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Association of modeled long-term personal exposure to ultrafine particles with inflammatory and coagulation biomarkers

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ABSTRACT

Background: Long-term exposure to fine particulate matter has been linked to cardiovascular disease and systemic inflammatory responses; however, evidence is limited regarding the effects of long-term exposure to ultrafine particulate matter (UFP, <100 nm). We used a cross-sectional study design to examine the association of long-term exposure to near-highway UFP with measures of systemic inflammation and coagulation.
Methods: We analyzed blood samples from 408 individuals aged 40–91 years living in three near-highway and three urban background areas in and near Boston, Massachusetts. We conducted mobile monitoring of particle number concentration (PNC) in each area, and used the data to develop and validate highly resolved spatiotemporal (hourly, 20 m) PNC regression models. These models were linked with participant time-activity data to determine individual time-activity adjusted (TAA) annual average PNC exposures. Multivariable regression modeling and stratification were used to assess the association between TAA-PNC and single peripheral blood measures of high-sensitivity *C*-reactive protein (hsCRP), interleukin-6 (IL-6), tumor-necrosis factor alpha receptor II (TNFRII) and fibrinogen.
Results: After adjusting for age, sex, education, body mass index, smoking and race/ethnicity, an interquartile-range (10,000 particles/cm^3) increase in TAA-PNC had a positive non-significant association with a 14.0% (95% CI: −4.6%, 36.2%) positive difference in hsCRP, an 8.9% (95% CI: −0.4%, 10.9%) positive difference in IL-6, and a 5.1% (95% CI: −0.4%, 10.9%) positive difference in TNFRII. Stratification by race/ethnicity revealed that TAA-PNC had larger effect estimates for all three inflammatory markers and was significantly associated with hsCRP and TNFRII in white non-Hispanic, but not East Asian participants. Fibrinogen had a negative non-significant association with TAA-PNC.
Conclusions: Our findings suggest an association between annual average near-highway TAA-PNC and subclinical inflammatory markers of CVD risk.

1. Introduction

Studies have shown associations of proximity to traffic with excess cardiovascular disease (CVD) risk and increases in biomarkers of systemic inflammation such as high sensitivity *C*-reactive protein (hsCRP) and interleukin-6 (IL-6) (Brugge et al., 2007; Hoffmann et al., 2009; Williams et al., 2009; Lanki et al., 2015; Brugge et al., 2013). Proximity may be a surrogate for exposure to traffic-related air pollutants (TRAPs) such as nitrogen oxides (NOx), nitrogen dioxide, black carbon, particulate matter <10 μm (PM$_{10}$), and ultrafine particles (UFP, <100 nm). Concentrations of these pollutants have been shown to be substantially elevated next to major roadways and highways (Karner et al., 2010; Padró-Martínez et al., 2012; Patton et al., 2014a).

Previous studies have associated UFP exposure with systemic inflammation and increased CVD risk. Animal studies show that UFP can promote inflammatory responses in the lungs as well as translocate to the circulatory system. This can lead to increases in atherosclerotic lesions, upregulation of genes for anti-oxidant responses to oxidative stress, and decreases in anti-inflammatory high density lipoprotein (Araujo et al., 2008; Araujo and Nel, 2009). Controlled human exposure

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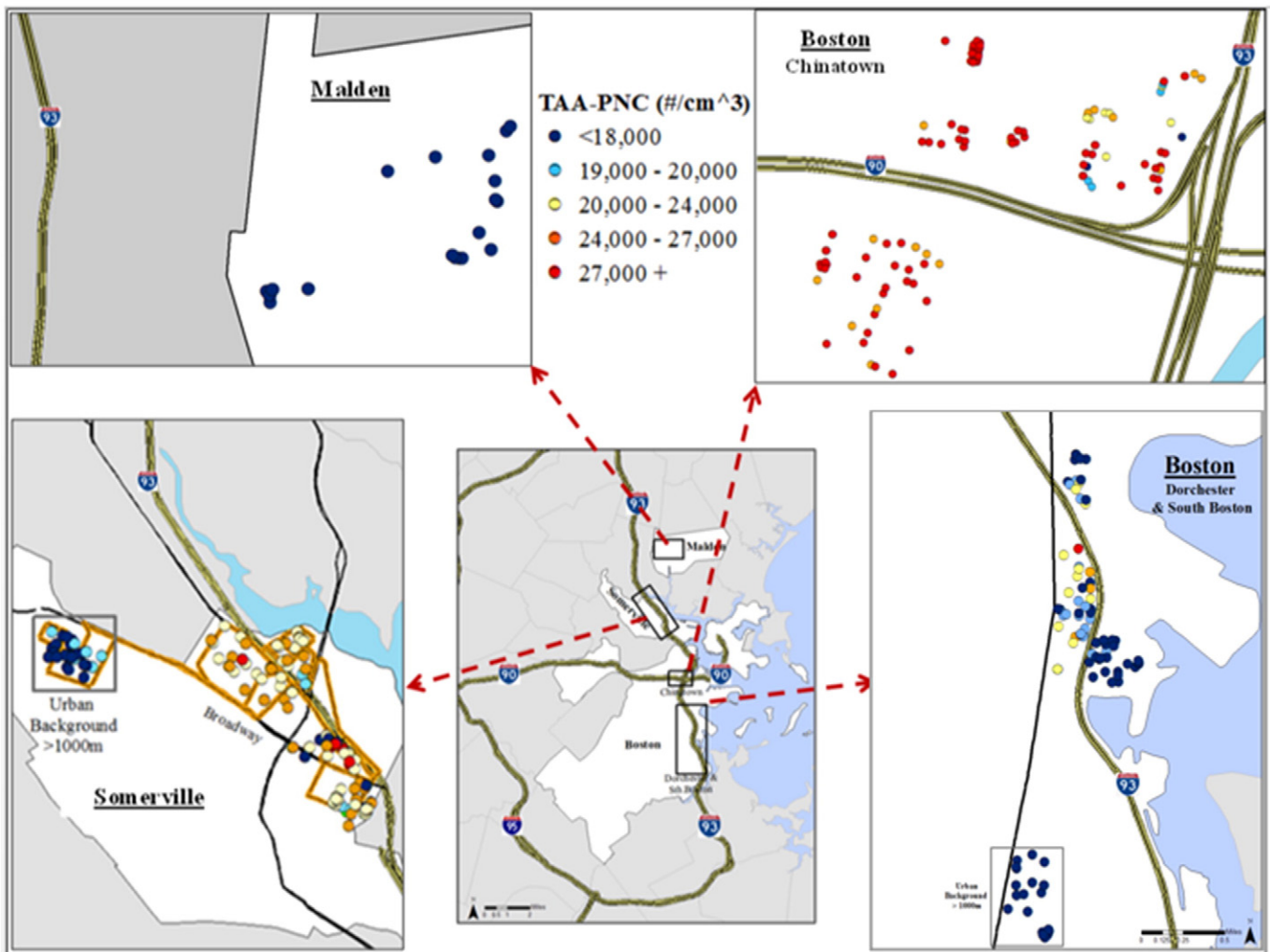E-mail address: kevin.lane@yale.edu (K.J. Lane).

Fig. 1. Time-activity adjusted annual average particle number concentration (TAA-PNC) by study area.

studies of UFP found associations with inflammatory and coagulation responses in the lungs as well as in peripheral blood (Devlin et al., 2014; Nemmar et al., 2002; Samet et al., 2009). Panel studies on short-term effects of particle number concentration (PNC) have reported increases in CRP, IL-6, tumor-necrosis factor alpha receptor II (TNFRII) and markers of coagulation such as D-dimer and von Willebrand Factor (vWF) with same day UFP exposure and up to three-week lags (Delfino et al., 2008; Hertel et al., 2010; Fuller et al., 2015). One study reported significant associations with hsCRP and a suggestive association with fibrinogen (Ruckerl et al., 2014).

The few studies on the cardiovascular effects of long-term exposure (e.g., ≥ 1 year) to individual TRAPs have produced inconsistent results (Gan et al., 2011; Gan et al., 2014). In particular, until recently, there had been little evidence for effects of long-term UFP exposure on cardiovascular health, in part due to exposure modeling constraints. A study of the California Teachers Study Cohort (Ostro et al., 2015) found a significant association of long-term exposure to UFP mass and constituents with all-cause, CVD, and ischemic heart disease mortality. Exposure was estimated with a chemical transport model at 4 × 4 km resolution. A study using another chemical transport model to examine multiple PM sizes at 1 × 1 km resolution (Viehmann et al., 2015) found that long-term exposure to UFP was significantly associated with hsCRP and fibrinogen in crude models, and positively but insignificantly associated in adjusted models. While both studies

found associations with long-term UFP, they utilized PNC models that could not capture within neighborhood (<1 × 1 km) near roadway PNC variability.

To our knowledge, there are no published studies that used intensive local monitoring of PNC to build highly spatiotemporally-resolved UFP models (20 m, hourly) and combined them with individual time-activity patterns in an epidemiological study. Assigning area ambient annual average at the residence introduces exposure misclassification for pollutants such as UFP that have high spatial and temporal variability (Buonanno et al., 2014; Gu et al., 2015; Lane et al., 2015). Given the substantial spatial and temporal variability of near roadway UFP concentrations in urban areas, highly resolved UFP exposure assessment should improve long-term epidemiological studies (HEI, 2013; Sioutas et al., 2005).

Our objectives were to develop individualized annual UFP exposure estimates and to evaluate associations with hsCRP, IL-6, TNFRII, and fibrinogen. These analyses were performed within the Community Assessment of Freeway Exposure and Health (CAFEH) study, a hypothesis driven cross-sectional, community based participatory research (CBPR) study evaluating cardiovascular health risks from exposure to UFP in near-roadway populations. We report here the association of annual average exposure to high resolution time activity adjusted (TAA) PNC with hsCRP, IL-6, TNFRII, and fibrinogen for study participants living in neighborhoods in the Boston area (Massachusetts, USA).

2. Material and methods

2.1. CAFEH study population

Participant recruitment was performed concurrently with air pollution monitoring in near-highway (≤500 m from Interstate Highways 90 and 93) and urban background areas (≥1000 m from Interstate Highways) including Somerville, Malden, and the Boston neighborhoods of Dorchester, South Boston, and Chinatown (Fig. 1). Individuals 40 + years of age completed an informed consent after being recruited in each neighborhood using a geographically-weighted, random-selection process, supplemented by a convenience sample of participants from senior housing developments in Dorchester and Somerville. The analysis reported here is of those participants who had a viable peripheral blood sample on all biomarkers and complete survey data ($n = 408$), of whom 327 were from the random sample and 81 were from the convenience sample. Details on study recruitment, questionnaire, clinics, blood storage and inflammatory assays have been previously published (Fuller et al., 2014). Here we present a brief summary, with more detail provided in Supplemental Text 1.

Recruitment was conducted in Somerville (near highway = 101 participants; urban background = 25 participants) from July 2009 to May 2010, in Dorchester (near highway = 75 participants; urban background = 21 participants) and South Boston (near highway = 15 participants) from September 2010 to April 2011, and in Chinatown (near highway = 133 participants) and its paired urban background neighborhood, Malden (40 participants), from June 2011 to February 2012. Recruitment of participants from high-rise buildings (only present in Chinatown) was restricted to residents who lived on one of the first four floors since we found no significant vertical differences in PNC up to 35 m (Wu et al., 2014).

Participants completed an in-home survey that included questions about demographics (e.g., age, sex, education, income, race/ethnicity, and employment status), recent illnesses, major cardiovascular diseases, hypertension, use of statins, insulin, or oral hypoglycemics, smoking status, and micro-environment time-activity. Peripheral blood was drawn at study clinics by registered nurses and analyzed for biomarkers using standard protocols. We measured height and weight for calculation of body mass index (BMI; in kg/m^2).

Geocoding of participant addresses was performed using a multi-stage process that included address verification by field staff during home visits. This was followed by parcel and street network geocoding accompanied by manual correction via orthophotos and apartment/multi-unit floor plans to reduce positional error (Lane et al., 2013; Brugge et al., 2013). We used ESRI ArcGIS v10.1 (ESRI, Redlands CA) software for all geographic information system (GIS) processes.

2.2. PNC monitoring, modeling and exposure assignment

Details on PNC monitoring, regression modeling and time-activity adjusted exposure assignment have been published (Padró-Martínez et al., 2012, Patton et al., 2014b; Patton et al., 2015; Lane et al., 2015). Here we present a brief summary with more detail in Supplemental Text 2. The Tufts Air Pollution Monitoring Laboratory (TAPL), a converted recreational vehicle equipped with fast-response monitoring instruments, was used to measure air pollutants. The TAPL was repeatedly driven over fixed routes in each study area during a range of hours of the day, days of the week and seasons. UFP were measured by a condensation particle counter (TSI Model 3775) as particle number concentration (PNC, 4–3000 nm). Multivariable regression modeling was used to build predictive models to estimate hourly natural log (LN) PNC at locations within the study areas. The PNC regression models utilized both spatial (side of and distance to highway, distance to nearest major road) and temporal (wind speed, wind direction, temperature, day of week, highway traffic volume and speed) variables to predict values. The models

were used to estimate ambient PNC at the residence of each participant for each hour of the year during which air monitoring was performed.

These estimates of exposure to PNC were adjusted for time-activity based on survey data to reflect the amount of time participants spent in each of the five micro-environments (details in Lane et al., 2013 and Supplemental Text 2). Time-activity questions were used to assign hourly locations for the most recent weekday and weekend for unemployed participants and for the most recent workday and non-workday for employed participants. Time was assigned by microenvironments in one-hour increments for (i) inside homes, (ii) outside homes, (iii) work/school, (iv) other non-highway locations, and (v) time on highways. Micro-environment time-activity data was found to be consistent in a subset of participants ($n = 169$) that completed a second questionnaire an average of 5.4 months after the initial questionnaire and resulted in less than an hour of mean difference in microenvironment time allocation. We assigned exposures to each participant for every hour of the air monitoring year. We also adjusted for infiltration of PNC into residences (Fuller et al., 2013).

2.3. Statistical analysis

We evaluated associations of biomarkers (hsCRP, IL-6, TNFRII, and fibrinogen) with TAA-PNC. Because three of the biomarkers (hsCRP, IL-6 and TNFRII) were not normally distributed, they were first log-transformed. Fibrinogen was normally distributed, but also examined as a percent change for association with TAA-PNC to be consistent with the other biomarkers. Generalized linear models (GLMs) were used to

Table 1
Population characteristics with viable blood samples and complete data on covariates ($n = 408$).

Characteristic	n	% or mean ± SD
Age (years, mean ± SD)	408	61 ± 13
BMI (kg/m^2, mean ± SD)	408	27.4 ± 6.8
Underweight (<18.5)	14	3%
Normal weight (18.5–24.9)	168	41%
Overweight (25–29.9)	117	29%
Obese (30 +)	109	27%
City/neighborhood		
Near highway (≤500 m)		
Somerville	100	24%
Dorchester/South Boston	90	22%
Chinatown	133	32%
Urban background (≥1000 m)		
Somerville	25	6%
Dorchester/South Boston	20	5%
Malden	40	10%
Sex		
Female	238	58%
Male	170	42%
Smoking		
Current	83	20%
Former	126	31%
Never	199	49%
Educational attainment		
<High school diploma	136	34%
High school diploma	123	30%
Undergraduate	99	24%
Graduate school	50	12%
Race/ethnicity		
White non-Hispanic	173	42%
East Asian	162	40%
Other	73	18%
Born in US		
Yes	179	44%
No	229	56%
Statin medication		
Yes	114	28%
No	294	72%
Diabetes medication		
Yes	33	9%
No	375	91%

test the association of TAA-PNC with LN hsCRP, LN IL-6, LN TNFRII (here-after referred to as hsCRP, IL-6 and TNFRII) as well as fibrinogen. We approached interpretation of statistical outcomes based on 95% confidence intervals, with effect estimates. Estimates are reported as percent change in inflammatory biomarker levels for an interquartile-range (IQR) change in TAA-PNC. Statistical analyses were performed using SAS (Statistical Analysis Software, Cary, North Carolina) version 9.1.2.

We started with univariate analysis for association between TAA-PNC and each biomarker. Regression analyses were then adjusted for age (years), sex (female, male), BMI (continuous, as kg/m²), smoking status (current, former, never), educational attainment (less than high school, high school diploma, undergraduate degree, graduate degree), race/ethnicity (detailed below) and nativity (born in the United States (US): yes, no). These variables are all known to be cardiovascular disease risk factors and/or predictors of some of our biomarkers of interest (McDade et al., 2011), including nativity (Corlin et al., 2014). For race/ethnicity, we had a large non-Hispanic white population and a large Chinese and Vietnamese population due to our recruitment in Chinatown, with more limited numbers for other racial/ethnic groups. Therefore, we grouped race/ethnicity into non-Hispanic white, East Asian (Chinese and Vietnamese), and other (African American, Haitian-Creole, white-Hispanic, Latino, Indian, Pakistani, Pacific Islander and Native American), a heterogeneous group comprised of multiple race/ethnicities each of limited sample size. Race/ethnicity and nativity were highly correlated with one another. For example, 100% of the East

Asian participants were foreign born. Accordingly, we developed regression models to examine effects of race/ethnicity and nativity separately while adjusting for the other cardiovascular risk factors. Additionally, the differences in both TAA-PNC exposure concentrations and inflammatory markers between East Asian and white non-Hispanic populations led us to conduct a stratified analysis between these two groups.

2.4. Additional analysis

Sensitivity analyses were performed to examine potential effects of additional variables and constraints on the relationship between TAA-PNC and the biomarkers. We tested BMI as a categorical term in place of the linear term as: 1) underweight (≤18.5 kg/m²) and normal weight (18.6–24.9 kg/m²), combined due to low sample size in the underweight group; 2) overweight (25–29.9 kg/m²); and 3) obese (≥30 kg/m²). We also considered a quadratic term along with the continuous linear term to account for potential U-shaped associations. We evaluated the effects of including statin medication use, diabetes medication use (insulin or oral hypoglycemic), personal income in place of education, season of blood sample, and neighborhood in our models. We also stratified by CVD risk factors age, sex, BMI, nativity, race/ethnicity, smoking status, diabetes and statin medications. Additional stratification was by random vs. convenience sample and distance from highway. Because the exposure regression model predicted LN-transformed PNC at the residence, we

Table 2
Distribution of biomarkers of systemic inflammation (high sensitivity *C*-reactive protein, (hsCRP), interleukin-6 (IL-6) and tumor necrosis factor alpha receptor II (TNFRII)) and coagulation (fibrinogen) by population characteristics.

Characteristic	hsCRP (mg/L)	IL-6 (pg/mL)	TNFRII (pg/mL)	Fibrinogen (mg/dL)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Total	1.27 (2.77)	1.28 (1.43)	2244 (1118)	448 (132)
City/neighborhood				
Near highway (<500 m)				
Somerville	2.02 (2.77)	1.74 (2.20)	2761 (1425)	470 (133)
Dorchester/South Boston	1.47 (3.91)	1.75 (1.92)	2155 (1018)	467 (124)
Chinatown	0.71 (1.63)	1.07 (0.90)	2004 (950)	425 (116)
Urban background (≥1000 m)				
Somerville	0.94 (1.02)	0.95 (0.87)	2252 (876)	410 (76)
Dorchester/South Boston	2.16 (5.40)	1.38 (1.31)	2137 (1038)	476 (287)
Malden	0.82 (1.32)	1.14 (0.78)	2315 (908)	492 (112)
Sex				
Female	1.18 (2.72)	1.22 (1.38)	2212 (1146)	456 (133)
Male	1.29 (2.73)	1.39 (1.56)	2349 (1001)	440 (131)
Age (quartiles)				
40–50 years	0.95 (2.06)	1.01 (1.10)	2100 (777)	424 (103)
51–60 years	1.58 (2.77)	1.22 (1.50)	2383 (778)	431 (137)
61–71 years	1.28 (2.79)	1.34 (1.80)	2509 (1199)	473 (120)
72–91 years	1.34 (2.83)	1.52 (1.71)	2762 (1334)	480 (147)
Smoking				
Current	1.40 (3.25)	1.44 (1.66)	2420 (1037)	460 (150)
Former	1.59 (2.78)	1.49 (2.06)	2440 (1427)	459 (140)
Never	0.91 (1.82)	1.16 (1.11)	2103 (1077)	439 (124)
Body mass index (kg/m²)				
Under & normal weight (≤24.9)	0.66 (1.44)	1.01 (0.79)	2006 (846)	425 (114)
Overweight (25–29.9)	1.45 (2.26)	1.47 (1.47)	2462 (1012)	443 (116)
Obese (30+)	2.73 (4.71)	1.97 (2.25)	2590 (1517)	510 (179)
Race/ethnicity				
White non-Hispanic	1.61 (3.0)	1.63 (2.00)	2520 (1257)	454 (133)
East Asian	0.72 (1.53)	1.07 (0.80)	2042 (943)	435 (132)
Other	2.04 (4.06)	1.56 (1.39)	2183 (978)	473 (133)
Born in US				
Yes	1.81 (3.16)	1.69 (2.17)	2473 (1271)	467 (137)
No	0.82 (1.73)	1.14 (1.04)	2102 (1024)	439 (123)
Statin medication				
Yes	2.48 (5.51)	2.01 (2.41)	2775 (1634)	544 (151)
No	1.11 (2.10)	1.89 (1.24)	2176 (1005)	457 (124)
Diabetes medication				
Yes	2.06 (4.02)	1.75 (1.68)	2553 (1895)	506 (152)
No	1.27 (2.71)	1.31 (1.38)	2589 (1097)	447 (129)

Table 3
Distribution of time-activity adjusted annual average particle number concentration (TAA-PNC) by distance to highway groups and demographic variables.

Characteristic	TAA-PNC (10^4 particles/cm^3)[a]		
	Median	IQR	Min–max
Total	2.3	1.0	0.9–3.5
City/neighborhood			
Near highway (≤500 m)			
Somerville	2.4	0.3	2.0–3.1
Dorchester/South Boston	1.8	0.4	1.1–2.8
Chinatown	2.8	0.4	1.7–3.5
Urban background (≥1000 m)			
Somerville	1.8	0.2	1.6–2.0
Dorchester/South Boston	1.3	0.3	1.0–1.6
Malden	1.0	0.1	0.9–1.2
Sex			
Female	2.3	0.9	0.9–3.4
Male	2.2	1.1	0.9–3.5
Age (quartiles)			
40–50 years	2.2	0.9	0.9–3.3
51–60 years	2.3	0.8	1.0–3.3
61–71 years	2.2	1.2	0.9–3.4
72–91 years	2.6	1.0	0.9–3.5
Smoking			
Current	2.4	1.1	0.9–3.5
Former	2.2	0.8	0.9–3.2
Never	2.1	0.8	0.9–3.1
Body mass index (kg/m^2)			
Under & normal weight (≤24.9)	2.4	1.0	0.9–3.5
Overweight (25–29.9)	2.4	0.9	0.9–3.4
Obese (30+)	2.1	0.9	0.9–3.0
Education			
Less than high school diploma	2.6	0.7	0.9–3.5
High school diploma	2.4	0.9	0.9–3.4
Undergraduate	2.0	1.0	0.9–3.1
Graduate school	1.8	0.7	0.9–3.0
Race/ethnicity			
White non-Hispanic	2.0	0.7	0.9–3.1
East Asian	2.8	0.7	0.9–3.5
Other	2.2	0.7	1.0–3.1
Born in US			
Yes	2.0	0.8	0.9–3.1
No	2.6	0.8	0.9–3.5

[a] Significant figures for PNC are to the 0.1×10^4.

also evaluated associations for residential ambient annual average (RAA) PNC and LN-transformed TAA-PNC with the biomarkers.

To examine the shape of the exposure-response functions, we produced generalized additive models (GAMs) in R version 3.1 with locally-weighted scatterplot smoothing (LOESS) (R, Vienna, Austria; Trevor, 2013). Separate GAMs were produced with adjustment for CVD risk factors and for those factors plus race/ethnicity.

3. Results

The majority of the study population was female, above the age of 60 years, overweight or obese, current or former smokers, and born outside of the US (Table 1). Non-Hispanic white and East Asian participants constituted 42% and 40% of the population, respectively.

East Asians were concentrated in the Chinatown and Malden study areas.

3.1. Biomarker concentrations by population characteristics

Differences in median blood biomarker concentrations by population characteristics are shown in Table 2. All four biomarkers were higher for participants who were older, a current or former smoker, born in the US, or using statin or diabetes medications. Biomarker levels were also higher in participants who were obese (25–29.9 kg/m^2) and overweight (25–29.9 kg/m^2). East Asian participants had lower median levels of all biomarkers than white non-Hispanics and the other race/ethnicity category. Sex was associated with a minor difference for IL-6, but not for any other biomarker.

3.2. TAA-PNC by population characteristics

There were differences in annual average TAA-PNC exposure by study area (Table 3 and Fig. 1). Chinatown participants had the highest median (28,000 particles/cm^3) and maximum (35,000 particles/cm^3) annual average exposures, while Malden had the lowest median (10,000 particles/cm^3) and minimum (9000 particles/cm^3) annual average exposures. Somerville participants experienced an exposure gradient based on proximity to Interstate-93 (median near highway annual average = 24.000 particles/cm^3; median urban background annual average = 18.000 particles/cm^3). Dorchester and South Boston participants had the lowest median near highway annual average TAA-PNC (18,000 particles/cm^3) out of the three near-highway neighborhoods, with an urban background median annual average of 13,000 particles/cm^3. Annual average TAA-PNC was higher among participants identifying as East Asian or born outside the US compared to those identifying as white non-Hispanics or born in the US. This is consistent with the preponderance of the East Asian population residing in Chinatown. Nevertheless, the range of TAA-PNC exposures for East Asians overlapped substantially with exposures for the rest of the study population. Additionally, median annual average TAA-PNC decreased with increasing educational attainment and was lowest among obese individuals (Table 3).

3.3. Association of TAA-PNC and biomarkers

In univariate analysis of the full population, there was almost no association between TAA-PNC and the inflammatory markers (Table 4). Bivariate analysis showed that adjusting for BMI, race/ethnicity, nativity and smoking status changed the effect estimate between TAA-PNC and all the biomarkers by >10%. Sex had a small effect on the relationship between TAA-PNC and IL-6, but not the other biomarkers. The descriptive statistics for biomarkers and TAA-PNC for racial and ethnic subpopulations (Tables 2 and 3) are consistent with the possibility of negative confounding, with unadjusted associations resulting in essentially null associations (Table 4). Consistent with negative confounding given patterns in Table 3, multivariable adjustment for age, sex, BMI, smoking status and education led to positive associations of TAA-PNC with

Table 4
Comparison of regression models for association between an interquartile-range change in time-activity adjusted annual average particle number concentration (IQR = 10.000 particles/cm^3) and biomarkers of systemic inflammation (hsCRP, IL-6 and TNFRII) and coagulation (fibrinogen).

Model	hsCRP	IL-6	TNFRII	Fibrinogen
	% change (95% CI)	% change (95% CI)	% change (95% CI)	% change (95% CI)
Unadjusted	−8.0% (−23.3%, 11.7%)	−2.1% (−12.9%, 10.2%)	−0.05% (−6.1%, 5.4%)	−3.3% (−7.0%, 0.4%)
Adjusted[a]	9.8% (−8.3%, 31.4%)	5.8% (−5.6%, 18.5%)	3.6% (−1.9%, 9.4%)	−1.9% (−5.5%, 1.6%)
Adjusted[b]	14.0% (−4.6%, 36.2%)	8.9% (−2.6%, 21.8%)	5.1% (−0.4%, 10.9%)	−1.9% (−5.5%, 1.6%)
Adjusted[c]	14.8% (−4.1%, 37.4%)	8.1% (−3.6%, 21.2%)	4.6% (−1.0%, 10.5%)	−2.1% (−5.7%, 1.5%)

[a] Adjusted for age, sex, continuous BMI, smoking status and education.
[b] Adjusted for age, sex, continuous BMI, smoking status, education and race/ethnicity.
[c] Adjusted for age, sex, continuous BMI, smoking status, education and nativity.

Table 5
Comparison of regression models for association between an interquartile-range change in time-activity adjusted annual average particle number concentration (IQR = 10.000 particles/cm^3) and biomarkers of systemic inflammation (hsCRP, IL-6 and TNFRII) and coagulation (fibrinogen) stratified into white non-Hispanic and East Asian participants.

Model	hsCRP	IL-6	TNFRII	Fibrinogen
	% change (95% CI)	% change (95% CI)	% change (95% CI)	% change (95% CI)
White non-Hispanic				
Unadjusted	36.3% (−0.9%, 73.5%)	28.7% (4.4%, 53.0%)	15.5% (7.3%, 7.8%)	2.3% (−5.6%, 10.2%)
Adjusted[a]	32.7% (3.7%, 67.2%)	22.6% (−0.2%, 45.5%)	16.8% (5.8%, 27.7%)	−0.02% (−0.7%, 0.7%)
East Asian				
Unadjusted	9.7% (−13.5%, 32.9%)	5.0% (−9.9%, 19.7%)	−0.3% (−7.9%, 1.3%)	−1.8% (−6.4%, −2.7%)
Adjusted[a]	6.1% (−18.3%, 31.0%)	2.6% (−12.2%, 17.3%)	0.1% (−1.2%, 1.4%)	−0.06% (−5.4%, 4.2%)

[a] Adjusted for age, sex, continuous BMI, smoking status and education.

hsCRP, IL-6 and TNFRII (adjustment a, Table 4). Separate adjustment by race/ethnicity (adjustment b, Table 4) and nativity (adjustment c, Table 4) increased the TAA-PNC effect estimates and strength of association for hsCRP, IL-6 and TNFRII, with the largest effect on hsCRP and IL-6. None of the associations achieved traditional thresholds for significance, but all had positive central estimates and some approached significance.

Table 5 shows results with the population stratified into white non-Hispanics and East Asians. In adjusted models, TAA-PNC was positively associated with IL-6 and significantly associated with hsCRP and TNFRII among white non-Hispanic participants. Effect estimates were similar in unadjusted and adjusted models. In adjusted models, East Asian participants had much smaller (and non-significant) associations between TAA-PNC and all three biomarkers of inflammation.

TAA-PNC was negatively associated with fibrinogen in unadjusted and adjusted analysis (Table 4). In adjusted models, stratification by race/ethnicity also resulted in little associations in non-Hispanic white participants. East Asians had a negative association that was attenuated following adjustment (Table 5).

3.4. Additional analyses

Statin and diabetes medication (insulin/oral hypoglycemic) use and season of blood draw were not significant independent predictors. Their inclusion modestly increased the effect estimates for the association between TAA-PNC and biomarkers of inflammation, but did not meaningfully change the relationships (Supplemental Table 1). BMI as a categorical term and as a quadratic term in place of linear BMI were also run in separate models and their inclusion did not meaningfully change the relationship between TAA-PNC and biomarkers. In a separate model we replaced TAA-PNC with the RAA-PNC which lowered effect estimates for hsCRP and TNFRII, but increased the effect estimate for IL-6.

Substituting personal income for educational attainment to account for socioeconomic status did not meaningfully change effect estimates of associations for biomarkers of inflammation or fibrinogen. Neighborhood was not a significant predictor for hsCRP, IL-6 or fibrinogen, but adjusting for neighborhood reduced the association between TAA-PNC and TNFRII to essentially null. Although our study was underpowered to fully explore interactions with TAA-PNC, we conducted a series of stratified analyses to further evaluate differences. In stratified analyses, associations differed by sex (IL-6, TNFRII and fibrinogen), age (hsCRP, IL-6), smoking (hsCRP, TNFRII), BMI (hsCRP, TNFRII), born in the US (IL-6, TNFRII), statin medication use (IL-6, TNFRII), and diabetes medication use (hsCRP, IL-6). Effects were generally greater in less healthy subpopulations. Log transformed TAA-PNC was examined and similar results were observed as for the non-transformed TAA-PNC (Supplemental Tables 3 and 4).

GAMs were built to examine the shape of the exposure-response curves. In unadjusted models, the curve for hsCRP was U-shaped, explaining in part the null findings in Table 3. However, adjusting for CVD risk factors and race/ethnicity in particular increased the slope at higher TAA-PNC levels, consistent with our

stratified results by race/ethnicity and reinforcing the interpretability of our fully adjusted models (Fig. 2). For IL-6 and TNFRII, adjustment for CVD risk factors and race/ethnicity also increased the exposure-response function at higher concentrations. Fibrinogen had a negative exposure-response curve in the unadjusted and adjusted GAMs.

4. Discussion

We used exposure models with high spatial-temporal resolution joined with individual time-activity patterns and found positive non-significant associations between annual average UFP exposures and multiple biomarkers of inflammation (hsCRP, IL-6 and TNFRII). We also found a negative non-significant association with fibrinogen. Stratification by race/ethnicity showed that TAA-PNC had larger effect estimates and was significantly associated with hsCRP and TNFRII in white non-Hispanic, but not East Asian participants. The association with systematic inflammatory markers is consistent with either chronic induction of pulmonary inflammation leading to a secondary systemic inflammation response or a primary systemic inflammatory response through particle translocation into the circulatory system. Both of these are expected to lead to cytokine responses and production of proteins such as hsCRP, IL-6 and TNFRII (Araujo et al., 2008; Rückerl et al., 2011; Simkhovich et al., 2008). Our findings are also consistent with studies that found associations between short-term PNC exposure and increases in hsCRP, IL-6 and TNFRII (Delfino et al., 2008; Hertel et al., 2010; Fuller et al., 2014).

Our analysis adds to the small, but growing evidence for a role of long-term exposure to UFP in adverse cardiovascular health impacts. Our significant results for non-Hispanic white populations are consistent with findings from other recent studies evaluating cardiovascular effects or inflammatory markers among predominantly non-Hispanic white populations (Ostro et al., 2015; Viehmann et al., 2015).

We saw limited evidence of a negative association with fibrinogen, although associations were essentially null, especially in adjusted models stratifying by race/ethnicity. Fibrinogen is an acute-phase protein important to the coagulation cascade, but studies of its association with TRAPs are inconclusive. Studies of short-term exposure to particulate matter have found positive associations with fibrinogen (Ghio et al., 2003; Rückerl et al., 2007), null associations (Pope et al., 2004; Samet et al., 2009), and a negative association (Seaton et al., 1999). The lack of a positive association between TAA-PNC and fibrinogen in our analysis could be due to PNC having a different mechanism of action on coagulation compared to inflammation, although the two pathways are also interconnected (Levi et al., 2004). To better understand the mechanistic effects of PNC on coagulation, future studies could include analysis of biomarkers at various stages of the coagulation pathway such as plasmin, von Willebrand factor, and D-dimer, markers that have been more consistently associated with acute TRAP exposure (Riediker et al., 2004; Yue et al., 2007).

Our study differs from previous research on long-term residential UFP health impacts in that we used a more finely resolved spatial UFP model (20 m, compared to 1–4 km) that leveraged extensive ambient
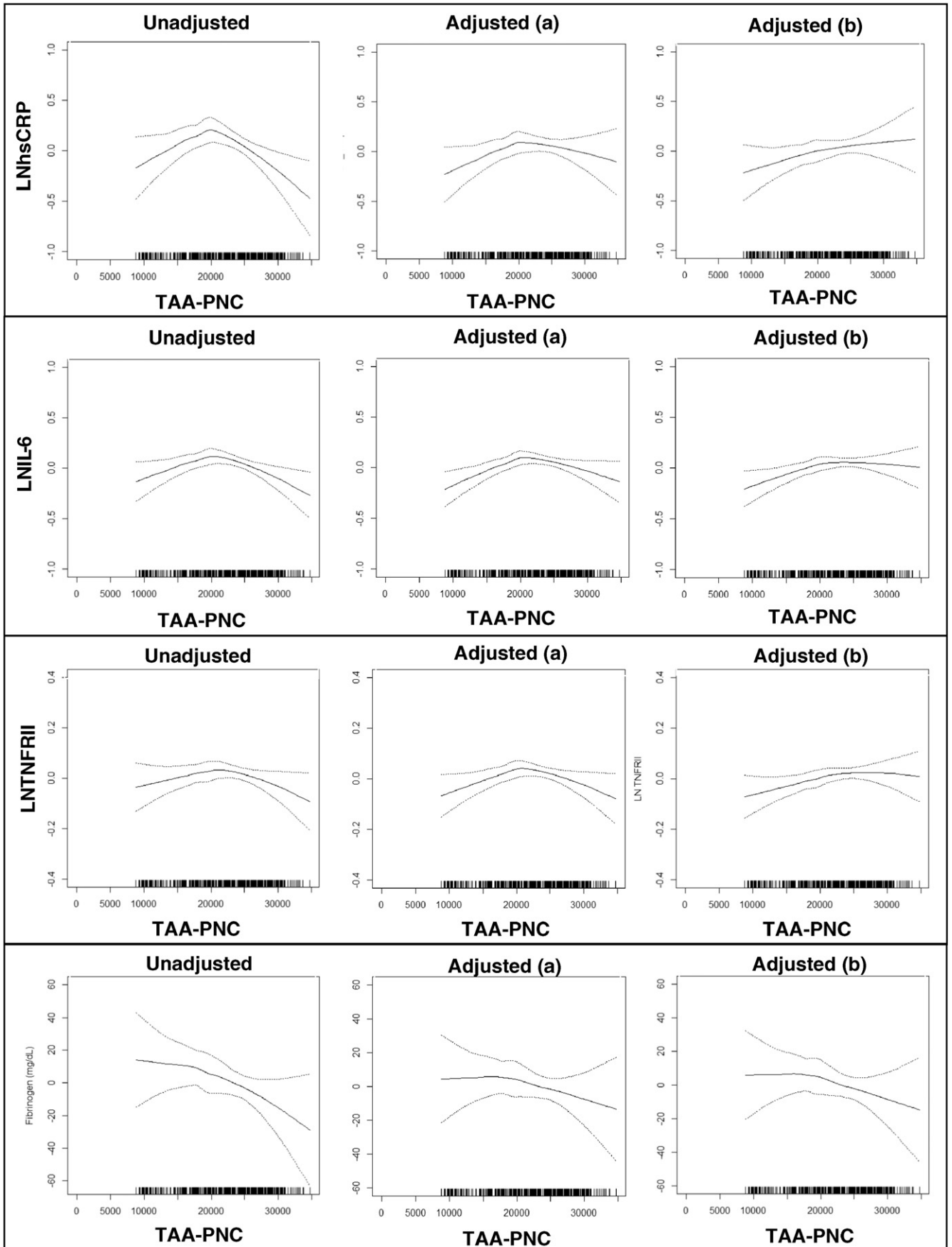
Fig. 2. Comparison of GAM with a LOESS TAA-PNC term for association with the biomarkers of systemic inflammation by additionally adjusting for race. Adjusted (a) for age, gender, BMI, smoking status and education. Adjusted (b) for age, gender, BMI, smoking status, education and race.

monitoring, combined with time-activity adjustment of exposures that may reduce exposure misclassification (Lane et al., 2015). We also had a diverse racial/ethnic study population, with a high percentage of East Asian participants (40%) who were not born in the US and who also tended to be the most highly exposed subpopulation. Interestingly, in our race/ethnicity stratified models for hsCRP, IL-6 and TNFRII (Table 5), we found white non-Hispanics had larger (and statistically significant) effect estimates compared to the East Asian participants. Previous studies have found differences in biomarkers of systemic inflammation by race/ethnicity (Corlin et al., 2014; Khera et al., 2005). Studies reported lower hsCRP concentrations in East Asian participants residing in the US compared to white participants (Albert et al., 2004; Kelley-Hedgepeth et al., 2008; Lakoski et al., 2006). Studies in Asia have also reported relatively low CRP levels (Ye et al., 2007). Similarly, in a prior analysis of the CAFEH study population, we found that East Asian participants had lower IL-6 and TNFRII as well as lower hsCRP concentrations compared to non-Hispanic white participants (Corlin et al., 2014). Studies have found that Chinese Americans have less CVD risk and lower inflammatory markers than other races/ethnicities (Palaniappan et al., 2004; Lakoski et al., 2006). A recent study found Chinese Americans had lower carotid intima-media thickness response to $PM_{2.5}$ exposures, irrespective of receiving higher exposures than white non-Hispanic and Latino race/ethnicities (Jones et al., 2015). It is possible that differences in systemic inflammatory markers by race/ethnicity lead to different response functions with ambient air pollutants. However, the mechanism remains unclear and could be related to differences in genetics, physical activity, nutrition and/or social cohesion.

We found differences in effect estimates by sex on the associations between TAA-PNC and TNFRII and fibrinogen. This agrees with previous literature of notable albeit non-uniform effect modification by sex on the relation of air pollution with inflammatory response (Clougherty, 2010). The lower association with TNFRII in women may reflect genetic differences that result in lower expression of TNFRII in female hearts compared to male hearts (Ramani et al., 2004). Differences in the relationship for fibrinogen may relate to differences in behaviors or activity patterns between men and women rather than genetic factors (Carter et al., 1997).

To help interpret our regression models, we can estimate the influence of both PNC and BMI on hsCRP in our study population. In linear multivariable models that adjusted for age, sex, BMI, smoking status and education, we found that a 10,000 particles/cm^3 change in TAA-PNC exposure was associated with a 14.0% change in hsCRP. Comparatively, a 1.8 kg/m^2 change in BMI would also be associated with a 14.0% change in hsCRP. To make this comparison more tangible, moving from exposure levels consistent with the urban background to exposure levels consistent with the near-highway neighborhood in Somerville (a change in median exposure from 18,000 to 24,000 particles/cm^3) would be associated with a change in mean hsCRP levels from 0.97 mg/L to 1.05 mg/L. In contrast, moving from a normal weight BMI of 22 kg/m^2 to an overweight BMI of 27 kg/m^2 equates to a change in mean hsCRP levels from 0.68 mg/L to 1.04 mg/L. Of note, our BMI effect estimates are slightly higher than those observed in another multi-ethnic study (Festa et al., 2001). Given that approximately 30 million Americans live within 300 m of a major roadway (US EPA, 2015), there could be significant public health implications from these small changes in hsCRP.

4.1. Strengths and limitations

Multiple aspects of the CAFEH study were strengthened by our collaborations with community partners. The initial impetus of the study originated as a request from the Somerville Transportation Equity Partnership. Community partners contributed to all aspects of the study, including overall study design, by providing expert local knowledge that helped us define study boundaries, design effective recruitment strategies, and improve geocoding by obtaining apartment floor plans through housing management. Community partners also collaborated with researchers on hiring and training of field staff, translation of documents, interpretation of results, writing of manuscripts and dissemination of findings.

The PNC regression model used here was developed from a dense mobile monitoring campaign that encompassed the residences of participants. This allowed us to model and estimate local hourly ambient PNC values. These values were subsequently adjusted for time-activity to produce individual TAA-PNC estimates, which may reduce exposure misclassification (Lane et al., 2015). TAA adjustment increased effect estimates in our analysis (Supplemental Table 4). Nevertheless, residual exposure misclassification likely remains due to the challenges in capturing all spatiotemporal contributors in a PNC regression model. Additional error may be due to inaccuracies in time-activity adjustment. However, our time activity adjustment was based on survey data that was highly reproducible (Lane et al., 2013), although it only covered five micro-environments.

CAFEH is a cross-sectional study; therefore we cannot determine the temporal nature of the exposure–response relationship or make causal inferences. In addition, our modest sample had considerable heterogeneity, especially for race/ethnicity, which complicated efforts to control for confounding. Our sample size also implies caution in interpreting the shape of the exposure-response functions in our GAMs, given substantially wider confidence intervals at the tails. Restricting the population to only random participants, however, did not substantially change our findings, increasing confidence generalizability.

PNC is correlated with other TRAPs such as road dust, other traffic-related coarse particles, particle-bound polycyclic aromatic hydrocarbons (pPAH), NOx, and CO (Johansson et al., 2007; Patton et al., 2014b), as well as traffic-related noise (Can et al., 2015). Exposures to these pollutants might confound or interact with PNC and each other (Karner et al., 2010; US EPA, 2015) and could explain portions of our observed associations. However, the mechanism by which gaseous pollutants like NOx influence cardiovascular health is less clear than for PNC. Further, $PM_{2.5}$ was shown to have little spatial variability throughout our study areas (Patton et al., 2014b).

5. Conclusions

We identified positive but non-significant associations of long-term TAA-PNC exposure with hsCRP, IL-6 and TNFRII, but not with fibrinogen, after adjusting for traditional CVD risk factors, including BMI and smoking status. Stratification by race/ethnicity resulted in stronger associations between TAA-PNC and biomarkers of inflammation among white non-Hispanic compared to East Asian participants. Adjustment by race/ethnicity also produced more interpretable exposure-response functions. Our findings reinforce the importance of studying near-highway PNC exposures and of examining differences in exposure patterns and associations among racial/ethnic sub-populations. Longitudinal cohort studies and multipollutant models will be needed to strengthen causal interpretation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2016.03.013.

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