HHS Public Access

Author manuscript

Environ Pollut. Author manuscript; available in PMC 2024 February 16.

Published in final edited form as:

Environ Pollut. 2023 September 01; 332: 121962. doi:10.1016/j.envpol.2023.121962.

Particulate matter, traffic-related air pollutants, and circulating C-reactive protein levels: The Multiethnic Cohort Study

Meera Sangaramoorthy[1], **Juan Yang**[1], **Chiuchen Tseng**[2], **Jun Wu**[3], **Beate Ritz**[4], **Timothy V. Larson**[5], **Scott Fruin**[2], **Daniel O. Stram**[2], **Sung-shim Lani Park**[6], **Adrian A. Franke**[6], **Lynne R. Wilkens**[6], **Jonathan M. Samet**[7], **Loïc Le Marchand**[6], **Salma Shariff-Marco**[1], **Christopher A. Haiman**[2], **Anna H. Wu**[2], **Iona Cheng**[1]

[1]Department of Epidemiology and Biostatistics, School of Medicine, University of California San Francisco, San Francisco, CA, USA

[2]Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

[3]Department of Environmental and Occupational Health, Program in Public Health, Susan and Henry Samueli College of Health Sciences, University of California, Irvine, Irvine, CA, USA

[4]Department of Epidemiology, School of Public Health, University of California, Los Angeles, Los Angeles, CA, USA

[5]Department of Civil & Environmental Engineering, University of Washington, Seattle, WA, USA

[6]Population Sciences in the Pacific Program (Cancer Epidemiology), University of Hawaii Cancer Center, Honolulu, HI, USA

[7]Department of Epidemiology, Colorado School of Public Health, Aurora, CO, USA

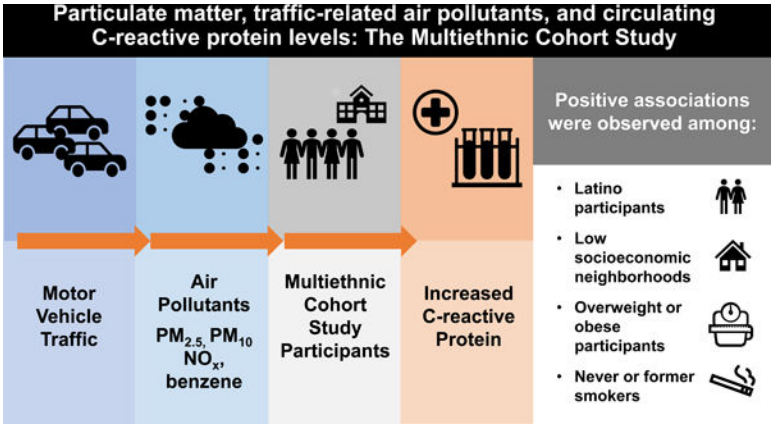
Abstract

Inhaled particles and gases can harm health by promoting chronic inflammation in the body. Few studies have investigated the relationship between outdoor air pollution and inflammation by race and ethnicity, socioeconomic status, and lifestyle risk factors. We examined associations of particulate matter (PM) and other markers of traffic-related air pollution with circulating levels of C-reactive protein (CRP), a biomarker of systemic inflammation. CRP was measured from blood samples obtained in 1994–2016 from 7,860 California residents participating in the Multiethnic Cohort (MEC) Study. Exposure to PM (aerodynamic diameter ≤ 2.5 μm [$PM_{2.5}$], ≤ 10 μm [PM_{10}], and between 2.5 and 10 μm [$PM_{10–2.5}$]), nitrogen oxides (NO_x, including nitrogen dioxide [NO_2]), carbon monoxide (CO), ground-level ozone (O_3), and benzene averaged over one or twelve months before blood draw were estimated based on participants' addresses. Percent change in geometric mean CRP levels and 95% confidence intervals (CI) per standard concentration increase of each pollutant were estimated using multivariable generalized linear regression. Among 4,305

Corresponding author: Iona Cheng, PhD, MPH, University of California, San Francisco, 550 16th Street, MH-2841 San Francisco, California, 94158; phone: 510-608-5276; fax: 510-608-5095; iona.cheng@ucsf.edu.

females (55%) and 3,555 males (45%) (mean age 68.1 [SD 7.5] years at blood draw), CRP levels increased with 12-month exposure to PM_{10} (11.0%, 95% CI: 4.2%, 18.2% per 10 μg/m^3), $PM_{10-2.5}$ (12.4%, 95% CI: 1.4%, 24.5% per 10 μg/m^3), NO_x (10.4%, 95% CI: 2.2%, 19.2% per 50 ppb), and benzene (2.9%, 95% CI: 1.1%, 4.6% per 1 ppb). In subgroup analyses, these associations were observed in Latino participants, those who lived in low socioeconomic neighborhoods, overweight or obese participants, and never or former smokers. No consistent patterns were found for 1-month pollutant exposures. This investigation identified associations of primarily traffic-related air pollutants, including PM, NO_x, and benzene, with CRP in a multiethnic population. The diversity of the MEC across demographic, socioeconomic, and lifestyle factors allowed us to explore the generalizability of effects of air pollution on inflammation across subgroups.

Graphical Abstract



Keywords

air pollution; C-reactive protein; particulate matter; nitrogen oxides; benzene; traffic

Introduction

Outdoor air pollution is a complex mixture of particles and gases generated largely from human-made combustion sources (Environmental Protection Agency, 2019). Motor vehicles are a major source of ambient air pollution, especially in urban and metropolitan areas (Environmental Protection Agency, 2019; Heydari et al., 2020). Although passage of the Clean Air Act of 1970 and subsequent amendments in the United States have helped reduce levels of air pollutants (Environmental Protection Agency, 2019), exposure to traffic-related compounds continues to be harmful to health by inducing adverse respiratory conditions and a number of chronic illnesses including cardiovascular disease, cancer, diabetes mellitus, and reproductive, neurological, and immune system disorders (National Institute of Environmental Health Sciences, 2020).

Air pollution can affect health by activating inflammation in the body through the signaling pathways of oxidative stress (Li et al., 2012; Liu et al., 2019; Romieu et al., 2008). In vitro studies have demonstrated the ability of air pollutants to induce production of

proinflammatory cytokines in lower airway alveolar macrophages and bronchial epithelial cells (Bayram et al., 2001; Becker et al., 2005; Driscoll et al., 1997) as well as upper airway nasal epithelial cells (Schierhorn et al., 1999). These cytokines stimulate the production of acute phase inflammatory proteins, including C-reactive protein (CRP), a widely used biomarker of systemic inflammation and clinical disease risk assessment (Agassandian et al., 2014; Moshage, 1997). Persistently high levels of CRP, first produced locally within the airway system then systemically by the liver, causes a cascade of physiological responses that can progress to cardiovascular disease, cancer, diabetes, asthma, and chronic obstructive pulmonary disease (Pahwa et al., 2021).

Epidemiological investigations have shown that levels of circulating CRP increase after exposure to particulate matter (PM) with aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) and less than or equal to 10 μm (PM_{10}) (Li et al., 2012; Liu et al., 2019), nitrogen oxides (NO_x, including nitrogen dioxide [NO_2]) (Elbarbary et al., 2021; Lanki et al., 2015; Xu et al., 2022), and ground-level ozone (O_3) (Xu et al., 2022). Previous studies have assessed either “long-term” exposures averaged over a period of greater than six months, often as a 12-month interval, or “short-term” exposures in intervals of days, weeks, or a month (Green et al., 2016; Liu et al., 2019; Wu et al., 2017; Xu et al., 2022). Short-term exposures are thought to capture acute effects while long-term exposures represent chronic effects (Xu et al., 2022).

In a recent meta-analysis, larger increases in CRP levels were seen for long-term exposures to $PM_{2.5}$ and PM_{10} (18% and 5.6% per 10 $\mu g/m^3$, respectively) than for short-term exposures (<1% per 10 $\mu g/m^3$ for both pollutants) (Liu et al., 2019). The authors concluded that stronger associations with long-term exposures reflected the cumulative effect of $PM_{2.5}$ and PM_{10} on inflammation over long durations. In contrast, results from a meta-analysis of gaseous pollutants found that short- but not long-term exposure to NO_2 and O_3 increased CRP levels (by 1.6% and 1.1% per 10 $\mu g/m^3$, respectively) (Xu et al., 2022). While other traffic-related air pollutants such as benzene and carbon monoxide (CO) have been shown to influence inflammation (Chen et al., 2021; Guo et al., 2020), we are not aware of population-based studies that have analyzed levels of outdoor benzene or CO in relation to CRP. Although analysis of specific air pollutants is helpful in identifying the most toxic components of air pollution, multiple compounds are highly correlated in the air pollution mixture due to common emission sources and related atmospheric chemical reactions (Chu et al., 2020; Sillman, 1999). Therefore, it is likely that particles and gases generated by traffic work together to trigger inflammation, rather than a single pollutant acting as an independent risk factor.

Prior studies of air pollution and CRP have been generally limited by small sample size and inadequate control for potential confounders such as smoking, nonsteroidal anti-inflammatory drugs, and history of inflammation-related conditions (e.g., obesity, cancer, cardiovascular disease) (Li et al., 2012; Liu et al., 2019). Furthermore, although racially and ethnically diverse populations have been assessed (Adar et al., 2015; Davis et al., 2020; Green et al., 2016; Hajat et al., 2015; Ostro et al., 2014; Wu et al., 2017), race- and ethnic-specific associations of air pollution and CRP have not been reported within the same study population. Underserved and underrepresented racial, ethnic, and socioeconomic groups

tend to reside in areas with higher levels of air pollution (Pratt et al., 2015). Circulating levels of CRP have been shown to differ by race and ethnicity with White populations having lower levels of circulating CRP in comparison to other groups (Nazmi and Victora, 2007). CRP levels are also consistently higher in women than men (Lakoski et al., 2006). Socioeconomic, behavioral, and physiological factors may account for these racial, ethnic, and sex variations in levels of CRP (Farmer et al., 2020), therefore investigations of air pollution and inflammation in susceptible subpopulations is an important public health objective.

In this report, we examine associations of PM and traffic-related air pollutants with circulating levels of CRP among California residents participating in the Multiethnic Cohort (MEC) Study. Our a priori hypothesis was that exposure to air pollution would increase CRP levels and associations would be modified by sex, race and ethnicity, socioeconomic status, body size, or smoking. To our knowledge, this is the largest investigation of air pollution and CRP involving a racially and ethnically diverse study population that examines both long- and short-term exposures. Most participants resided in Los Angeles County, one of the largest metropolitan areas in the U.S., with historically high levels of outdoor air pollution despite recent declines (IQAir., 2019) and inequities in pollution levels across communities defined by race, ethnicity, and socioeconomic status (Su et al., 2009).

Material and Methods

Study Population

The MEC is a population-based prospective cohort study of African American, Japanese American, Latino, Native Hawaiian, and White residents in California (largely from Los Angeles County) and Hawaii. Between 1993 and 1996, over 215,000 adult men and women, aged 45 to 75 years were identified predominantly through driver's license files. Participants completed a mailed, self-administered baseline questionnaire on demographic characteristics, diet, anthropometric measures, medical history, family history of cancer, and lifestyle factors including detailed information on smoking. Full details of the study population and design have been described previously (Kolonel et al., 2000). The Institutional Review Boards of the University of Southern California, the University of Hawaii, and the University of California, San Francisco approved the protocol for this study report.

The current analysis was conducted among California MEC participants, as equivalent air pollution data for Hawaii are not available. A high sensitivity protein test was used to measure CRP concentration from fasting blood samples obtained between 1994 and 2016 on 9,596 California MEC participants of the MEC biospecimen sub cohort (Kocarnik et al., 2018; Morimoto et al., 2014; Park et al., 2020). Information on current body size, smoking, and menopausal hormone therapy use was assessed via a short questionnaire at time of specimen collection. California MEC participants with CRP values were representative of the full California MEC cohort by sex, body mass index (BMI), and smoking status, however the proportion of Japanese American and White participants were lower (6% and 2%) in the CRP study population compared to the larger cohort (12% and 14%).

We excluded 44 participants with missing or extreme/outlier values for self-reported height or weight that resulted in extreme values for BMI (<15, >50 kg/m^2), 163 participants with no residential address information prior to date at blood draw or addresses that could not be geocoded, and 1,529 participants with a cancer diagnosis prior to blood draw or prevalent heart attack or stroke at baseline. Exclusion of 641 participants with CRP levels over 10 mg/L (which may indicate severe infection or inflammatory disease) did not change our results, therefore no exclusions based on CRP levels were made. The final study population included 7,860 MEC participants from California (4,445 Latino, 2,756 African American, 528 Japanese American, 128 White, and 3 Native Hawaiian). A flow chart on participant selection for this study is included in Supplemental Figure 1 and the distribution of year of blood draw for the study population is provided in Supplemental Figure 2.

C-reactive protein

High sensitivity CRP assays were performed by the Analytical Biochemistry Shared Resource at the University of Hawaii Cancer Center (Conroy et al., 2013; Morimoto et al., 2014; Ollberding et al., 2013). CRP from blood serum samples was assessed using a Cobas MiraPlus clinical chemistry analyzer (Roche Diagnostics, Indianapolis, IN) and a latex particle enhanced immunoturbidimetry-based kit from Pointe Scientific (Lincoln Park, MI) following the manufacturer's protocol (Chai et al., 2017; Morimoto et al., 2014). The intra-batch coefficient of variation based on 96 blinded duplicate and 9 triplet samples for CRP was 3.5–5.0% and the lower limit of detection was 0.1 mg/L (Conroy et al., 2013; Morimoto et al., 2014; Ollberding et al., 2013).

Outdoor Air Pollution

Average monthly concentrations of air pollutants were assigned for each MEC participant based on residential address at blood draw geocoded to latitude and longitude coordinates as the geographic unit (Cheng et al., 2020; Cheng et al., 2022; Wu et al., 2020). Concentrations of $PM_{2.5}$ from 1993 to 2016 were obtained from a fine-resolution geoscience-derived model that provides validated, publicly available $PM_{2.5}$ outputs at a 1-km resolution over North America by statistically fusing chemical transport modeling (GEOS-Chem) outputs and satellite-based aerosol optical depth (hereafter called satellite-based $PM_{2.5}$) with ground-based $PM_{2.5}$ measurements using geographically weighted regression (Meng et al., 2019). The estimated $PM_{2.5}$ concentrations were generally consistent with direct ground-based $PM_{2.5}$ measurements for annual concentrations from 1988 to 2016 (R^2 = 0.6 to 0.85), with an estimated error of <30% through 1998 and <20% from 1999. Empirical Bayesian Kriging interpolation was used to estimate largely regional concentrations of PM_{10}, coarse PM ($PM_{10–2.5;}$ aerodynamic diameter between 2.5 and 10 μm), NO_x, NO_2, CO, and O_3 (Wu et al., 2016) using measured concentrations from U.S. Environmental Protection Agency routine air monitoring data, except for kriging $PM_{2.5}$ concentrations in 1993–1999, which were modeled based on PM_{10}, meteorology, and land use data at the monitoring sites with PM_{10} measurements (Li et al., 2017b) before applying empirical Bayesian kriging. Previous leave-one-out cross-validation methods yielded R^2 values of 0.65–0.74 (Wu et al., 2016). For NO_x and NO_2, a land use regression (LUR) model was used to estimate regional and local source emissions based on air monitoring data from spatially dense air monitoring campaigns (2006–2007) and spatial data on land use and traffic characteristics; monthly

scaling factors for temporal adjustment were applied based on routinely collected long-term air monitoring data nearest to the participant's address (Su et al., 2009; Wu et al., 2020). The cross-validation analyses suggested a prediction accuracy of 87–91% for the annual average concentrations of LUR NO_x and NO_2. For benzene, monthly average concentrations in 1993–2016 were assigned based on measurements from the Environmental Protection Agency's air monitors located within 20 km radius buffer from residential addresses with less than 50% missing air monitoring data (Wu et al., 2020). For this analysis, we assessed exposures at twelve months (long-term) and one month (short-term) prior to blood draw. A correlation matrix of air pollutant concentrations is presented in Supplemental Table 1 and the interquartile range of pollutants are presented in Supplemental Table 2.

Neighborhood Socioeconomic Status

A composite measure of neighborhood socioeconomic status (nSES) was based on principal component analysis of seven census-based indicators of socioeconomic status: education, median household income, percent living 200% below poverty level, percent blue-collar workers, percent older than 16 years in workforce without job, median rent, and median house value (Yang et al., 2014; Yost et al., 2001) and assigned to participants' census block group at blood draw. This index was categorized into quintiles based on the nSES distribution of all Los Angeles County block groups. Low and high nSES were defined as quintiles 1–3 and 4–5, respectively.

Statistical Analysis

We used generalized linear regression models to estimate the association between exposure to each air pollutant and circulating CRP levels. Models adjusted for variables associated with markers of inflammation in the literature, including risk factors assessed at blood draw: age (continuous), smoking status (never, former, current, unknown), smoking pack years (continuous), body mass index (BMI) (kg/m^2; underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), obese (≥30)), and nonsteroidal anti-inflammatory drug (NSAID) use (no, yes, unknown) and at baseline: sex (male, female), race and ethnicity (African American, Japanese American, Latino, Native Hawaiian, White), diet [total energy intake (continuous, kcal/day), Alternate Mediterranean Diet Score (values ranging from 0 to 9 and unknown)], comorbidities (none, high blood pressure, diabetes, unknown). In analyses restricted to females, models were additionally adjusted for menopausal hormone therapy use at blood draw (never estrogen use, with or without past or current progesterone use; past estrogen use, with or without past progesterone use; current estrogen use alone; current estrogen use with past or present progesterone use; unknown). We also adjusted for the sub studies that contributed to the MEC biospecimen repository and CRP data (sub study 1, 2, or 3) (Kocarnik et al., 2018; Morimoto et al., 2014; Park et al., 2020). Although alcohol intake, educational attainment, and nSES were considered as possible confounders, they were not associated with CRP in models co-adjusted for all covariates, and therefore, not included in our final parsimonious multivariable models. We log-transformed CRP levels and derived percent change in geometric mean of CRP and 95% confidence intervals (CI). A 1 percentage change in CRP corresponded to a standard unit increase in an air pollutant concentration, based on units used in previous studies (Cheng et al., 2022; Liu et al., 2019; Xu et al., 2022): per 10 $\mu g/m^3$ for $PM_{2.5}$, PM_{10}, and $PM_{10–2.5}$, 50 parts per billion (ppb) for

NO_X, 20 ppb for NO_2, 1000 ppb for CO, 10 ppb for O_3, and 1 ppb for benzene. Stratified analyses were conducted by sex, race and ethnicity, nSES at blood draw, BMI at blood draw, and smoking at blood draw. In sensitivity analyses limited to participants who did not move (i.e. those who had one residential address since baseline), results were compared by distance to major roadways (<500 m vs. ≥500 m). Heterogeneity of associations were tested by including an interaction term for each pollutant and subgroup. All *p* values presented are two-sided with a significance level of 0.05. Analyses were performed using SAS 9.2 statistical software (SAS Institute, Cary, NC).

Results

The study population consisted of older adults (mean age 68.1 [SD 7.5]) of whom 4,305 were female (55%) and 3,555 were male (45%) (Table 1). Most study participants were either Latino (56.6%) or African American (35.1%), while fewer were Japanese American (6.7%) or White (1.6%). Latino participants had the highest mean total energy intake (2,460 kcal/day) and highest proportion with diabetes (11%) compared to other racial and ethnic groups. African American participants had the highest proportions of obesity (30%) and high blood pressure (40%), and lowest use of menopausal estrogen hormone therapy (19% of females). Japanese American participants had the lowest proportion of obesity (4%) and energy intake (1,951 kcal/day). Current (15%) and former (48%) smoking status as well as mean pack years of smoking (14) were highest among White participants, who also reported the highest estrogen hormone therapy use (30% of females).

Crude 12- and 1-month estimated mean concentrations of most air pollutants were higher for males compared to females (Supplemental Table 3). Mean concentrations of most 12- and 1-month air pollutants decreased incrementally with increasing nSES quintiles, except for PM_{10} and $PM_{10–2.5}$ (Supplemental Table 4). Standard deviations for 1-month exposures were generally larger than standard deviations for 12-month exposures, except for benzene.

In fully adjusted models (Table 2), mean levels of CRP in the overall study population increased with 12-month average exposure to PM_{10} (11.0%, 95% CI: 4.2%, 18.2% per 10 $\mu g/m^3$), $PM_{10–2.5}$ (12.4%, 95% CI: 1.4%, 24.5% per 10 $\mu g/m^3$), NO_x (10.4%, 95% CI: 2.2%, 19.2% per 50 ppb), and benzene (2.9%, 95% CI: 1.1%, 4.6% per 1 ppb). When we analyzed other correlated co-pollutants (Supplemental Table 5), CRP levels increased with increasing NO_2 and CO, and decreased with increasing O_3. Statistically significant associations were not found for pollutants assessed 1 month before blood draw in the overall population. Unadjusted mean CRP levels were higher among female participants (4.4 mg/L [SD 4.6]) than male participants (3.1 mg/L [SD 3.8]). Among females, mean CRP levels increased with 12-month exposure to PM_{10} (10.3%, 95% CI 1.5%, 19.8% per 10 $\mu g/m^3$) and NO_x (14.3%, 95% CI: 3.0%, 26.8% per 50 ppb) and decreased with 1-month exposure to $PM_{2.5}$ (−6.4%, 95% CI: −12.0%, −0.4% per 10 $\mu g/m^3$). Among males, CRP increased 3.4% (95% CI: 0.9%, 5.9%) per 1 ppb of 12-month exposure to benzene. Statistically significant heterogeneity in effects by sex were not detected for any pollutant.

There was no statistically significant heterogeneity in associations across the four racial and ethnic groups (Table 3). Though sample sizes were limited, White participants (n=128) had

the highest (4.7 mg/L [SD 5.3]) and Japanese American participants (n=528) had the lowest (1.9 mg/L [SD 2.8]) unadjusted mean CRP levels compared to other groups. Marginally statistically significant increases in CRP were found for 12-month $PM_{2.5}$ among White participants (91.4% , 95% CI: −0.4%, 267.6% per 10 μg/m^3) and PM_{10} among Japanese American participants (37.8% , 95% CI: −0.6%, 91.0% per 10 μg/m^3), while statistically significant associations for 12-month exposures were observed only for Latino participants, the largest racial and ethnic group (n=4,445): CRP increased by 13.0% (95% CI: 4.2%, 22.6%) per 10 μg/m^3 PM_{10}, 26.5% (95% CI: 10.8%, 44.4%) per 10 μg/m^3 $PM_{10–2.5}$, and 3.2% (95% CI: 1.0%, 5.4%) per 1 ppb benzene. Associations for 1-month exposures were not seen across racial and ethnic groups.

Among participants with low nSES, CRP increased with 12-month PM_{10} (11.6% per 10 μg/m^3), $PM_{10–2.5}$ (17.7% per 10 μg/m^3), NO_x (11.0% per 50 ppb), and benzene (3.1% per 1 ppb) (Table 4). Furthermore, statistically significant associations were limited to participants who were overweight or obese (Supplemental Table 6) and never or former smokers, although the number of current smokers in the study was low (n=650) (Supplemental Table 7). *P* values for heterogeneity by nSES, BMI, or smoking were ≥0.05 for all pollutants.

In sensitivity analyses, we detected statistically significant heterogeneity (*P* value 0.04) by distance to major roadways among participants who did not move for 1-month exposure to $PM_{2.5}$ (Supplemental Table 8). For every 10 μg/m^3 increase in $PM_{2.5}$, CRP increased among participants living <500 m to roadways (8.5%, 95 CI: −2.1%, 20.2%) and decreased among participants living ≥500 m away from roadways (−6.0%, 95 CI: −12.3%, 0.8%). There were no clear differences in the 12-month exposures by distance to roadways, however, for larger-sized PM fractions, increases in CRP were stronger among participants who resided farther from roadways.

Discussion

In this study of multiethnic residents largely from Los Angeles County, we observed strong positive associations of 12-month exposure to PM_{10}, $PM_{10–2.5}$, NO_x, and benzene with circulating levels of CRP and suggestive evidence of variation in associations by sex, race and ethnicity, nSES, BMI, and smoking status, although tests for heterogeneity were not statistically significant due to limited sample sizes in some subgroups. Twelve-month exposure to pollutants such as NO_2, CO, and O_3, which are generated from the same traffic sources as NO_x and benzene, were also associated with CRP levels, further emphasizing the potential toxic impact of traffic on health over time. No consistent pattern of associations were seen for 1-month pollutant exposures, which may be due to the higher measurement variability of these pollutants in our study.

Using data from 11 prior studies that assessed long-term exposure to PM, a recent meta-analysis estimated that CRP levels increased by 18.01% (95% CI: 5.96%, 30.06%) and 5.61% (95% CI: 0.79%, 10.44%) per 10 μg/m^3 increase of $PM_{2.5}$ and PM_{10}, respectively (Liu et al., 2019). In the MEC, we found an 11.0% (95% CI: 4.2%, 18.2%) increase in CRP per 10 μg/m^3 of 12-month average exposure to PM_{10}, with comparable increases in female (10.3%, 95% CI: 1.5%, 19.8%) and male (9.2%, 95% CI: −0.8%, 20.2%)

participants. Though estimates were not formally statistically significant, we also found suggestive evidence of increased CRP levels with 12-month average exposure to $PM_{2.5}$ both in the overall study population (4.9%, 95% CI: −4.8%, 15.6%) and for participants living in close proximity (< 500 m) to major roadways, who had estimates (11.7%, 95% CI: −8.8%, 37.0%) similar in magnitude to those reported in the literature. The latter finding suggests that, without considering distance to roadway traffic, our measure of satellite-based $PM_{2.5}$ may not sufficiently distinguish between traffic-related combustion sources versus other sources or secondary aerosols that are homogeneously distributed in the study region. Satellite-based $PM_{2.5}$ was a more refined measure than kriging $PM_{2.5}$ given that historical $PM_{2.5}$ concentrations in 1994–1999 were modeled based on measured PM_{10} along with meteorological and spatial data, and further spatially interpolated by kriging in the absence of measured $PM_{2.5}$ data (Cheng et al., 2022; Li et al., 2017a).

In the same meta-analytic report, based on 32 prior studies of short-term PM exposures, CRP increased more modestly compared to long-term PM exposures: 0.83% (95% CI: 0.30%, 1.37%) and 0.39% (95% CI: −0.04%, 0.82%) per 10 $\mu g/m^3$ of $PM_{2.5}$ and PM_{10}, respectively. In the MEC, we detected statistically significant heterogeneity for 1-month average exposure to $PM_{2.5}$ by distance to roadways, wherein CRP increased among participants who lived closer to roads but decreased among those who lived farther away from roads. This finding indicates that $PM_{2.5}$ originating from fossil fuel combustion of motor vehicles may be more relevant to CRP than other secondary sources. Similarly, although we did not detect an overall association between 1-month exposure to PM_{10} and CRP, increased CRP levels were seen only among participants who resided near major roadways.

Few studies have assessed the association of PM with CRP in a racially and ethnically diverse study population, and none have reported race and ethnicity specific estimates (Hajat et al., 2015; Ostro et al., 2014). Consistent with our findings, the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort of African American, Chinese, Hispanic, and White adults aged 45–84 years from six metropolitan cities in the U.S. including Los Angeles, reported no statistically significant association between CRP and ambient $PM_{2.5}$ one year before blood draw or for shorter term exposures of 0 to 5 days before blood draw (Hajat et al., 2015). Since the MESA did not assess $PM_{2.5}$ by proximity to roadways, we are unable to compare our findings of a stronger effect of $PM_{2.5}$ closer to major roads. The MESA did not detect associations between $PM_{10–2.5}$ and CRP (Adar et al., 2015), whereas, in our MEC study, we found a 12.4% (95% CI: 1.4%, 24.5%) increase overall and a larger 26.5% (95% CI: 10.8%, 44.4%) increase among Latino participants for CRP per 10 $\mu g/m^3$ of 12-month exposure to $PM_{10–2.5}$.

In the Study of Women's Health Across the Nation (SWAN), a cohort of African American, Chinese, Japanese, Hispanic, and White middle-aged women recruited from five different metropolitan sites, including Los Angeles, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ one year before blood draw was associated with increased CRP levels (25%, 95% CI: 10.2%, 42.9%), with stronger associations among those with low income (Ostro et al., 2014). In the MEC, we also saw larger increases in CRP with 12-month exposure to $PM_{2.5}$ for those residing in low nSES areas compared to high nSES areas though estimates and tests for heterogeneity were

not formally statistically significant. No associations were found between CRP and $PM_{2.5}$ one month before blood draw in the SWAN (Green et al., 2016). In contrast, we found a statistically significant inverse association between 1-month $PM_{2.5}$ and CRP among MEC females. While many studies of short-term $PM_{2.5}$ and CRP have observed no associations or positive associations, some studies have reported a decrease in CRP levels, as we found in the MEC (Delfino et al., 2009; Huang et al., 2012; Liu et al., 2019). However, as discussed earlier, our finding of significant heterogeneity in 1-month exposure to $PM_{2.5}$ by distance to roadways supports the importance of examining proximity to traffic sources when analyzing traffic-related exposure to $PM_{2.5}$. Finally, CRP increased by 4.1% ($p < 0.10$) per 4 $\mu g/m^3$ $PM_{10–2.5}$ over a one year period in the SWAN (Davis et al., 2020). Translating this increase to the same unit scale as the MEC, the SWAN study found a 10.3% increase in CRP per 10 $\mu g/m^3$ of $PM_{10–2.5}$, which is comparable to findings in the MEC of an overall increase of 12.4% (95% CI: 1.4%, 24.5%) and an increase of 13.1% (95% CI: −1.7%, 30.2%) among female participants. To our knowledge, neither the MESA nor the SWAN have reported findings on PM_{10}.

Particles of different sizes are released into the atmosphere through different mechanisms. For example, traffic-related $PM_{2.5}$ is primarily generated from combustion (exhaust emissions) and secondary atmospheric reactions while $PM_{10–2.5}$ near roadways is a product of mechanical grinding of vehicle parts and resuspension of solid material (non-exhaust emissions) (Adar et al., 2014). Due to differences in origin, particles classified by size are composed of unique mixtures of elements that can impact the body through different molecular pathways targeting various organ systems downstream. Compared to smaller $PM_{2.5}$, which can deposit more directly into the lungs and enter the circulatory system more quickly, larger $PM_{10–2.5}$ deposits in the upper respiratory tract and releases metals and other soluble toxins that then trigger inflammation (Ljubimova et al., 2018). There is evidence that $PM_{10–2.5}$ size fractions have higher component levels of endotoxin (Adar et al., 2015) and greater inflammatory potential due to more expression of genes that cause inflammation (Ljubimova et al., 2018) than $PM_{2.5}$. It is plausible that differing biological pathways of PM_{10}, $PM_{10–2.5}$, and $PM_{2.5}$, determined by each fraction's unique composition, contributed to variation in the magnitude and strength of associations with CRP in our study, however, additional data from large, population-based studies are needed to confirm our findings.

In a recent meta-analysis of 27 studies of CRP and gaseous air pollutants, increases in CRP were found for short-term exposure to NO_2 (1.60%, 95% CI: 0.49%, 2.72% per 10 $\mu g/m^3$) and O_3 (1.05%, 95% CI: 0.09%, 2.02% per 10 $\mu g/m^3$), but no associations were seen for long-term exposures (Xu et al., 2022). The MESA study did not find associations between CRP and NO_x or NO_2 exposures averaged over one year (Hajat et al., 2015). In the SWAN, 6-month exposure to O_3 was associated with increased CRP levels 3.2% (95% CI: 0.1%, 6.5%) per 10 ppb, but one year and one month exposures had no effect (Green et al., 2016) and neither NO_2 nor CO were associated with CRP, regardless of the time interval of exposure (Wu et al., 2017). In contrast, we found strong positive associations between CRP and 12-month exposure to NO_x and NO_2 assessed by both LUR and kriging interpolation, with estimates in the overall study population ranging between 10.4% and 14.3% (p values <0.05) per 50 ppb of NO_x and per 20 ppb of NO_2. For 1-month NO_x and NO_2 exposures, increases in CRP ranged from 1.9% to 4.1% and were not statistically significant. Other

large cohort studies in the U.S. (Iyer et al., 2022), Europe (Cai et al., 2017; Lanki et al., 2015), and China (Elbarbary et al., 2021) have reported positive associations with long-term NO_x and/or NO_2 and CRP, as we did.

Outdoor sources of NO_x include fossil fuel combustion from motor vehicles and power plants or other industrial complexes (Blomberg, 2000; Hesterberg et al., 2009). Both NO_x and NO_2 chemically react to produce co-pollutants such as PM and O_3 (Environmental Protection Agency, 2021) and are therefore important markers of the overall pollution mixture generated by motor vehicle traffic. Our observation of an inverse association between O_3 and CRP is likely attributable to the negative correlation between O_3 and NO_X, due to the photochemical reaction between these two gases (Sillman, 1999), further supporting the strong association of NO_X and NO_2 with CRP and emphasizing their role as traffic-related pollutants.

To our knowledge, there have not been any large U.S. studies on benzene and CRP. Ambient benzene is produced largely by gasoline-powered vehicles and its concentration decreases significantly with greater distance from roads (Karner et al., 2010). Our finding of increased levels of CRP with increasing benzene further underscores the importance of motor vehicle traffic in the inflammation-disease pathway.

Similar to our findings, several previous studies have not observed associations between air pollution and markers of inflammation among smokers (Hoffmann et al., 2009; Panasevich et al., 2009; Pilz et al., 2018). Current smokers tend to have higher systemic inflammation than non-smokers (Yanbaeva et al., 2007). In our study, mean CRP levels for current, former, and never smokers were 4.3 mg/L, 3.8 mg/L, and 3.6 mg/L, respectively. Therefore, higher CRP levels in current smokers may have limited our ability to detect the unique contribution of air pollution on CRP levels due to the larger influence of tobacco smoke on inflammation (Panasevich et al., 2009; Pilz et al., 2018; Yanbaeva et al., 2007).

This MEC study included high proportions of Latino and African American participants and, along with Japanese American participants, we are able to report on associations in racial and ethnic populations often underrepresented in epidemiological research. Considering that most prior studies of air pollution and CRP were conducted in largely White populations, the extent to which their findings are generalizable to understudied racial and ethnic minorities is not known. Although statistically significant associations for 12-month air pollution measures and CRP were observed for Latino participants only, Latino participants were the largest racial and ethnic group, accounting for almost 57% of our study population. Therefore, we cannot rule out the possibility that we would have seen significant estimates for other racial and ethnic groups if sample sizes were larger.

The interaction of race, ethnicity, and socioeconomic status in the U.S. is a product of historical racial and ethnic segregation and other forms of structural racism (Bailey et al., 2017). In this study, 25% of African American and 22% of Latino participants lived in the lowest quintile of nSES compared to 5% of White participants. Underrepresented racial and ethnic groups, especially those living in lower socioeconomic neighborhoods, may experience greater exposure to air pollution and a larger burden of the detrimental health

effects of pollution (Pratt et al., 2015). Although we did not find statistical heterogeneity in associations of air pollution and CRP by nSES, findings from this study make an important contribution to the limited literature on air pollution and CRP in racial and ethnic minorities in the U.S. and may help inform future air pollution regulation and policies for areas with high concentrations of underrepresented racial and ethnic groups and those residing in areas of low nSES.

Some limitations of this study need to be considered. Only one measurement of CRP was available. Although we were able to estimate associations between air pollution and CRP, we are unable to make causal inferences due to our cross-sectional study design. Levels of CRP in healthy individuals are thought to be stable over time (Emerging Risk Factors et al., 2010; Lee et al., 2007; Navarro et al., 2012) although some studies have found CRP values to fluctuate more than other biomarkers (DeGoma et al., 2012; Hardikar et al., 2014). Cumulative lifetime exposure to air pollutants, which we were unable to assess, may have played a role in CRP levels in our participants. Our assessment of air pollution exposure was based on location of primary residence and we did not have information on other locations (i.e. work, commute, recreational/sports activities, school) where exposure could occur. It is estimated that adults in California spend a majority of their time indoors (Klepeis et al., 2001). Although indoor/outdoor air pollution are correlated, unmeasured indoor pollutants may have influenced CRP levels in our study (Blomberg, 2000; Vardoulakis et al., 2020). We were unable to assess total caloric intake, Alternate Mediterranean Diet Score, and comorbidities at blood draw and therefore used baseline values. In order to assess the potential impact of temporal changes since baseline, we conducted a sensitivity analysis among 1,011 participants who had diet and comorbidity data from the MEC follow-up questionnaire prior to blood draw. In this subsample, we found very similar air pollutant and CRP associations adjusting for either baseline or updated follow-up values of total energy intake, Alternate Mediterranean Diet Score, and comorbidities. Meteorological parameters may confound associations between air pollution and systemic inflammation (Khafaie et al., 2013). In sensitivity analyses, associations between air pollutants and CRP were similar with additional adjustment for maximum air temperature (Abatzoglou, 2013) and a heat index that incorporates heat and humidity (Dahl et al., 2019). Our findings of no formally statistically significant associations for $PM_{2.5}$ may reflect the mixing of effects of primary traffic-related combustion $PM_{2.5}$ and secondary formation of $PM_{2.5}$ through photochemical processes in the Los Angeles basin, which tends to produce more $PM_{2.5}$ inland. The larger measurement variability of our 1-month exposures compared to our 12-month exposures likely reduced statistical power to detect associations with CRP for short vs. long term exposures, thereby explaining some of our overall results, especially those for PM_{10}. Considering these specific limitations to our exposure assessment, misclassification may have affected our estimates, although any misclassification would most likely be non-differential (Jurek et al., 2008; Jurek et al., 2005). Finally, we modeled components of air pollution using previously validated methods (satellite-based spatiotemporal modeling, kriging interpolation and LUR model) (Cheng et al., 2020), casting a wide net to assess multiple constituents of air pollution from different sources. Therefore, due to the inevitably high correlation of individual components of air

pollution, we interpret the observed associations as reflecting a general association between CRP and the atmospheric mixture of particulate matter and traffic-related air pollution.

Conclusions

This investigation in a multiethnic population of California residents identified associations between outdoor air pollution mainly from traffic sources and circulating levels of CRP. Currently, there is limited understanding of the extent of effect modification of these associations by individual characteristics and the neighborhood environment. The racial, ethnic, and socioeconomic diversity of the MEC, coupled with the variation in lifestyle factors across participants, allowed for examining the generalizability of the effects of air pollution on inflammation across specific subgroups. Our results suggest that the effects of air pollutants on inflammation may vary by sex, race, ethnicity, nSES, BMI, smoking, and proximity to major roadways, however, future studies are warranted to investigate these differences in a variety of geographical areas with a focus on underserved and at-risk populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institute Environment Science (grant number R01ES026171); National Cancer Institute (grant numbers U01 CA164973, 5-R21-CA094723–03, P01CA138338); USC Norris Comprehensive Cancer Center (Core) Support (grant number P30 CA014089); University of Hawaii Cancer Center Core Support (grant number P30 CA71789); Environmental Exposures, Host Factors, and Human Disease (grant number P30 ES0070480); California Air Resource Board (contract number 04–323); and the Slim Initiative in Genomic Medicine for the Americas (SIGMA), a joint U.S.-Mexico project funded by the Carlos Slim Foundation. The authors are grateful to the study participants and research team of the MEC.

Abbreviations:

BMI	body mass index
CO	carbon monoxide
CRP	c-reactive protein
LUR	land use regression
MESA	Multi-Ethnic Study of Atherosclerosis
MEC	Multiethnic Cohort
nSES	neighborhood socioeconomic status
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
O3	ozone

NSAID	nonsteroidal anti-inflammatory drug
PM	particulate matter
$PM_{2.5}$	particulate matter with aerodynamic diameter less than or equal to 2.5 μm
PM_{10}	particulate matter with aerodynamic diameter less than or equal to 10 μm
$PM_{10–2.5}$	particulate matter with aerodynamic diameter between 2.5 and 10 μm
SWAN	Study of Women's Health Across the Nation

References

Abatzoglou JT, 2013. Development of gridded surface meteorological data for ecological applications and modelling. International Journal of Climatology 33, 121–131.

Adar SD, D'Souza J, Mendelsohn-Victor K, Jacobs DR, Cushman M, Sheppard L, Thorne PS, Burke GL, Daviglus ML, Szpiro AA, Diez Roux AV, Kaufman JD, Larson TV, 2015. Markers of inflammation and coagulation after long-term exposure to coarse particulate matter: a cross-sectional analysis from the multi-ethnic study of atherosclerosis. Environ Health Perspect 123, 541–548. [PubMed: 25616153]

Adar SD, Filigrana PA, Clements N, Peel JL, 2014. Ambient Coarse Particulate Matter and Human Health: A Systematic Review and Meta-Analysis. Curr Environ Health Rep 1, 258–274. [PubMed: 25152864]

Agassandian M, Shurin GV, Ma Y, Shurin MR, 2014. C-reactive protein and lung diseases. Int J Biochem Cell Biol 53, 77–88. [PubMed: 24853773]

Bailey ZD, Krieger N, Agenor M, Graves J, Linos N, Bassett MT, 2017. Structural racism and health inequities in the USA: evidence and interventions. Lancet 389, 1453–1463. [PubMed: 28402827]

Bayram H, Sapsford RJ, Abdelaziz MM, Khair OA, 2001. Effect of ozone and nitrogen dioxide on the release of proinflammatory mediators from bronchial epithelial cells of nonatopic nonasthmatic subjects and atopic asthmatic patients in vitro. J Allergy Clin Immunol 107, 287–294. [PubMed: 11174195]

Becker S, Mundandhara S, Devlin RB, Madden M, 2005. Regulation of cytokine production in human alveolar macrophages and airway epithelial cells in response to ambient air pollution particles: further mechanistic studies. Toxicol Appl Pharmacol 207, 269–275. [PubMed: 15993911]

Blomberg A, 2000. Airway inflammatory and antioxidant responses to oxidative and particulate air pollutants - experimental exposure studies in humans. Clin Exp Allergy 30, 310–317. [PubMed: 10691887]

Cai Y, Hansell AL, Blangiardo M, Burton PR, BioShaRe, de Hoogh K, Doiron D, Fortier I, Gulliver J, Hveem K, Mbatchou S, Morley DW, Stolk RP, Zijlema WL, Elliott P, Hodgson S, 2017. Long-term exposure to road traffic noise, ambient air pollution, and cardiovascular risk factors in the HUNT and lifelines cohorts. Eur Heart J 38, 2290–2296. [PubMed: 28575405]

Chai W, Morimoto Y, Cooney RV, Franke AA, Shvetsov YB, Le Marchand L, Haiman CA, Kolonel LN, Goodman MT, Maskarinec G, 2017. Dietary Red and Processed Meat Intake and Markers of Adiposity and Inflammation: The Multiethnic Cohort Study. J Am Coll Nutr 36, 378–385. [PubMed: 28628401]

Chen RJ, Lee YH, Chen TH, Chen YY, Yeh YL, Chang CP, Huang CC, Guo HR, Wang YJ, 2021. Carbon monoxide-triggered health effects: the important role of the inflammasome and its possible crosstalk with autophagy and exosomes. Arch Toxicol 95, 1141–1159. [PubMed: 33554280]

Cheng I, Tseng C, Wu J, Yang J, Conroy SM, Shariff-Marco S, Li L, Hertz A, Gomez SL, Le Marchand L, Whittemore AS, Stram DO, Ritz B, Wu AH, 2020. Association between ambient

air pollution and breast cancer risk: The multiethnic cohort study. Int J Cancer 146, 699–711. [PubMed: 30924138]

Cheng I, Yang J, Tseng C, Wu J, Shariff-Marco S, Park SL, Conroy SM, Inamdar PP, Fruin S, Larson T, Setiawan VW, DeRouen MC, Gomez SL, Wilkens LR, Le Marchand L, Stram DO, Samet J, Ritz B, Wu AH, 2022. Traffic-related Air Pollution and Lung Cancer Incidence: The California Multiethnic Cohort Study. Am J Respir Crit Care Med 206, 1008–1018. [PubMed: 35649154]

Chu BW, Ma QX, Liu J, Ma JZ, Zhang P, Chen TZ, Feng QC, Wang CY, Yang N, Ma HN, Ma JJ, Russell AG, He H, 2020. Air Pollutant Correlations in China: Secondary Air Pollutant Responses to NOx and SO2 Control. Environmental Science & Technology Letters 7, 695–700.

Conroy SM, Maskarinec G, Morimoto Y, Franke AA, Cooney RV, Wilkens LR, Goodman MT, Hernadez BY, Le Marchand L, Henderson BE, Kolonel LN, 2013. Non-hodgkin lymphoma and circulating markers of inflammation and adiposity in a nested case-control study: the multiethnic cohort. Cancer Epidemiol Biomarkers Prev 22, 337–347. [PubMed: 23300021]

Dahl K, Licker R, Abatzoglou JT, Declet-Barreto J, 2019. Increased frequency of and population exposure to extreme heat index days in the United States during the 21st century. Environmental Research Communications 1.

Davis E, Malig B, Broadwin R, Ebisu K, Basu R, Gold EB, Qi L, Derby CA, Park SK, Wu XM, 2020. Association between coarse particulate matter and inflammatory and hemostatic markers in a cohort of midlife women. Environ Health 19, 111. [PubMed: 33153486]

DeGoma EM, French B, Dunbar RL, Allison MA, Mohler ER 3rd, Budoff MJ, 2012. Intraindividual variability of C-reactive protein: the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 224, 274–279. [PubMed: 22846611]

Delfino RJ, Staimer N, Tjoa T, Gillen DL, Polidori A, Arhami M, Kleinman MT, Vaziri ND, Longhurst J, Sioutas C, 2009. Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. Environ Health Perspect 117, 1232–1238. [PubMed: 19672402]

Driscoll KE, Carter JM, Hassenbein DG, Howard B, 1997. Cytokines and particle-induced inflammatory cell recruitment. Environ Health Perspect 105 Suppl 5, 1159–1164. [PubMed: 9400717]

Elbarbary M, Oganesyan A, Honda T, Morgan G, Guo Y, Guo Y, Negin J, 2021. Systemic Inflammation (C-Reactive Protein) in Older Chinese Adults Is Associated with Long-Term Exposure to Ambient Air Pollution. Int J Environ Res Public Health 18.

Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J, 2010. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 375, 132–140. [PubMed: 20031199]

Environmental Protection Agency, 2019. Our Nation's Air, Washington D.C.

Environmental Protection Agency, 2021. Nitrogen Dioxide (NO2) Pollution, Washington, DC.

Farmer HR, Wray LA, Xian Y, Xu H, Pagidipati N, Peterson ED, Dupre ME, 2020. Racial Differences in Elevated C-Reactive Protein Among US Older Adults. J Am Geriatr Soc 68, 362–369. [PubMed: 31633808]

Green R, Broadwin R, Malig B, Basu R, Gold EB, Qi L, Sternfeld B, Bromberger JT, Greendale GA, Kravitz HM, Tomey K, Matthews K, Derby CA, Jackson EA, Green R, Ostro B, 2016. Long- and Short-term Exposure to Air Pollution and Inflammatory/Hemostatic Markers in Midlife Women. Epidemiology 27, 211–220. [PubMed: 26600256]

Guo H, Ahn S, Zhang L, 2020. Benzene-associated immunosuppression and chronic inflammation in humans: a systematic review. Occup Environ Med

Hajat A, Allison M, Diez-Roux AV, Jenny NS, Jorgensen NW, Szpiro AA, Vedal S, Kaufman JD, 2015. Long-term exposure to air pollution and markers of inflammation, coagulation, and endothelial activation: a repeat-measures analysis in the Multi-Ethnic Study of Atherosclerosis (MESA). Epidemiology 26, 310–320. [PubMed: 25710246]

Hardikar S, Song X, Kratz M, Anderson GL, Blount PL, Reid BJ, Vaughan TL, White E, 2014. Intraindividual variability over time in plasma biomarkers of inflammation and effects of long-term storage. Cancer Causes Control 25, 969–976. [PubMed: 24839050]

Hesterberg TW, Bunn WB, McClellan RO, Hamade AK, Long CM, Valberg PA, 2009. Critical review of the human data on short-term nitrogen dioxide (NO2) exposures: evidence for NO2 no-effect levels. Crit Rev Toxicol 39, 743–781. [PubMed: 19852560]

Heydari S, Tainio M, Woodcock J, de Nazelle A, 2020. Estimating traffic contribution to particulate matter concentration in urban areas using a multilevel Bayesian meta-regression approach. Environ Int 141, 105800. [PubMed: 32474298]

Hoffmann B, Moebus S, Dragano N, Stang A, Mohlenkamp S, Schmermund A, Memmesheimer M, Brocker-Preuss M, Mann K, Erbel R, Jockel KH, 2009. Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. Environ Health Perspect 117, 1302–1308. [PubMed: 19672412]

Huang W, Zhu T, Pan X, Hu M, Lu SE, Lin Y, Wang T, Zhang Y, Tang X, 2012. Air pollution and autonomic and vascular dysfunction in patients with cardiovascular disease: interactions of systemic inflammation, overweight, and gender. Am J Epidemiol 176, 117–126. [PubMed: 22763390]

IQAir., 2019. 2019 World Air Quality Report Region & City PM2.5 Ranking v8

Iyer HS, Hart JE, Fiffer MR, Elliott EG, Yanosky JD, Kaufman JD, Puett RC, Laden F, 2022. Impacts of long-term ambient particulate matter and gaseous pollutants on circulating biomarkers of inflammation in male and female health professionals. Environ Res 214, 113810. [PubMed: 35798268]

Jurek AM, Greenland S, Maldonado G, 2008. How far from non-differential does exposure or disease misclassification have to be to bias measures of association away from the null? Int J Epidemiol 37, 382–385. [PubMed: 18184671]

Jurek AM, Greenland S, Maldonado G, Church TR, 2005. Proper interpretation of non-differential misclassification effects: expectations vs observations. Int J Epidemiol 34, 680–687. [PubMed: 15802377]

Karner AA, Eisinger DS, Niemeier DA, 2010. Near-roadway air quality: synthesizing the findings from real-world data. Environ Sci Technol 44, 5334–5344. [PubMed: 20560612]

Khafaie MA, Salvi SS, Ojha A, Khafaie B, Gore SS, Yajnik CS, 2013. Systemic inflammation (C-reactive protein) in type 2 diabetic patients is associated with ambient air pollution in Pune City, India. Diabetes Care 36, 625–630. [PubMed: 23172977]

Klepeis NE, Nelson WC, Ott WR, Robinson JP, Tsang AM, Switzer P, Behar JV, Hern SC, Engelmann WH, 2001. The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants. J Expo Anal Environ Epidemiol 11, 231–252. [PubMed: 11477521]

Kocarnik JM, Richard M, Graff M, Haessler J, Bien S, Carlson C, Carty CL, Reiner AP, Avery CL, Ballantyne CM, LaCroix AZ, Assimes TL, Barbalic M, Pankratz N, Tang W, Tao R, Chen D, Talavera GA, Daviglus ML, Chirinos-Medina DA, Pereira R, Nishimura K, Buzkova P, Best LG, Ambite JL, Cheng I, Crawford DC, Hindorff LA, Fornage M, Heiss G, North KE, Haiman CA, Peters U, Le Marchand L, Kooperberg C, 2018. Discovery, fine-mapping, and conditional analyses of genetic variants associated with C-reactive protein in multiethnic populations using the Metabochip in the Population Architecture using Genomics and Epidemiology (PAGE) study. Hum Mol Genet 27, 2940–2953. [PubMed: 29878111]

Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC, Stram DO, Monroe KR, Earle ME, Nagamine FS, 2000. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 151, 346–357. [PubMed: 10695593]

Lakoski SG, Cushman M, Criqui M, Rundek T, Blumenthal RS, D'Agostino RB Jr., Herrington DM, 2006. Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. Am Heart J 152, 593–598. [PubMed: 16923436]

Lanki T, Hampel R, Tiittanen P, Andrich S, Beelen R, Brunekreef B, Dratva J, De Faire U, Fuks KB, Hoffmann B, Imboden M, Jousilahti P, Koenig W, Mahabadi AA, Kunzli N, Pedersen NL, Penell J, Pershagen G, Probst-Hensch NM, Schaffner E, Schindler C, Sugiri D, Swart WJ, Tsai MY, Turunen AW, Weinmayr G, Wolf K, Yli-Tuomi T, Peters A, 2015. Air Pollution from Road Traffic and Systemic Inflammation in Adults: A Cross-Sectional Analysis in the European ESCAPE Project. Environ Health Perspect 123, 785–791. [PubMed: 25816055]

Lee SA, Kallianpur A, Xiang YB, Wen W, Cai Q, Liu D, Fazio S, Linton MF, Zheng W, Shu XO, 2007. Intra-individual variation of plasma adipokine levels and utility of single measurement of these biomarkers in population-based studies. Cancer Epidemiol Biomarkers Prev 16, 2464–2470. [PubMed: 18006938]

Li L, Wu AH, Cheng I, Chen J-C, Wu J, 2017a. Spatiotemporal estimation of historical PM_{2.5} concentrations using PM₁₀, meteorological variables, and spatial effect. Atmospheric Environment 166, 182.

Li LF, Wu AH, Cheng I, Chen JC, Wu J, 2017b. Spatiotemporal estimation of historical PM2.5 concentrations using PM10, meteorological variables, and spatial effect. Atmospheric Environment 166, 182–191.

Li Y, Rittenhouse-Olson K, Scheider WL, Mu L, 2012. Effect of particulate matter air pollution on C-reactive protein: a review of epidemiologic studies. Rev Environ Health 27, 133–149. [PubMed: 23023922]

Liu Q, Gu X, Deng F, Mu L, Baccarelli AA, Guo X, Wu S, 2019. Ambient particulate air pollution and circulating C-reactive protein level: A systematic review and meta-analysis. Int J Hyg Environ Health 222, 756–764. [PubMed: 31103472]

Ljubimova JY, Braubach O, Patil R, Chiechi A, Tang J, Galstyan A, Shatalova ES, Kleinman MT, Black KL, Holler E, 2018. Coarse particulate matter (PM2.5–10) in Los Angeles Basin air induces expression of inflammation and cancer biomarkers in rat brains. Sci Rep 8, 5708. [PubMed: 29632393]

Meng J, Li C, Martin RV, van Donkelaar A, Hystad P, Brauer M, 2019. Estimated Long-Term (1981–2016) Concentrations of Ambient Fine Particulate Matter across North America from Chemical Transport Modeling, Satellite Remote Sensing, and Ground-Based Measurements. Environ Sci Technol 53, 5071–5079. [PubMed: 30995030]

Morimoto Y, Conroy SM, Ollberding NJ, Kim Y, Lim U, Cooney RV, Franke AA, Wilkens LR, Hernandez BY, Goodman MT, Henderson BE, Kolonel LN, Le Marchand L, Maskarinec G, 2014. Ethnic differences in serum adipokine and C-reactive protein levels: the multiethnic cohort. Int J Obes (Lond) 38, 1416–1422. [PubMed: 24522245]

Moshage H, 1997. Cytokines and the hepatic acute phase response. J Pathol 181, 257–266. [PubMed: 9155709]

National Institute of Environmental Health Sciences, 2020. Air Pollution and Your Health, in: Health, N.I.o., U.S. Department of Health and Human Services (Eds.), Research Triangle Park, NC

Navarro SL, Brasky TM, Schwarz Y, Song X, Wang CY, Kristal AR, Kratz M, White E, Lampe JW, 2012. Reliability of serum biomarkers of inflammation from repeated measures in healthy individuals. Cancer Epidemiol Biomarkers Prev 21, 1167–1170. [PubMed: 22564866]

Nazmi A, Victora CG, 2007. Socioeconomic and racial/ethnic differentials of C-reactive protein levels: a systematic review of population-based studies. BMC Public Health 7, 212. [PubMed: 17705867]

Ollberding NJ, Kim Y, Shvetsov YB, Wilkens LR, Franke AA, Cooney RV, Maskarinec G, Hernandez BY, Henderson BE, Le Marchand L, Kolonel LN, Goodman MT, 2013. Prediagnostic leptin, adiponectin, C-reactive protein, and the risk of postmenopausal breast cancer. Cancer Prev Res (Phila) 6, 188–195. [PubMed: 23466816]

Ostro B, Malig B, Broadwin R, Basu R, Gold EB, Bromberger JT, Derby C, Feinstein S, Greendale GA, Jackson EA, Kravitz HM, Matthews KA, Sternfeld B, Tomey K, Green RR, Green R, 2014. Chronic PM2.5 exposure and inflammation: determining sensitive subgroups in mid-life women. Environ Res 132, 168–175. [PubMed: 24792413]

Pahwa R, Goyal A, Bansal P, Jialal I, 2021. Chronic Inflammation, StatPearls, Treasure Island (FL).

Panasevich S, Leander K, Rosenlund M, Ljungman P, Bellander T, de Faire U, Pershagen G, Nyberg F, 2009. Associations of long- and short-term air pollution exposure with markers of inflammation and coagulation in a population sample. Occup Environ Med 66, 747–753. [PubMed: 19687019]

Park SL, Li Y, Sheng X, Hom V, Xia L, Zhao K, Pooler L, Setiawan VW, Lim U, Monroe KR, Wilkens LR, Kristal BS, Lampe JW, Hullar M, Shepherd J, Loo LLM, Ernst T, Franke AA, Tiirikainen M, Haiman CA, Stram DO, Le Marchand L, Cheng I, 2020. Genome-Wide Association Study of Liver Fat: The Multiethnic Cohort Adiposity Phenotype Study. Hepatol Commun 4, 1112–1123. [PubMed: 32766472]

Pilz V, Wolf K, Breitner S, Ruckerl R, Koenig W, Rathmann W, Cyrys J, Peters A, Schneider A, group KO-S, 2018. C-reactive protein (CRP) and long-term air pollution with a focus on ultrafine particles. Int J Hyg Environ Health 221, 510–518. [PubMed: 29428699]

Pratt GC, Vadali ML, Kvale DL, Ellickson KM, 2015. Traffic, air pollution, minority and socio-economic status: addressing inequities in exposure and risk. Int J Environ Res Public Health 12, 5355–5372. [PubMed: 25996888]

Romieu I, Castro-Giner F, Kunzli N, Sunyer J, 2008. Air pollution, oxidative stress and dietary supplementation: a review. Eur Respir J 31, 179–197. [PubMed: 18166596]

Schierhorn K, Zhang M, Matthias C, Kunkel G, 1999. Influence of ozone and nitrogen dioxide on histamine and interleukin formation in a human nasal mucosa culture system. Am J Respir Cell Mol Biol 20, 1013–1019. [PubMed: 10226072]

Sillman S, 1999. The relation between ozone, NOx and hydrocarbons in urban and polluted rural environments. Atmospheric Environment 33, 1821–1845.

Su JG, Morello-Frosch R, Jesdale BM, Kyle AD, Shamasunder B, Jerrett M, 2009. An Index for Assessing Demographic Inequalities in Cumulative Environmental Hazards with Application to Los Angeles, California. Environmental Science & Technology 43, 7626–7634. [PubMed: 19921871]

Vardoulakis S, Giagloglou E, Steinle S, Davis A, Sleeuwenhoek A, Galea KS, Dixon K, Crawford JO, 2020. Indoor Exposure to Selected Air Pollutants in the Home Environment: A Systematic Review. Int J Environ Res Public Health 17.

Wu AH, Wu J, Tseng C, Yang J, Shariff-Marco S, Fruin S, Larson T, Setiawan VW, Masri S, Porcel J, Jain J, Chen TC, Stram DO, Marchand LL, Ritz B, Cheng I, 2020. Association Between Outdoor Air Pollution and Risk of Malignant and Benign Brain Tumors: The Multiethnic Cohort Study. JNCI Cancer Spectr 4, pkz107. [PubMed: 32211584]

Wu J, Laurent O, Li L, Hu J, Kleeman M, 2016. Adverse Reproductive Health Outcomes and Exposure to Gaseous and Particulate-Matter Air Pollution in Pregnant Women. Res Rep Health Eff Inst 2016, 1–58. [PubMed: 29659239]

Wu XM, Basu R, Malig B, Broadwin R, Ebisu K, Gold EB, Qi L, Derby C, Green RS, 2017. Association between gaseous air pollutants and inflammatory, hemostatic and lipid markers in a cohort of midlife women. Environ Int 107, 131–139. [PubMed: 28732305]

Xu Z, Wang W, Liu Q, Li Z, Lei L, Ren L, Deng F, Guo X, Wu S, 2022. Association between gaseous air pollutants and biomarkers of systemic inflammation: A systematic review and meta-analysis. Environ Pollut 292, 118336. [PubMed: 34634403]

Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF, 2007. Systemic effects of smoking. Chest 131, 1557–1566. [PubMed: 17494805]

Yang J, Schupp CW, Harrati A, Clarke CA, Keegan THM, Gomez SL, 2014. Developing an area-based socioeconomic measure from American Community Survey data. Cancer Prevention Institute of California, Fremont, Calfornia.

Yost K, Perkins C, Cohen R, Morris C, Wright W, 2001. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. Cancer Causes Control 12, 703–711. [PubMed: 11562110]

Table 1:

Study characteristics of California Multiethnic Cohort participants by race and ethnicity

	All [a] (n=7,860)	Latino (n=4,445)	African American (n=2,756)	Japanese American (n=528)	White (n=128)
Sex					
Female, n (%)	4,305 (54.8)	2336 (52.6)	1,635 (59.3)	260 (49.2)	74 (57.8)
Male, n (%)	3,555 (45.2)	2109 (47.5)	1,121 (40.7)	268 (50.8)	54 (42.2)
Mean (SD) age at blood draw, years	68 (7.5)	68 (7)	68 (8)	70 (8)	67 (8)
BMI at blood draw, % obese (≥30 kg/m^2)	26	26	30	4	17
Mean (SD) total energy intake at baseline, kcal/day	2,268 (1,195)	2,460 (1,298)	2,029 (1,039)	1,951 (718)	2,064 (891)
Dietary Patterns Alternate Mediterranean Diet Score at baseline, % high score 6–9	23	20	27	23	27
Smoking status at blood draw					
% Current	8	7	11	6	15
% Former	44	42	46	44	48
Mean (SD) smoking pack years at blood draw	7 (13)	6 (12)	9 (14)	9 (15)	14 (19)
Comorbidities at baseline					
% High blood pressure	30	24	40	33	33
% Diabetes	8	11	5	3	6
Nonsteroidal anti-inflammatory drugs at blood draw, % use	31	31	31	31	28
Current estrogen hormone therapy, with or without progesterone at blood draw, % use [b]	21	20	19	28	30

[a] Includes n=3 Native Hawaiian males not included in race-stratified analyses.

[b] Among females only.

Table 2:

Association of exposure to air pollutant measures and circulating levels of C-reactive protein by sex among California Multiethnic Cohort participants

	All			Females			Males			
N	**7,860**			**4,305**			**3,555**			
Mean (SD) CRP, mg/L	**3.8 (4.3)**			**4.4 (4.6)**			**3.1 (3.8)**			
Air Pollutant	**Mean CRP % Change [a]**	**95% CI**	***p* value**	**Mean CRP % Change [a]**	**95% CI**	***p* value**	**Mean CRP % Change [a]**	**95% CI**	***p* value**	***P* heterogeneity by sex**
Twelve-month average exposures [b]										
Satellite-based [c] $PM_{2.5}$ per 10 μg/m^3	4.9%	(−4.8%, 15.6%)	0.34	6.3%	(−6.3%, 20.6%)	0.34	2.0%	(−12.1%, 18.3%)	0.80	0.57
Kriging [d] PM_{10} per 10 μg/m^3	**11.0%**	**(4.2%, 18.2%)**	**<0.01**	**10.3%**	**(1.5%, 19.8%)**	**0.02**	9.2%	(−0.8%, 20.2%)	0.07	0.51
Kriging [d] $PM_{10-2.5}$ per 10 μg/m^3	**12.4%**	**(1.4%, 24.5%)**	**0.03**	13.1%	(−1.7%, 30.2%)	0.09	10.5%	(−5.1%, 28.8%)	0.20	0.56
LUR [e] NO_X per 50 ppb	**10.4%**	**(2.2%, 19.2%)**	**0.01**	**14.3%**	**(3.0%, 26.8%)**	**0.01**	6.7%	(−4.9%, 19.7%)	0.27	0.34
Benzene per 1 ppb	**2.9%**	**(1.1%, 4.6%)**	**<0.01**	1.7%	(−0.7%, 4.1%)	0.17	**3.4%**	**(0.9%, 5.9%)**	**0.01**	0.63
One-month average exposures [b]										
Satellite-based [c] $PM_{2.5}$ per 10 μg/m^3	−2.7%	(−7.4%, 2.2%)	0.27	**−6.4%**	**(−12.0%, −0.4%)**	**0.04**	1.8%	(−5.7%, 9.9%)	0.65	0.09
Kriging [d] PM_{10} per 10 μg/m^3	0.2%	(−2.8%, 3.4%)	0.89	−3.3%	(−7.1%, 0.7%)	0.11	3.5%	(−1.3%, 8.5%)	0.16	0.06
Kriging [d] $PM_{10-2.5}$ per 10 μg/m^3	0.9%	(−3.7%, 5.7%)	0.72	−0.8%	(−6.7%, 5.5%)	0.80	2.6%	(−4.4%, 10.0%)	0.48	0.57
LUR [e] NO_X per 50 ppb	2.5%	(−1.5%, 6.6%)	0.22	3.1%	(−2.3%, 8.7%)	0.26	1.7%	(−3.9%, 7.7%)	0.56	0.72
Benzene per 1 ppb	4.7%	(−1.1%, 10.9%)	0.12	5.3%	(−2.6%, 13.8%)	0.19	3.8%	(−4.5%, 12.9%)	0.38	0.71

[a] Models adjusted for age at blood draw (continuous), sex in overall models (female, male), race and ethnicity (African American, Japanese American, Latino, Native Hawaiian, White), sub study, BMI at blood draw (kg/m^2; underweight, normal, overweight, obese), total energy intake at baseline (continuous, kcal/day), Alternate Mediterranean Diet Score at baseline (0–9, unknown), smoking status at blood draw (never, former, current, unknown), smoking pack years at blood draw (continuous), comorbidities at baseline (none, high blood pressure, diabetes, unknown), NSAID medication use at blood draw (no, yes, unknown), and hormone therapy use at blood draw in female models (never estrogen use, with or without past or current progesterone use; past estrogen use, with or without past progesterone use; current estrogen use alone; current estrogen use with past or present progesterone use; unknown).

[b] Exposure assessment is prior to blood draw.

[c] From spatiotemporal model.

[d] From Kriging interpolation.

[e] From land use regression (LUR) model.

Table 3:

Association of exposure to air pollutant measures and circulating levels of C-reactive protein by race and ethnicity among California Multiethnic Cohort participants

	Latino			African American			Japanese American			White			
N [a]	**4,445**			**2,756**			**528**			**128**			
Mean (SD) CRP, mg/L	**3.8 (4.3)**			**4.1 (4.5)**			**1.9 (2.8)**			**4.7 (5.3)**			
Air Pollutant	**Mean CRP % Change** [b]	**95% CI**	***p* value**	**Mean CRP % Change** [b]	**95% CI**	***p* value**	**Mean CRP % Change** [b]	**95% CI**	***p* value**	**Mean CRP % Change** [b]	**95% CI**	***p* value**	***p* heterogeneity by race and ethnicity**
Twelve-month average exposures [c]													
Satellite-based [d] $PM_{2.5}$ per 10 μg/m^3	−1.0%	(−13.1%, 12.9%)	0.88	0.5%	(−14.7%, 18.4%)	0.95	49.2%	(−2.9%, 129.3%)	0.07	91.4%	(−0.4%, 267.6%)	0.05	0.07
Kriging [e] PM_{10} per 10 μg/m^3	**13.0%**	**(4.2%, 22.6%)**	**<0.01**	5.0%	(−6.0%, 17.2%)	0.39	37.8%	(−0.6%, 91.0%)	0.05	10.3%	(−28.4%, 70.2%)	0.66	0.33
Kriging [e] $PM_{10-2.5}$ per 10 μg/m^3	**26.5%**	**(10.8%, 44.4%)**	**<0.01**	−3.2%	(−19.2%, 16.1%)	0.73	7.9%	(−37.9%, 87.3%)	0.79	−20.4%	(−66.3%, 88.2%)	0.61	0.10
LUR [f] NO_X per 50 ppb	8.9%	(−0.8%, 19.6%)	0.07	8.8%	(−6.8%, 26.9%)	0.29	12.9%	(−18.2%, 55.9%)	0.46	31.0%	(−26.6%, 133.8%)	0.36	0.94
Benzene per 1 ppb	**3.2%**	**(1.0%, 5.4%)**	**<0.01**	2.6%	(−0.6%, 5.9%)	0.11	5.4%	(−3.9%, 15.6%)	0.26	0.9%	(−6.6%, 9.0%)	0.82	0.89
One-month average exposures [c]													
Satellite-based [d] $PM_{2.5}$ per 10 μg/m^3	−1.4%	(−7.2%, 4.8%)	0.65	−6.1%	(−14.1%, 2.6%)	0.16	−6.0%	(−24.4%, 17.0%)	0.58	32.3%	(−11.8%, 98.3%)	0.18	0.38
Kriging [e] PM_{10} per 10 μg/m^3	0.5%	(−3.2%, 4.4%)	0.79	0.2%	(−5.5%, 6.3%)	0.93	−1.3%	(−14.7%, 14.3%)	0.86	−13.5%	(−31.7%, 9.4%)	0.23	0.69
Kriging [e] $PM_{10-2.5}$ per 10 μg/m^3	1.8%	(−3.9%, 7.9%)	0.54	0.5%	(−7.5%, 9.3%)	0.90	−1.6%	(−22.6%, 25.2%)	0.90	−27.2%	(−50.4%, 6.9%)	0.11	0.45
LUR [f] NO_X per 50 ppb	3.6%	(−1.2%, 8.7%)	0.15	0.1%	(−7.1%, 7.7%)	0.99	3.3%	(−13.2%, 22.9%)	0.72	12.5%	(−20.6%, 59.5%)	0.51	0.82

Benzene per 1 ppb	6.8%	(−1.0%, 15.2%)	0.09	1.1%	(−8.1%, 11.4%)	0.82	10.3%	(−15.2%, 43.3%)	0.47	21.0%	(−21.7%, 86.9%)	0.39	0.70

[a] Excludes n=3 Native Hawaiian participants included in overall analyses.

[b] Models adjusted for age at blood draw (continuous), sex (female, male), sub study, BMI at blood draw (kg/m^2; underweight, normal, overweight, obese), total energy intake at baseline (continuous, kcal/day), Alternate Mediterranean Diet Score at baseline (0–9, unknown), smoking status at blood draw (never, former, current, unknown), smoking pack years at blood draw (continuous), comorbidities at baseline (none, high blood pressure, diabetes, unknown), and NSAID medication use at blood draw (no, yes, unknown).

[c] Exposure assessment is prior to blood draw.

[d] From spatiotemporal model.

[e] From Kriging interpolation.

[f] From land use regression (LUR) model.

Table 4:

Association of exposure to air pollutant measures and circulating levels of C-reactive protein by neighborhood socioeconomic status (nSES) at blood draw among California Multiethnic Cohort participants

	Low nSES (Quintiles 1–3)			High nSES (Quintiles 4–5)			
N [a]	**5,338**			**2,521**			
Mean (SD) CRP, mg/L	**4.0 (4.4)**			**3.3 (4.0)**			
Air Pollutant	**Mean CRP % Change** [b]	**95% CI**	***p* value**	**Mean CRP % Change** [b]	**95% CI**	***p* value**	***p* heterogeneity by nSES**
Twelve-month average exposures [c]							
Satellite-based [d] $PM_{2.5}$ per 10 μg/m^3	7.5%	(−5.4%, 22%)	0.27	−1.5%	(−16.0%, 15.5%)	0.85	0.39
Kriging [e] PM_{10} per 10 μg/m^3	**11.6%**	**(3.2%, 20.8%)**	**0.01**	9.1%	(−1.8%, 21.3%)	0.11	0.73
Kriging [e] $PM_{10-2.5}$ per 10 μg/m^3	**17.7%**	**(3.3%, 34.2%)**	**0.01**	5.7%	(−10.7%, 25.0%)	0.52	0.31
LUR [f] NO_X per 50 ppb	**11.0%**	**(0.9%, 22.1%)**	**0.03**	2.8%	(7.8%, 19.7%)	0.73	0.39
Benzene per 1 ppb	**3.1%**	**(1.0%, 5.1%)**	**<0.01**	1.8%	(−1.4%, 5.0%)	0.28	0.49
One-month average exposures [c]							
Satellite-based [d] $PM_{2.5}$ per 10 μg/m^3	−0.4%	(−6.1%, 5.6%)	0.88	−8.0%	(−15.9%, 0.5%)	0.06	0.13
Kriging [e] PM_{10} per 10 μg/m^3	0.9%	(−2.8%, 4.8%)	0.63	−1.1%	(−6.5%, 4.6%)	0.69	0.54
Kriging [e] $PM_{10-2.5}$ per 10 μg/m^3	2.2%	(−3.5%, 8.1%)	0.46	−0.4%	(−8.3%, 8.2%)	0.93	0.62
LUR [f] NO_X per 50 ppb	3.1%	(−1.4%, 7.9%)	0.18	−2.3%	(−10.0%, 6.0%)	0.57	0.24
Benzene per 1 ppb	5.9%	(−1.0%, 13.4%)	0.10	1.8%	(−8.4%, 13.1%)	0.74	0.52

[a] Excludes n=1 participants with unknown nSES.

[b] Models adjusted for age at blood draw (continuous), sex (female, male), race and ethnicity (African American, Japanese American, Latino, Native Hawaiian, White), sub study, BMI at blood draw (kg/m^2; underweight, normal, overweight, obese), total energy intake at baseline (continuous, kcal/day), Alternate Mediterranean Diet Score at baseline (0–9, unknown), smoking status at blood draw (never, former, current, unknown), smoking pack years at blood draw (continuous), comorbidities at baseline (none, high blood pressure, diabetes, unknown), and NSAID medication use at blood draw (no, yes, unknown).

[c] Exposure assessment is prior to blood draw.

[d] From spatiotemporal model.

[e] From Kriging interpolation.

$f_{\text{From land use regression (LUR) model}}$