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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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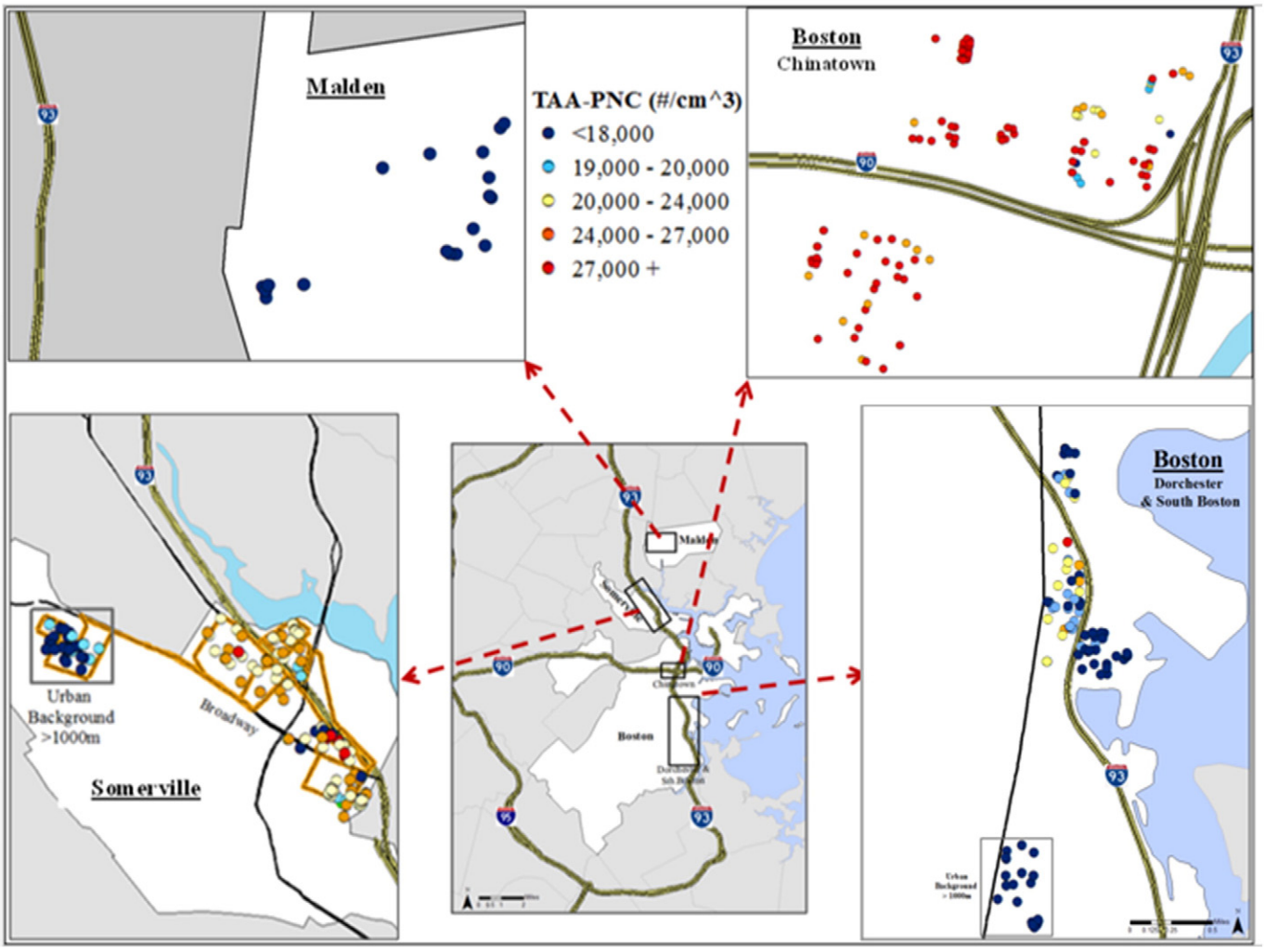

Fig. 1. Time-activity adjusted annual average particle number concentration (TAA-PNC) by study area.

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).