis. We evaluated effect modification using interaction terms and stratification for variables suggested in the literature or identified in the larger CAFEH study including BMI, age, work status, income, education, diabetes, hypertension medications, statin medications, and type of sample (random or convenience). Statistical analyses were performed in R, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria), using the nlme package.

Results

Characteristics of the study participants from both random and convenience samples are summarized in Table 1. A total of 145 participants attended the clinic at least once. After removal of ineligible participants, valid blood samples were obtained one or more times from 142 individuals, for a total of 250 separate samples. Thirty-six participants provided one blood sample, 104 provided two blood samples, and two provided three blood samples. Only samples taken on or after November 14, 2009 were included in the analysis to coincide with PNC measurements. The mean age of participants was 58.6 (SD: 11.8), 70% were female and 78% self-identified as white. Over half (55%) did not work outside the home and very few of workers did so near highways or busy roadways [38]. About a quarter of participants took statins to control high cholesterol (27%), as well as other medications to control hypertension (21%), diabetes (15%), and inflammation (24%). There were differences between random and convenience sample participants for some demographic variables including age and race, with the convenience sample tending to be older, more often retired, and more often white than the participants in the random sample. Because of the limited sample size, we analyzed the groups together for main analyses. (A subsequent stratified analysis did not show any difference in effect estimates between groups [data not shown].) Descriptive statistics for PNC concentrations and meteorological variables are listed in Table 2. Median PNC concentration was 14,135 (interquartile range [IQR]: 7314–19,964) at the SPH, 10,936 (IQR: 7318–15,641) at the MAC, and 22,065 (IQR: 16,229–31,085) for predicted concentrations.

Summary statistics for markers of inflammation and coagulation are listed in Table 3. Samples from four participants were above the laboratory-defined upper limit of detection for IL-6 and were set to 50 pg/mL for analysis, the maximum level detectable. Spearman correlations between pairs of biomarkers were strongest between hs-CRP and IL-6 ($r = 0.61$) and for hs-CRP with fibrinogen ($r = 0.58$), and were below 0.5 between pairs of the other biomarkers. Levels on average were high, for example the mean hs-CRP level was consistent with high risk for future myocardial infarction or stroke [39].

Results of multivariate mixed effects models for each exposure metric and outcomes are summarized in Table 4. Model residuals were independent and centered around zero. For PNC measured at the SPH the estimated percent changes generally increased for IL-6, hs-CRP, and fibrinogen with longer lags and MAs (Fig. 2). The greatest effect estimates were a

91.5% (95% confidence interval [CI]: 9.4%, 235%) increase in IL-6, a 74% (95% CI: -6.6%, 223.0%) increase in hs-CRP, and a 58.7 pg/mL (95% CI: -12.8%, 130.2%) increase in fibrinogen with each 5000 unit increase in the 28-day MA of PNC. However, CIs widened with increasing lags and MAs and included zero for most estimates. There were statistically significant associations for a 28-day MA with IL-6, a 2-day lag with fibrinogen, and 7-day and 14-day MA with TNF-RII. Analyses using PNC concentrations at the MAC did not identify strong trends in effect estimates with the biomarkers. There was, however, a statistically significant 12.3% (95% CI: -17.8%, -6.4%) decrease in hs-CRP for a 5000 unit increase in current day PNC concentration measured at the MAC. No other associations or trends were identified using predicted PNC for any of the biomarkers. The complete case analysis showed similar estimates as the main results (results not shown).

We examined effect modification for the 28-day MA. PNC measured at the SPH was associated with a significantly higher IL-6 level (143%, 95% CI: 23.0–380.1) for participants not taking statins compared with a nonsignificant lower IL-6 level (15.5%, 95% CI: 64.0, 99.0) for those taking this medication. We did not observe any other effect modification.

Discussion

To our knowledge, we are one of the first to test relationships of acute changes of near-highway, central site, and predicted residential PNC with biomarkers. PNC measured at a central site was associated with IL-6, TNF-RII, and fibrinogen for our predominantly near-highway population. Effect estimates generally increased with longer averaging times for IL-6, hs-CRP, and fibrinogen, and CIs were highly skewed, although most associations did not reach statistical significance. However, neither PNC measured at the near-highway site nor predicted residential concentrations showed associations with any of the biomarkers.

Results using the central monitor at SPH showed similar trends as prior studies that also used central site measurements to estimate the effect of PNC on markers of inflammation [25,26]. Ruckerl et al. [25] reported an association between 2-day lag PNC and increases in hs-CRP above the 90th percentile in coronary heart disease patients. Zeka et al. [26] noted that 2-day and 7-day average PNC exposure was associated with a 4% increase and 2% increase in fibrinogen, respectively. Hertel et al. [8] showed significant associations between modeled PNC and hs-CRP that increased with longer MAs up to 28 days. The highest increase was 7.1% (95% CI: 1.85, 12.62), which was associated with an IQR increase in 21-day MA (~4500 particles/cm³ change). Delfino et al. [6,30] identified positive associations between particle number and quasi-UFP (PM_{0.25}) measured at the residence ranging from lag 0 to 9 days with CRP, IL-6, and TNF-RII.

Although we observed elevated effect estimates in biomarkers of inflammation and coagulation with higher PNC concentration, CIs were wide, and we take a cautious approach with our interpretation. Short-term effects may be smaller than long-term effects, and therefore, statistical significance of associations between PNC measurements and biomarkers may be more difficult owing to our limited sample size. It is also possible that the true association may be obscured by effect modification, however, we tested many

possible effect modifiers with one notable effect. We observed a differential response of IL-6 for those participants that did not take statins, a finding also noted in previous studies [8,40,41].

We did not find associations between near-highway or predicted PNC with any of the biomarkers. Although hourly values were moderately well correlated between the central and near-highway monitors ($r = 0.50$), they may reflect PNC of differing composition (secondary vs. primary) that in turn have differing effects on inflammatory markers [42–44]. The PNC regression model was developed via a dense mobile monitoring effort that encompassed all the participants residing in the study area, and should therefore be representative of the range of ambient PNC measured within the study area. The cross-validated R^2 values obtained for the CAFEH Somerville model (0.38–0.47) were similar to those for other models with spatial and temporal constraints (0.23–0.51) [34,45–47]. It is also possible that the true causal factor is not PNC and that that factor is correlated better with the central site than the near-highway site or predicted concentrations. There may be more temporal variability in PNC in near-roadway environments evidenced by the lack of distinct seasonal variation at the near-highway site, compared with the central site [29,48]. The use of different measurement instruments may be a source of error, however, colocation monitoring showed high correlations between instruments ($r \sim 0.95$), albeit with 20% lower readings for the instrument used at the MAC [29]. It is also possible, in the case of the near-highway site, that missing data may decrease the ability to detect associations. However, a complete case analysis was conducted that showed similar estimates as the main results presented. Indoor-generated PNC was not considered in this analysis, however, comparisons of a subset of residences in this analysis indicated similar levels indoors and outdoors [49].

Conclusion

Our finding that central site PNC data were associated with blood markers of inflammation whereas similar data from a near-highway site near the residences and predicted residential values based on mobile monitoring were not associated is not easy to explain. But it does not appear to be due to error in the near-highway data to the extent we could assess that possibility or significant error in the residential model. There is a need for additional studies with larger sample sizes to test the reproducibility of these findings in other populations and study areas.

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Fig. 1.
Study area showing monitoring sites and participant residences.

Fig. 2.

Relationships of biomarkers with central site (SPH) ambient particle number concentration. Expected change in the biomarker is expressed as percent change (coefficient and 95% CI) per 5000 particles/cm³ change in exposure for IL-6, hs-CRP, and TNF-RII and absolute change (coefficient and 95% CI) per 5000 particles/cm³ change in exposure for fibrinogen.

Table 1Characteristics of study participants ($N = 142$)

Characteristic, No. (%) (except where indicated)	All participants ($N = 142$)	Random sample ($n = 86$)	Convenience sample ($n = 56$)
Age (y) (Mean $\pm$ SD)	58.6 $\pm$ 11.8	55.5 $\pm$ 11.5	63.5 $\pm$ 10.7
Sex			
Female	99 (70)	59 (68)	40 (73)
Male	43 (30)	28 (32)	15 (27)
Race or ethnicity			
White	111 (78)	62 (71)	49 (87)
Non-white	29 (20)	25 (29)	7 (12)
Education			
Less than High School	29 (20)	13 (15)	16 (21)
Completed High School	59 (42)	32 (38)	27 (48)
Completed Jr. College or college	53 (38)	40 (47)	13 (23)
Employment			
Work full- or part-time	63 (45)	50 (59)	13 (23)
Retired, disabled, or unemployed	76 (55)	34 (40)	42 (76)
Residence time (y) (Mean $\pm$ SD)	17.5 $\pm$ 17.2	19.1 $\pm$ 18.0	14.1 $\pm$ 15.0
Smoking			
Current	31 (23)	15 (18)	16 (29)
Past	56 (41)	31 (38)	25 (45)
Never	50 (36)	36 (44)	14 (25)
Secondhand smoke	26 (19)	15 (17)	11 (20)
BMI (kg/m ²) (Mean $\pm$ SD)	29.4 $\pm$ 7.0	29.0 $\pm$ 7.2	30.0 $\pm$ 6.6
Medications			
Statins	38 (27)	20 (23)	18 (32)
Antihypertensives	30 (21)	17 (19)	13 (23)
Diabetes	22 (15)	9 (10)	13 (23)
Anti-inflammatories	35 (24)	19 (22)	16 (28)

Table 2

Descriptive statistics of PNC for monitored and predicted data from November 14, 2009 through September 25, 2010

Measurement	No. of days (%), <i>n</i> = 390	Mean $\pm$ SD	Min	25th percentile	Median	75th percentile	Max
Daily average PNC concentration							
SPH	315 (100%)	14,163 $\pm$ 7243	3201	7314	14,135	19,964	31,978
MAC	275 (87%)	15,544 $\pm$ 11,525	654	7318	10,936	15,641	166,610
RHA *	315 (100%)	24,075 $\pm$ 9748	8231	16,229	22,065	31,085	57,840

max = maximum; min = minimum; RHA = residential hourly-averaged concentrations.

* 24-hour average measurement across all participants.

Table 3Summary statistics for biomarkers ($N = 250$ measurements from 142 participants)

Biomarker	Mean $\pm$ SD	Min	25th percentile	Median	75th percentile	Max
IL-6 (pg/mL) *	3.68 $\pm$ 7.91	0.33	0.95	1.63	3.24	50.00
hs-CRP (mg/L)	4.19 $\pm$ 8.44	0.08	0.79	1.76	3.81	74.29
TNF-RII (pg/mL)	3013 $\pm$ 1499	1222	2144	2630	3317	10,360
Fibrinogen (mg/dL)	395.7 $\pm$ 86.5	171.8	332.5	383.5	436.0	689.6

max = maximum; min = minimum.

* Values above the maximum limit of the method were set to the maximum value (50 pg/mL).

Table 4

Adjusted mean percent changes (and 95% CIs) in blood biomarker levels for a 5000 particles/cm³ increase in PNC at the central (SPH) site, near-highway (MAC) site, and RHA based on current, lagged, and MA exposure metrics

PNC exposure metric	IL-6*	hs-CRP[†]	TNF-R1P[‡]	Fibrinogen[§]
	Estimated percent change (95% CI)	Estimated percent change (95% CI)	Estimated percent change (95% CI)	Absolute change (95% CI)
SPH				
Current	-3.5 (-12.7, 6.6)	-11.2 (-20.1, 1.3)	-0.9 (-4.5, 2.8)	-10.0 (-20.2, 0.2)
1-day lag	-1.7 (-14.5, 13.1)	-12.4 (-24.8, 2.0)	1.9 (-3.5, 7.7)	-0.5 (-16.3, 15.2)
2-day lag	9.3 (-3.6, 23.8)	13.3 (-1.3, 30.2)	0.4 (-4.0, 5.0)	15.3 (1.8, 28.9)
3-day MA	14.8 (-5.0, 38.8)	-3.7 (-22.0, 18.9)	3.8 (-4.0, 12.2)	13.6 (-8.7, 35.9)
7-day MA	5.6 (-18.9, 37.7)	8.4 (-18.7, 44.7)	15.9 (5.9, 27.0)	22.5 (-6.0, 50.9)
14-day MA	30.8 (-5.1, 80.4)	19.0 (-15.9, 68.2)	13.2 (0.3, 27.7)	25.4 (-12.9, 63.6)
21-day MA	41.9 (-3.5, 108.7)	40.8 (-8.3, 116.1)	12.4 (-5.2, 33.2)	34.0 (-15.4, 83.5)
28-day MA	91.5 (9.4, 235.0)	73.7 (-6.6, 223.0)	8.6 (-15.7, 39.8)	58.7 (-12.8, 130.2)
MAC				
Current	-5.1 (-10.1, 1.1)	-12.3 (-17.8, -6.4)	-0.7 (-3.0, 1.6)	-2.3 (-8.2, 3.7)
1-day lag	0.6 (-7.1, 9.0)	-6.8 (-14.1, 1.1)	1.1 (-1.9, 4.1)	-2.5 (-10.3, 5.3)
2-day lag	1.7 (-6.4, 10.4)	-3.5 (-11.5, 5.3)	1.2 (-2.0, 4.5)	7.1 (-1.4, 15.6)
3-day MA	5.0 (-5.8, 17.1)	-3.0 (-12.6, 7.8)	1.6 (-2.8, 6.3)	0.8 (-10.8, 12.3)
7-day MA	-1.4 (-14.1, 13.2)	-4.5 (-16.7, 9.4)	3.9 (-0.6, 8.5)	8.9 (-3.6, 21.4)
14-day MA	2.6 (-13.2, 21.3)	-7.2 (-22.8, 11.6)	2.1 (-4.2, 8.8)	5.2 (-12.7, 23.1)
21-day MA	-0.8 (-23.6, 28.7)	-8.5 (-31.9, 23.0)	0.7 (-10.0, 12.7)	3.5 (-28.3, 35.3)
28-day MA	-3.2 (-28.8, 31.5)	14.7 (-15.6, 55.8)	11.3 (-2.8, 27.5)	16.4 (-18.6, 51.4)
RHA				
Current	-2.8 (-7.6, 2.2)	-3.2 (-8.4, 2.2)	-0.1 (-1.8, 1.7)	-3.4 (-8.9, 2.0)
1-day lag	0.2 (-4.9, 5.6)	-4.0 (-9.5, 1.8)	-0.2 (-1.9, 1.7)	-3.5 (-8.9, 1.8)
2-day lag	1.2 (-3.7, 6.4)	-0.9 (-6.3, 4.8)	0.5 (-1.3, 2.4)	1.7 (-3.7, 7.2)
3-day MA	-0.6 (-7.1, 6.3)	-3.2 (-10.3, 4.4)	0.7 (-1.8, 3.4)	1.8 (-5.4, 9.0)
7-day MA	-7.7 (-15.1, 0.3)	-5.8 (-14.2, 3.5)	-0.5 (-3.6, 2.7)	2.1 (-7.3, 11.5)
14-day MA	-7.0 (-18.1, 6.4)	-2.3 (-16.1, 13.9)	1.1 (-3.8, 6.3)	3.8 (-10.4, 17.9)
21-day MA	-2.7 (-16.8, 13.8)	6.2 (-11.1, 27.0)	1.4 (-4.7, 7.9)	7.7 (-8.6, 22.0)
28-day MA	-4.8 (-19.9, 13.2)	6.4 (-12.4, 29.2)	2.2 (-4.7, 9.6)	4.2 (-13.7, 22.2)

RHA = residential hourly -averaged concentrations.

Bold values are significant at the 5% level of significance (alpha<0.05).

* Adjusted for age, education, body mass index, smoking, hypertensive medications, income, and weekday.

[†] Adjusted for age, body mass index, employment, income, and weekday.

[‡] Adjusted for age, race, education, body mass index, congestive heart failure, employment, and ambient temperature.

[§] Adjusted for age, education, body mass index, smoking, congestive heart failure, weekday, and ambient temperature.