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Coarse Particulate Matter and Markers of Inflammation and Coagulation in the Multi-Ethnic Study of Atherosclerosis (MESA) Population: A Repeat Measures Analysis

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Background: In contrast to fine particles, less is known of the inflammatory and coagulation impacts of coarse particulate matter ($PM_{10–2.5}$, particulate matter with aerodynamic diameter $\leq$10 μm and >2.5 μm). Toxicological research suggests that these pathways might be important processes by which $PM_{10–2.5}$ impacts health, but there are relatively few epidemiological studies due to a lack of a national $PM_{10–2.5}$ monitoring network.

Objectives: We used new spatiotemporal exposure models to examine associations of both 1-y and 1-month average $PM_{10–2.5}$ concentrations with markers of inflammation and coagulation.

Methods: We leveraged data from 7,071 Multi-Ethnic Study of Atherosclerosis and ancillary study participants 45–84 y of age who had repeated plasma measures of inflammatory and coagulation biomarkers. We estimated $PM_{10–2.5}$ at participant addresses 1 y and 1 month before each of up to four exams (2000–2012) using spatiotemporal models that incorporated satellite, regulatory monitoring, and local geographic data and accounted for spatial correlation. We used random effects models to estimate associations with interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen, and D-dimer, controlling for potential confounders.

Results: Increases in $PM_{10–2.5}$ were not associated with greater levels of inflammation or coagulation. A 10-$\mu g/m^3$ increase in annual average $PM_{10–2.5}$ was associated with a 2.5% decrease in CRP [95% confidence interval (CI): −5.5, 0.6]. We saw no association between annual average $PM_{10–2.5}$ and the other markers (IL-6: −0.7%, 95% CI: −2.6, 1.2; fibrinogen: −0.3%, 95% CI: −0.9, 0.3; D-dimer: −0.2%, 95% CI: −2.6, 2.4). Associations consistently showed that a 10-$\mu g/m^3$ increase in 1-month average $PM_{10–2.5}$ was associated with reduced inflammation and coagulation, though none were distinguishable from no association (IL-6: −1.2%, 95% CI: −3.0 , 0.5; CRP: −2.5%, 95% CI: −5.3, 0.4; fibrinogen: −0.4%, 95% CI: −1.0, 0.1; D-dimer: −2.0%, 95% CI: −4.3, 0.3).

Discussion: We found no evidence that $PM_{10–2.5}$ is associated with higher inflammation or coagulation levels. More research is needed to determine whether the inflammation and coagulation pathways are as important in explaining observed $PM_{10–2.5}$ health impacts in humans as they have been shown to be in toxicology studies or whether $PM_{10–2.5}$ might impact human health through alternative biological mechanisms. https://doi.org/10.1289/EHP12972

Introduction

Fine particulate matter ($PM_{2.5}$, aerodynamic diameter $\leq$2.5 μm) has been ranked as one of the top 10 risk factors for morbidity and mortality.[1] Even at low levels of $PM_{2.5}$ currently observed in the United States (US), it is estimated that over 80,000 lives are lost prematurely each year in the United States.[2] Mechanistically, inflammation, which can enhance coagulation activity, has been proposed as a key pathway by which $PM_{2.5}$ can impact health.[3–5] Inflammation and coagulation are contributors to chronic disease processes such as atherosclerosis[6] and its downstream sequelae such as myocardial infarctions and strokes.[3,5] Inflammation and coagulation also contribute to respiratory diseases such as chronic obstructive pulmonary disease[7] and asthma.[8]

Inflammation and coagulation are important biological mechanisms for the observed associations between these health effects and particulate matter (PM) of all sizes. However, to date, most research on the impacts of PM has focused on the smaller size fraction of $PM_{2.5}$.[9–27] Although relatively few epidemiological studies have evaluated associations of inflammation and coagulation with larger particles such as PM_{10} (PM with aerodynamic diameter $\leq$10 μm)[24–28] and $PM_{10–2.5}$ (aerodynamic diameter $\leq$10 μm and >2.5 μm),[13,17,19,27,29–32] *in vitro*,[33,34] *in vivo* inhalation,[35] and *in vivo* intratracheal instillation[36,37] toxicological research has found evidence that $PM_{10–2.5}$ exposures likely initiate inflammatory pathways. This gap in the epidemiological evidence on the inflammatory effects of $PM_{10–2.5}$ is noteworthy because the US Environmental Protection Agency (EPA) has determined that the evidence is suggestive of—but not sufficient to infer—a causal association between $PM_{10–2.5}$ and incident cardiovascular disease.[38–49] Indeed, the EPA's conclusion notes that among other factors, such as the potential for copollutant confounding and possible exposure measurement error, the gaps in knowledge regarding the proposed mechanistic pathways, especially for long-term exposures, contribute to the uncertainty of the EPA's determination.[4]

A major challenge that has contributed to the small body of literature on the health impacts of $PM_{10–2.5}$ is the limited spatial-extent of measurement data available from regulatory monitors to

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estimate $PM_{10–2.5}$ exposure for use in epidemiological studies.[47] This limitation has often compelled researchers to develop alternative approaches to estimate $PM_{10–2.5}$ where study participants live. For example, one of only a few studies of the relationship between $PM_{10–2.5}$ and inflammation or coagulation[29] used measurements that were collected during a spatially intensive field substudy within the Multi-Ethnic Study of Atherosclerosis (MESA) to generate an exposure prediction model based on a land-use regression with spatial correlation structure.[50] Those predictions were, however, only available for three of the six MESA sites and, perhaps as a result, the findings were uncertain and consistent with a wide range of effects. Another study used $PM_{10–2.5}$ estimates derived from a measurement campaign and land-use regression for participants in the European Study of Cohorts for Air Pollution Effects (ESCAPE) project[51] and found mixed associations between $PM_{10–2.5}$ and inflammation and coagulation blood markers.[13] A more recent study used $PM_{10–2.5}$ estimates derived from a national spatiotemporal model and found positive associations with $PM_{10–2.5}$ and interleukin-6 (IL-6) and C-reactive protein (CRP) in a cohort of men, but not women.[27]

In the analysis presented herein, we aimed to extend and validate the work of Adar et al.[29] by using new spatiotemporal models for $PM_{10–2.5}$ derived using regulatory monitor data and satellite measurements for all six MESA sites.[52] Specifically, we used these $PM_{10–2.5}$ predictions to assess the epidemiological associations of 1-y average $PM_{10–2.5}$ concentrations with two markers of inflammation (IL-6 and CRP) and two markers of coagulation (fibrinogen and D-dimer) in the full MESA cohort across multiple exams. We also leveraged the temporal resolution of the satellite data to newly evaluate associations with 1-month average $PM_{10–2.5}$ concentrations.

Methods

Study Population

We conducted this analysis using data from participants of MESA, including new recruits of the MESA Air Pollution ancillary study (MESA Air). In brief, MESA recruited 6,814 White, Black, Hispanic, and Chinese women and men between July 2000 and August 2002 who were 45–84 y of age and free from clinical cardiovascular disease.[53] Participants were recruited from Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota. Using the same inclusion criteria, the MESA Air ancillary study recruited 257 additional participants in 2006–2007 from Rockland County, New York, as well as Los Angeles and Riverside Counties, California.[54]

Baseline exams took place from July 2000 to August 2002 for the main MESA cohort. There were then follow-up exams that occurred between 2002 and 2011 (exam 2: September 2002–February 2004; exam 3: March 2004–September 2005; exam 4: September 2005–May 2007; exam 5: April 2010–December 2011). Baseline exams took place from February 2006 to May 2007 for the MESA Air new recruits, with a follow-up exam between March 2011 and February 2012. Institutional review board approval was granted at each study site and the coordinating center (i.e., Wake Forest University School of Medicine, University of Minnesota, Northwestern University, Columbia University, Johns Hopkins University, University of California, Los Angeles, and University of Washington). Written informed consent was obtained from all participants.

Inflammation and Coagulation Biomarkers

Fasting blood samples were collected from participants at their baseline visit and analyzed at the University of Vermont Laboratory for Clinical Biochemistry Research.[53,55] Our analysis considered four biomarkers (i.e., IL-6, CRP, fibrinogen, and D-dimer), which were determined *a priori* based on previous research showing links with air pollution and their hypothesized roles in inflammatory and coagulation processes.[4,9,13,19,25,29,56] IL-6 was measured in plasma using ultrasensitive enzyme-linked immunosorbent assay (Quantikine HS Human IL-6 Immunoassay; R&D Systems) with a lower limit of detection (LOD) of <0.094 pg/mL [coefficient of variation (CV): 6.3%]. CRP was measured in plasma with a particle enhanced immunonephelometric assay using the BNII nephelometer (N High Sensitivity CRP; Dade Behring, Inc.) and had an LOD of 0.158 μg/mL. CRP intra-assay CVs ranged from 2.3% to 4.4%, and interassay CVs ranged from 2.1% to 5.7%. Fibrinogen was measured in plasma using the BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring, Inc.) and had an LOD of 15.4375 mg/dL. Fibrinogen intra-assay and interassay CVs were 2.7% and 2.6%, respectively. D-dimer was measured in plasma using an immuno-turbidimetric method on the Sta-R analyzer (Liatest D-DI; Diagnostica Stago) (analytical CV: 8%) and had an LOD of 0.01 μg/mL.

Blood samples were similarly taken and analyzed at the same laboratory in subsequent exams among subsets of participants through three ancillary studies with testing for IL-6, CRP, and fibrinogen in 1,968 participants at either exam 2 or 3, IL-6 and D-dimer levels in 1,002 participants at either exam 3 or exam 4, IL-6, CRP, fibrinogen, and D-dimer in 1,303 participants at exam 5, and CRP, fibrinogen, and D-dimer in ∼720 participants at exams 4 and exam 5 (Table S1). Changes in sample sizes across exams and biomarkers are due to the differing priorities of the MESA ancillary studies that collected the data.

Air Pollution

$PM_{10–2.5}$ concentration predictions are described in Pedde et al.[52] Briefly, we used measurements of aerosol optical depth (AOD) from the National Aeronautics and Space Administration (NASA) Terra satellite along with land-use regression and spatial smoothing to estimate $PM_{10–2.5}$ within the six areas where MESA participants resided. In this multistage approach, we first calibrated AOD (1-km^2 resolution) with daily EPA measurements of PM_{10} and $PM_{2.5}$ using area-specific mixed-modeling with land-use regression. Spatial and temporal predictors included elevation, land use, vegetation, planetary boundary layer, population, distance to roads, rails, large water bodies, and meteorological terms (air pressure, air temperature, evaporation, precipitable water, specific humidity, u-wind, and v-wind). We then used spatial smoothing in generalized additive mixed effects models to predict daily PM_{10} and $PM_{2.5}$ when AOD was missing. Finally, we estimated daily $PM_{10–2.5}$ by taking the difference of spatially matched PM_{10} and $PM_{2.5}$ daily predictions. Our $PM_{10–2.5}$ predictions were well correlated with measured concentrations estimated from collocated $PM_{2.5}$ and PM_{10} sites, with mean spatial CV R^2 across all six sites of 0.7, although CV R^2 were only 0.3 and 0.5 in Winston-Salem, North Carolina, and Chicago, respectively.[52] The mean temporal CV R^2 as estimated at the daily time scale was lower at 0.3 (ranging from 0.2 in Baltimore to 0.4 in Los Angeles).[52]

To understand the role of long-term exposure to $PM_{10–2.5}$ on health, we assigned 1-y average $PM_{10–2.5}$ concentrations for each participant based on their residential history and exam dates using R statistical software (version 3.6.1; R Development Core Team). For the MESA baseline exam (2000–2002), we based the 1-y average on 2001 because AOD was first collected on the Terra satellite in late February 2000. We estimated $PM_{10–2.5}$ 1-y average concentrations for the subsequent exam periods based on the exact date of the exam. We also assigned 1-month average $PM_{10–2.5}$ concentrations for each participant based on their residential history and exam dates to reflect shorter-term exposures.

Covariates

We used data—collected via a technician-administered questionnaire—on sex, race/ethnicity, and education at baseline as well as time-varying information on age, employment status, family income, passive and active exposure to cigarette smoke, current alcohol usage, and weekly physical activity level, as well as recent infections (urinary or sinus in the past 2 wk) recorded at each exam. Baseline and follow-up exam home addresses were linked to 2000 US Census tract data to determine neighborhood-level population density and to socioeconomic status (SES) measures derived from the 2000 US Census and the 2005–2009 and 2007–2011 American Community Surveys.[57] Based on the results of principal components analysis (PCA), the following variables were included in the summary neighborhood-level SES measure: median household income, percentage with household income <USD $50,000, percentage interest/dividend/rental income, median value of owner-occupied homes, percentage with at least a high school degree, percentage with at least a Bachelor's degree, and percentage with managerial/professional occupations.[57] For other environmental characteristics, we gathered meteorological data (temperature and relative humidity) from the National Oceanic and Atmospheric Administration's (NOAA) National Climatic Data Center and Normalized Difference Vegetation Index (NDVI) values from the NASA Terra satellite. We also used predictions of the copollutants, $PM_{2.5}$ and nitrogen oxides (NO_X), from the MESA Air spatiotemporal model.[58,59]

Statistical Analyses

Using exam 1 data for the original MESA cohort and data for the MESA Air new recruits at the time of exam 4, we computed baseline descriptive statistics for all participants, as well as by quartile of individual baseline estimated $PM_{10-2.5}$ concentrations. Quartiles were determined after first subtracting baseline mean site $PM_{10-2.5}$ concentrations from baseline estimated individual $PM_{10-2.5}$ concentrations given the differences in $PM_{10-2.5}$ concentrations across study sites. Then we used mixed effects models with random intercepts to account for within-person clustering in the repeated measurements to estimate the associations between $PM_{10-2.5}$ concentrations and the four biomarkers. Prior to modeling, all blood markers were log transformed to reduce skewness. For each blood marker analysis, we also restricted the analyses to participants with complete information on that outcome, exposures, and key covariates, within an exam. Models were staged to assess the sensitivity of results to potential confounders, including factors that influence health through access to care, disinvestment, or biological processes and/or by factors that influence air pollution. In the minimally adjusted model, we adjusted for age, sex, race/ethnicity (specified as non-Hispanic White, non-Hispanic Black, Hispanic, or Chinese from self-report), study site (Baltimore County; Chicago; Forsyth County; Los Angeles County; New York, New York; and St. Paul, as well as Rockland County, New York County, and Riverside County), and calendar time (using splines with 48 degrees of freedom (df): 4 df per year). We adjusted for race/ethnicity in our models because it can be correlated with air pollution levels and related to health due to systemic racism in the United States and resulting racial segregation and disinvestment in minoritized communities. Our second model additionally adjusted for characteristics likely to reflect SES or place including education at baseline (high school or less; some college; technical school certificate or associates/bachelors/graduate degree), employment status (working or not at time of exam), family income (average across all exams of the midpoint of 13 income bands ranging from USD $3,000 to USD $25,000 wide), neighborhood SES and population density at the home address at the time of each exam, meteorology (temperature and relative humidity on the day of the exam, modeled as a spline with 6 df per year), and vegetation levels (the median, 25th, and 75th percentiles of monthly levels within ~1 km of a participant's address(es) 1 y or 1 month prior to each exam). We also adjusted for aspects of health behavior at each exam including active and passive smoke exposure (never smoker/no passive smoke, never smoker/passive smoke, former smoker/no passive smoke, former smoker/passive smoke, current smoker), alcohol usage (binary), and physical activity (continuous; minutes of intentional exercise per week). Finally, our third and *a priori* defined primary model also adjusted for $PM_{2.5}$ and NO_X concentrations (averaged over the 1 y or 1 month prior to each exam). We reported all associations per 10 $\mu g/m^3$ along with their 95% confidence intervals (CIs).

In sensitivity analyses, we included further adjustment for recent infection. We also assessed the exclusion of health behaviors (i.e., smoke exposure, alcohol usage, and physical activity level) from our primary model because these factors might plausibly be a downstream consequence of air pollution exposure if people modified their behaviors based on health changes. We assessed the sensitivity of our primary model results to exclusion of extreme outlier values of the blood markers (identified by plotting the distribution of each blood marker and using the cut points from Hajat et al. 2015: IL-6 ≥10 pg/mL, CRP ≥30 mg/L, fibrinogen ≥1,000 mg/dL, and D-dimer ≥18 μg/mL) and, separately, to the exclusion of exam 1 measures for the original MESA cohort given the small temporal misalignment between our $PM_{10-2.5}$ predicted concentrations and the dates of exam 1. We also restricted our analysis to only participants in the Chicago, St. Paul, and Winston-Salem sites at the first exam to allow for a better comparison of our results with those from previous work in this cohort.[29] Separately, we excluded participants from Winston-Salem because the predictive performance of our $PM_{10-2.5}$ exposure model was less robust at that site.[52] Finally, because older adults and people in proinflammatory states may be more susceptible to the health effects of air pollution[3,60] and the chemical components of $PM_{10-2.5}$ may differ by study site,[29,50] we evaluated the potential for effect modification by age (<54, 54–64, 64–74, >74 y at time of exam 1), baseline level of each blood marker (<75th percentile vs. ≥75th percentile), and study site using interaction terms between pollution and effect modifier in our primary models. Statistical significance was set at $p < 0.05$.

Data processing was done in SAS 9.4 (SAS Institute Inc.), whereas all statistical modeling was performed using R software (version 3.3.2).

Results

Table 1 shows summary statistics at baseline for the covariates and blood measurements used in our analyses. Across the 6,377 participants with complete $PM_{10-2.5}$ exposure and covariate information, the mean age at baseline was 62 y +10, and 53% of the participants were female. Overall, 39% of participants were non-Hispanic White, 27% were non-Hispanic Black, 22% were Hispanic, and 12% were Chinese. Mean $PM_{10-2.5}$ concentrations in the year before baseline were 16.9 $\mu g/m^3$ (+13.5 $\mu g/m^3$) (Figure 1; Table S5). Concentrations were similar across time (Figures S1 and S2; Tables S6 and S7), though there were notable differences across study site (Figure 1). For example, mean estimated participant-level $PM_{10-2.5}$ concentrations were 3.7 $\mu g/m^3$ in Winston-Salem and 3.9 $\mu g/m^3$ in Baltimore, whereas mean concentrations reached 41.4 $\mu g/m^3$ in Rockland County. Correlations between baseline $PM_{10-2.5}$ with $PM_{2.5}$ and NO_X were 0.19 and 0.21, respectively (Table S2). Although participants who met our inclusion criteria differed from excluded individuals in terms of baseline $PM_{10-2.5}$ concentrations,

Table 1. Summary statistics [mean ± SD, *n* (percent), or geometric mean GSD] by quartile of baseline annual average $PM_{10-2.5}$ concentration and overall in the Multi-Ethnic Study of Atherosclerosis (MESA) and MESA Air Pollution (MESA Air) cohorts (2000–2012).

Characteristic	Number missing[a]	All[b]	Quartile 1[b] (−32.9, −4.0 μg/m³)	Quartile 2[b] (−4.0, −0.3 μg/m³)	Quartile 3[b] (−0.3, 3.1 μg/m³)	Quartile 4[b] (3.1, 35.3 μg/m³)
Number	—	6,377	1,594	1,582	1,642	1,559
Age (y)	0	62 ± 10	62 ± 10	62 ± 10	62 ± 10	63 ± 10
Sex (%)	0	—	—	—	—	—
Female	—	3,394 (53.2)	836 (52.5)	838 (53.0)	895 (54.5)	825 (52.9)
Male	—	2,983 (46.8)	758 (47.6)	744 (47.0)	747 (45.5)	734 (47.1)
Race/ethnicity (%)	0	—	—	—	—	—
White	—	2,482 (38.9)	371 (23.3)	587 (37.1)	644 (39.2)	880 (56.5)
Chinese	—	744 (11.7)	263 (16.5)	187 (11.8)	159 (9.7)	135 (8.7)
Black	—	1,732 (27.2)	637 (40.0)	422 (26.7)	448 (27.3)	225 (14.4)
Hispanic	—	1,419 (22.3)	323 (20.3)	386 (24.4)	391 (23.8)	319 (20.5)
Study site (%)	0	—	—	—	—	—
Baltimore	—	952 (14.9)	213 (13.4)	215 (13.6)	316 (19.2)	208 (13.3)
Chicago	—	1,101 (17.3)	485 (30.4)	67 (4.2)	212 (12.9)	337 (21.6)
Los Angeles	—	1,373 (21.5)	345 (21.6)	328 (20.7)	219 (13.3)	481 (30.9)
New York	—	1,109 (17.4)	347 (21.8)	327 (20.7)	184 (11.2)	251 (16.1)
St. Paul	—	885 (13.9)	21 (1.3)	402 (25.4)	375 (22.8)	87 (5.6)
Winston-Salem	—	957 (15.0)	183 (11.5)	243 (15.4)	336 (20.5)	195 (12.5)
Average income (%)	69	—	—	—	—	—
<USD $30,000	—	2,359 (37.0)	617 (38.7)	629 (39.8)	649 (39.5)	464 (29.8)
USD $30,000–$50,000	—	1,420 (22.3)	353 (22.2)	382 (24.2)	386 (23.5)	299 (19.2)
USD $50,000–$75,000	—	1,149 (18.0)	273 (17.1)	272 (17.2)	326 (19.9)	278 (17.8)
>USD $75,000	—	1,449 (22.7)	351 (22.0)	299 (18.9)	281 (17.1)	518 (33.2)
Employed (%)	24	—	—	—	—	—
Yes	—	3,442 (54.0)	846 (53.1)	836 (52.8)	897 (54.6)	863 (55.4)
No	—	2,935 (46.0)	748 (46.9)	746 (47.2)	745 (45.4)	696 (44.6)
Education level (%)	23	—	—	—	—	—
High school or less	—	2,287 (35.9)	592 (37.1)	604 (38.2)	657 (40.0)	434 (27.8)
High school and some college	—	1,047 (16.4)	246 (15.4)	257 (16.3)	266 (16.2)	278 (17.8)
> College degree	—	3,043 (47.7)	756 (47.4)	721 (45.6)	719 (43.8)	847 (54.3)
Active and passive smoking status (%)	204	—	—	—	—	—
Never smoker/no passive smoke	—	2,060 (32.3)	538 (33.8)	521 (32.9)	500 (30.5)	501 (32.1)
Never smoker/passive smoke	—	1,145 (18.0)	287 (18.0)	290 (18.3)	300 (18.3)	268 (17.2)
Former smoker/no passive smoke	—	1,286 (20.2)	296 (18.6)	279 (17.6)	335 (20.4)	376 (24.1)
Former smoker/passive smoke	—	1,066 (16.7)	264 (16.6)	277 (17.5)	280 (17.1)	245 (15.7)
Current smoker	—	820 (12.9)	209 (13.1)	215 (13.6)	227 (13.8)	169 (10.8)
Current alcohol use (%)	50	—	—	—	—	—
Yes	—	3,528 (55.3)	845 (53.0)	866 (54.7)	881 (53.7)	936 (60.0)
No	—	2,849 (44.7)	749 (47.0)	716 (45.3)	761 (46.4)	623 (40.0)
Physical activity (MET-Min/wk)	19	1,589 ± 2,354	1,529 ± 2,367	1,572 ± 2,503	1,545 ± 2,286	1,714 ± 2,252
Recent infection (%)	0	—	—	—	—	—
Yes	—	615 (9.6)	172 (10.8)	138 (8.7)	166 (10.1)	139 (8.9)
No	—	5,762 (90.4)	1,422 (89.2)	1,444 (91.3)	1,476 (89.9)	1,420 (91.1)
Neighborhood SES (unitless)	76	−0.3 ± 1.4	−0.2 ± 1.3	−0.05 ± 1.2	0.01 ± 1.1	−0.9 ± 1.6
Population density (persons per square kilometer)	74	10,459 ± 17,001	10,314 ± 14,085	10,840 ± 18,665	9,137 ± 17,481	11,615 ± 17,359
Temperature (°C)	57	12.9 ± 9.2	13.3 ± 8.9	13 ± 9.1	11.5 ± 10	13.8 ± 8.4
Relative humidity (%)	57	68.2 ± 15.3	68.2 ± 15.1	67.6 ± 15.2	68.6 ± 15.2	68.4 ± 15.9
25th Percentile NDVI (unitless)	148	0.30 ± 0.11	0.30 ± 0.11	0.30 ± 0.11	0.30 ± 0.10	0.29 ± 0.12
50th Percentile NDVI (unitless)	148	0.41 ± 0.15	0.41 ± 0.15	0.42 ± 0.14	0.43 ± 0.14	0.38 ± 0.16
75th Percentile NDVI (unitless)	148	0.47 ± 0.16	0.45 ± 0.16	0.49 ± 0.16	0.49 ± 0.15	0.43 ± 0.18
$PM_{2.5}$ (μg/m³)	293	16.5 ± 3.5	16.9 ± 3.2	16.1 ± 3.8	15.9 ± 3.2	17 ± 3.5
NO_X (ppm)	203	49.8 ± 26.9	55.5 ± 27.3	49.4 ± 29	45.6 ± 26.2	49 ± 23.7
Blood markers						
IL-6 (pg/mL)	454	1.5 (1.2)	1.5 (1.1)	1.6 (1.2)	1.6 (1.3)	1.4 (1.1)
IL-6 (geometric mean)	454	1.2 (1.9)	1.2 (2.0)	1.3 (1.9)	1.3 (2.0)	1.2 (1.9)
CRP (mg/L)	169	3.8 (5.8)	3.9 (6.1)	3.7 (5.1)	4.1 (6.5)	3.5 (5.4)
CRP (geometric mean)	169	2.0 (3.1)	2.0 (3.1)	2.0 (3.0)	2.1 (3.1)	1.8 (3.1)
Fibrinogen (mg/dl)	48	348.9 (75.1)	348.7 (74.6)	352.6 (74.7)	346.5 (75.1)	347.9 (75.8)
Fibrinogen (geometric mean)	48	341.2 (1.2)	341.1 (1.2)	345 (1.2)	338.7 (1.2)	340.1 (1.2)
D-dimer (μg/mL)	52	0.4 (0.6)	0.4 (0.8)	0.4 (0.5)	0.4 (0.6)	0.3 (0.5)
D-dimer (geometric mean)	52	0.2 (2.5)	0.2 (2.5)	0.2 (2.5)	0.2 (2.5)	0.2 (2.5)

Note: Given the differences in $PM_{10-2.5}$ concentrations across study sites, quartile thresholds for this table were determined after first subtracting baseline mean site $PM_{10-2.5}$ concentrations from baseline estimated individual $PM_{10-2.5}$ concentrations. —, no data; CRP, C-reactive protein; GSD, geometric standard deviation; IL-6, interleukin-6; MET, metabolic equivalent; NDVI, normalized difference vegetation index; NO_X, nitrogen oxides; $PM_{10-2.5}$, coarse particulate matter of aerodynamic diameter ≤10 μm and >2.5 μm; $PM_{2.5}$, fine particulate matter of aerodynamic diameter <2.5 μm; SD, standard deviation; SES, socioeconomic status.

[a]This column shows the number of missing observations from the 7,071 total participants ($n = 6{,}814$ from the original MESA cohort at exam 1 and $n = 257$ MESA Air new recruits at the time of exam 4).

[b]The "All" category and each quantile-specific column represent participants from the original MESA cohort ($n = 6{,}814$) at exam 1 and the MESA Air new recruits ($n = 257$) at the time of exam 4 who have complete $PM_{10-2.5}$ prediction and covariate data ($n = 6{,}377$).

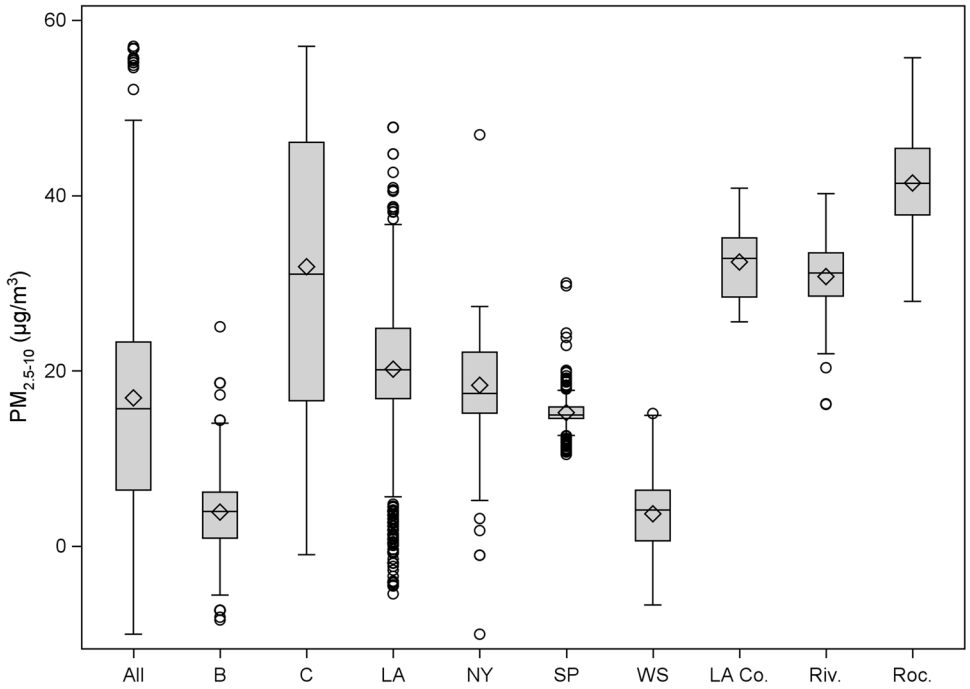

Figure 1. Distribution of individual-level estimates of $PM_{10–2.5}$ concentrations at participant addresses 1-y prior to baseline in the Multi-Ethnic Study of Atherosclerosis (MESA) and MESA Air Pollution (MESA Air) cohorts (2000–2012). See Table S5 for corresponding numeric data. Data are for participants from the original MESA cohort ($n = 6{,}814$) at exam 1 and the MESA Air new recruits ($n = 257$) at the time of exam 4 who have complete exposure and covariate data ($n = 6{,}377$). Boxes span from the 25th to the 75th percentile, horizontal bars represent the median, diamonds represent the mean, whiskers extend to the highest observation within 1.5 times the length of the interquartile range above the 75th percentile and to the lowest observation within 1.5 times the length of the interquartile range below the 25th percentile, and outliers are represented as points. $PM_{10–2.5}$, coarse particulate matter of aerodynamic diameter ≤ 10 µm and >2.5 µm. Note: All, all study sites; B, Baltimore; C, Chicago; LA, Los Angeles; NY, New York; SP, St. Paul; WS, Winston-Salem; LA Co., MESA Air new recruits Los Angeles County; Riv., MESA Air new recruits Riverside CA; Roc., MESA Air new recruits Rockland NY.

race/ethnicity, and site, markers of inflammation and coagulation were very similar across these two sets of participants (Table S3).

Using our primary model specification, we generally saw no association between 1-y average $PM_{10–2.5}$ concentrations and markers of inflammation and coagulation. The exception was CRP, which showed that increases in $PM_{10–2.5}$ were associated with lower levels of CRP, though this result was not distinguishable from no association (Table 2). The size of the associations varied by outcome: A 10-$\mu g/m^3$ increase in the 1-y average $PM_{10–2.5}$ was associated with a 0.7% decrease in IL-6 (95% CI: −2.6, 1.2), 2.5% decrease in CRP (95% CI: −5.5, 0.6), 0.3% decrease in fibrinogen (95% CI: −0.9, 0.3), and 0.2% decrease in D-dimer (95% CI: −2.6, 2.4). The 1-month average concentration results consistently showed that $PM_{10–2.5}$ was associated with reduced inflammation and coagulation, though none were distinguishable from no association. A 10-$\mu g/m^3$ increase in 1-month average $PM_{10–2.5}$ was associated with a 1.2% decrease in IL-6 (95% CI: −3.0, 0.5), 2.5% decrease in CRP (95% CI: −5.3, 0.4), 0.4% decrease in fibrinogen (95% CI: −1.0, 0.1), and 2.0% decrease in D-dimer (95% CI: −4.3, 0.3). These results were thus largely unsupportive of the hypothesis that increases in $PM_{10–2.5}$ are associated with increased inflammation and coagulation.

The results from the main model for 1-y and 1-month average $PM_{10–2.5}$ concentrations were largely unchanged with additional adjustment for recent infection, elimination of adjustment for health behaviors, exclusion of observations with outlier values of the blood measures, or exclusion of participants from Winston-Salem (Table S4). Excluding measurements from exam 1 changed the direction of all annual-average associations and with two of the blood markers in the 1-month exposure analyses, although these results all remained indistinguishable from the null. Similarly, restricting the analysis to only the baseline exam for the three sites within the MESA and Coarse Particulate Matter (MESA Coarse) substudy largely resulted in even more dramatic decreases in inflammation and coagulation makers with higher $PM_{10–2.5}$ concentrations. In analyses of effect modification, we found limited evidence of differences across groups, and none were consistent across inflammatory or coagulation metrics (Figure S3; Table S8).

Discussion

In this repeated-measures analysis we found no evidence that 1-y or 1-month average exposure to $PM_{10–2.5}$ is associated with increases in markers of inflammation or coagulation. In fact, there was evidence that increases in 1-month average exposures to $PM_{10–2.5}$ were associated with lower levels of all blood makers, though the CIs show the results are consistent with a wide range of effects. The lack of precision in our estimates may simply indicate that the study design and data were inadequate to detect measurable effects. However, the fact that our findings were consistently in the opposite direction of that which we hypothesized may indicate that there may be alternative biological mechanisms—such as autonomic activation—by which $PM_{10–2.5}$ might impact health. Therefore, more evidence may be needed to determine whether and how $PM_{10–2.5}$ may be detrimental to human health.

Although we did not find evidence that $PM_{10–2.5}$ initiates an increase in inflammation or coagulation in participants of the MESA cohort, there is evidence from the toxicological research that $PM_{10–2.5}$ exposures initiate inflammatory pathways. For example, an *in vitro* study that measured the $PM_{2.5}$ and $PM_{10–2.5}$ impacts on inflammatory mediators found that exposures to both size fractions induced IL-6 production, and it is important to note that IL-6 production was more elevated in mouse macrophages after

Table 2. Percent change (95% CI) in inflammation and coagulation markers per 10 $\mu g/m^3$ of $PM_{10-2.5}$ in 1-y average and 1-month average exposure analyses, by level of model adjustment and outcome measure in the Multi-Ethnic Study of Atherosclerosis (MESA) and MESA Air Pollution (MESA Air) cohorts (2000–2012).

Outcome measure	Model 1[a]	Model 2[b]	Primary model[c]	*n* (average *n* per person)[d]
1-y average				
Inflammation				
IL-6	−1.0 (−2.6, 0.7)	−0.6 (−2.5, 1.2)	−0.7 (−2.6, 1.2)	9,506 (1.5)
CRP	−2.6 (−5.3, 0.1)	−1.9 (−4.9, 1.1)	−2.5 (−5.5, 0.6)	9,896 (1.5)
Coagulation				
Fibrinogen	−0.6 (−1.1, −0.1)	−0.4 (−1.0, 0.2)	−0.3 (−0.9, 0.3)	10,089 (1.5)
D-dimer	−1.7 (−3.8, 0.5)	−0.9 (−3.3, 1.6)	−0.2 (−2.6, 2.4)	9,103 (1.4)
1-month average				
Inflammation				
IL-6	−1.4 (−3.0, 0.2)	−1.2 (−2.9, 0.6)	−1.2 (−3.0, 0.5)	9,299 (1.5)
CRP	−3.0 (−5.5, −0.5)	−2.4 (−5.2, 0.4)	−2.5 (−5.3, 0.4)	9,648 (1.5)
Coagulation				
Fibrinogen	−0.6 (−1.1, −0.1)	−0.5 (−1.0, 0.05)	−0.4 (−1.0, 0.1)	9,830 (1.5)
D-dimer	−3.1 (−5.1, −1.0)	−2.1 (−4.4, 0.2)	−2.0 (−4.3, 0.3)	8,884 (1.4)

Note: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; NDVI, normalized vegetation index; NO_X, nitrogen oxides; NSES, neighborhood socioeconomic status; $PM_{2.5}$, fine particulate matter of aerodynamic diameter <2.5 μm; $PM_{10-2.5}$, coarse particulate matter of aerodynamic diameter ≤10 μm and >2.5 μm.
[a]Linear mixed effects regression models for 10 $\mu g/m^3$ increase in $PM_{10-2.5}$, adjusted for age, sex, race/ethnicity, site, and calendar time.
[b]Linear mixed effects regression models for 10 $\mu g/m^3$ increase in $PM_{10-2.5}$, additionally adjusted for education, employment, income, NSES, population density, active and passive smoke exposure, alcohol, physical activity level, temperature, relative humidity, and NDVI.
[c]Linear mixed effects regression models for 10 $\mu g/m^3$ increase in $PM_{10-2.5}$, additionally adjusted for $PM_{2.5}$ and NO_X (Primary Model).
[d]Total number of observations and average number of observations per participant used in the models.

activation with $PM_{10-2.5}$ than in mouse macrophages after activation with $PM_{2.5}$.[33] Lung IL-6 proteins were increased after $PM_{10-2.5}$ exposure in both an *in vitro* study with human alveolar macrophages[34] and in an *in vivo* inhalation study in rats.[35] Again, both studies found greater increases with exposure to $PM_{10-2.5}$ than smaller PM size fractions. Levels of fibrinogen in the blood of rats also increased in two intratracheal instillation *in vivo* studies after exposure to urban $PM_{10-2.5}$ and $PM_{2.5}$, again with larger increases in rats exposed to $PM_{10-2.5}$ than in those exposed to $PM_{2.5}$.[36,37] Collectively, these toxicology studies suggest that inflammation and coagulation might play key roles in the process by which $PM_{10-2.5}$ impacts health.

Although our findings are inconsistent with the toxicological research, the results are similar to some of the limited—and largely inconsistent[4]—epidemiological work that has evaluated $PM_{10-2.5}$ and these markers, though the similarities differed by blood marker. For example, the cross-sectional[13] and longitudinal[30] studies that have evaluated longer-term $PM_{10-2.5}$ and fibrinogen in different cohorts have also found lower levels of fibrinogen with higher $PM_{10-2.5}$ concentrations, although all associations were imprecise. For CRP, studies have more consistently found some evidence that higher long-term $PM_{10-2.5}$ concentrations led to increases in CRP.[13,27,30] Those findings are different from those in this investigation and the earlier work in baseline samples from only three of the six MESA cities in Adar et al.,[29] both of which found imprecise evidence of reductions in all of the blood markers with higher longer-term $PM_{10-2.5}$ concentrations. Notably, when restricting our analysis to the same population and time periods as those analyzed in our earlier work, our results were consistent, suggesting robust findings in this cohort with different exposure models.

Our 1-month average exposure findings were consistent with those in a cross-sectional study that also found inverse associations between 1-month average $PM_{10-2.5}$ and IL-6 and CRP in a cohort of women but not with those in a cohort of men and found that higher 1-month average $PM_{10-2.5}$ was associated with higher levels of IL-6 and CRP.[27] Studies with shorter exposure periods also had inconsistent results; one repeat measures analysis among elderly individuals with ischemic heart disease found some evidence that increases in short-term $PM_{10-2.5}$ concentrations led to higher levels of CRP and fibrinogen,[19] whereas a separate repeat measures analysis found some evidence that increases in short-term $PM_{10-2.5}$ concentrations led to lower levels of CRP and fibrinogen for lag times of up to 3 d.[31]

One potential explanation for the differences between findings from epidemiological studies of $PM_{10-2.5}$ and the toxicological research may relate to the physics of particle deposition in the body and the associated challenges in creating comparable doses in exposure across species. It may be that the instillation and inhalation of particles in animals[61] does not accurately mimic the delivery of $PM_{10-2.5}$ in humans, given the functional and structural differences in the respiratory tracts in experimental animals in comparison with humans. For example, although rats are exclusively nose breathers, humans breathe through the nose when at rest and increasingly through the mouth as activity levels rise.[62] Structurally, rats also have a monopodial branching structure of their lungs that can allow increased penetration of large particles into the alveolar regions in comparison with humans, and clearance rates of particles also differ across species.[62] Collectively, this may result in dissimilar $PM_{10-2.5}$ doses across species that influence the inflammatory impacts of the particles.

Another possible explanation for the results in this study, which are consistent with earlier work in this cohort[29] and are in the direction opposite to what we had hypothesized, is selection bias. Although the biomarker substudies in MESA recruited participants approximately randomly, stratified on race and place, the overall MESA cohort is selected to be healthy older adults because participants were 45–84 y of age and free of cardiovascular disease at baseline. Thus, if selection into or survival and continuation in the study also tracked with higher $PM_{10-2.5}$ exposures, then the observed associations could be a biased downward. That could translate into results counter to the hypotheses, though we have no evidence that this occurred. There is also the possibility of residual confounding, though our use of random intercepts by person reduces the likelihood of bias resulting from between-person differences.

Information bias may also have contributed to our unexpected findings. Although our $PM_{10-2.5}$ prediction model performed well spatially overall, the performance varied across locations, and one site (Winston-Salem) had much lower predictive ability than the others. Although this could have affected our epidemiological results, we found that our results were largely unchanged with the exclusion of participants from that study site. Another limitation of our work is our use of only 2001 concentrations in estimating exam

1 annual average exposure, given that the exams occurred between 2000 and 2002. Although this approach created some small temporal misalignment, recent work found that spatial contrasts in PM concentrations across all US Census tracts have remained consistent over 36 y, such that typically areas with high concentrations remained high and areas with low concentrations remained low.[63]

For our analysis of monthly concentrations, it is important to note that our prediction models had poorer temporal performance when evaluated at the daily scale. Such errors should be reduced with our aggregation to the monthly scale, but they likely still remain. In addition, we may have introduced a different type of error in our use of a monthly average. We selected that averaging period based on the availability of the data we could obtain, but this selection could add noise in our models if the most critical exposure window was on the order of days to a week. Collectively, these errors may have induced bias into our results. Because we have no reason to believe these errors were differential, however, we expect any bias to be toward the null and not capable of flipping the directionality of these associations. Another potential issue is that some research suggests that there are temporal variations in measures of inflammation and coagulation biomarkers,[64] but we did not have information on the time of day at which samples were collected. Any systematic differences in timing of blood draws across sites would be accounted for by our fixed effect for location, however, and we would not expect any other trends in time of day to track with exposure levels.

It may also be that the biological indicators we examined did not most accurately reflect the inflammatory or coagulative mechanisms directly relevant to $PM_{10–2.5}$. Similarly, our exposure estimation also did not allow us to assess the impacts of specific components of coarse PM, but rather only total coarse PM mass. This may be important, because previous work showed inflammatory impacts of exposure to the endotoxin and copper components of $PM_{10–2.5}$, but not total mass.[29] Nonetheless, a flipping of the sign due to these limitations is not expected. Finally, the restriction of MESA to adults 45 y of age and older may also limit the generalizability of our findings to younger adults and children, though we did not find compelling evidence of different associations by age.

In spite of these limitations, our use of spatially resolved satellite-based $PM_{10–2.5}$ predictions is a major strength of this work, because it allowed us to estimate exposures at a 1-km^2 resolution across all of the MESA cities, even where there are no ground-level measurements. This approach represents a great improvement from that of earlier work that relied on data from a participant's nearest EPA PM_{10} and $PM_{2.5}$ monitors within 20 km to assign exposure for studying the relationship between inflammation and long-term $PM_{10–2.5}$.[30] In addition, this model enabled us to include all participants from the MESA study in our analysis, more than doubling the study population of our earlier work[29,50] and allowing us to newly leverage longitudinal measurements from this large geographically and ethnically diverse cohort. Notably, although the use of satellite-based models is not uncommon for $PM_{2.5}$,[65,66] to date, few epidemiological studies on the health effects of $PM_{10–2.5}$ exposure have taken advantage of these types of exposure predictions. As such, the approach used here represents a substantial improvement over methods that do not account for spatial variation in air pollution concentrations across an area and the reported results are the largest and most geographically diverse of its kind in the US population to date.

Conclusion

This repeated measures assessment found no evidence that increases in $PM_{10–2.5}$ concentrations resulted in increased inflammation or coagulation in older adults in the United States, though the lack of precision in our estimates also makes these findings inconclusive. Additional epidemiological studies may be needed to confirm our findings and assess whether there are alternative mechanisms by which $PM_{10–2.5}$ might impact health.

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References

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380(9859):2224–2260, PMID: 23245609, https://doi.org/10.1016/S0140-6736(12)61766-8.
2. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389:(10082):1907–1918, https://doi.org/10.1016/S0140-6736(17)30505-6.
3. Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, et al. American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American heart association. Circulation 121(21):2331–2378, PMID: 20458016, https://doi.org/10.1161/CIR.0b013e3181dbece1.
4. US EPA (US Environmental Protection Agency). 2019. Integrated Science Assessment (ISA) for Particulate Matter. (Final Report, Dec 2019). US Environmental Protection Agency, Washington, DC. EPA/600/R-19/188. https://assessments.epa.gov/risk/document/&deid=347534 [accessed 17 October 2022].
5. van Eeden SF, Yeung A, Quinlam K, Hogg JC. 2005. Systemic response to ambient particulate matter: relevance to chronic obstructive pulmonary disease. Proc Am Thorac Soc 2(1):61–67, PMID: 16113470, https://doi.org/10.1513/pats.200406-035MS.
6. Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, et al. 2016. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. Lancet 388(10045):696–704, PMID: 27233746, https://doi.org/10.1016/S0140-6736(16)00378-0.
7. Ling SH, van Eeden SF. 2009. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 4:233–243, PMID: 19554194, https://doi.org/10.2147/copd.s5098.
8. Klümper C, Krämer U, Lehmann I, von Berg A, Berdel D, Herberth G, et al. 2015. Air pollution and cytokine responsiveness in asthmatic and non-asthmatic children. Environ Res 138:381–390, PMID: 25769127, https://doi.org/10.1016/j.envres.2015.02.034.

9. Hajat A, Allison M, Diez-Roux AV, Jenny NS, Jorgensen NW, Szpiro AA, et al. 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(3):310–320, PMID: 25710246, https://doi.org/10.1097/EDE.0000000000000267.
10. Viehmann A, Hertel S, Fuks K, Eisele L, Moebus S, Möhlenkamp S, et al. 2015. Long-term residential exposure to urban air pollution, and repeated measures of systemic blood markers of inflammation and coagulation. Occup Environ Med 72(9):656–663, PMID: 26163546, https://doi.org/10.1136/oemed-2014-102800.
11. Hennig F, Fuks K, Moebus S, Weinmayr G, Memmesheimer M, Jakobs H, et al. 2014. Association between source-specific particulate matter air pollution and hs-CRP: local traffic and industrial emissions. Environ Health Perspect 122(7):703–710, PMID: 24755038, https://doi.org/10.1289/ehp.1307081.
12. Ostro B, Malig B, Broadwin R, Basu R, Gold EB, Bromberger JT, et al. 2014. Chronic PM2.5 exposure and inflammation: determining sensitive subgroups in mid-life women. Environ Res 132:168–175, PMID: 24792413, https://doi.org/10.1016/j.envres.2014.03.042.
13. Lanki T, Hampel R, Tiittanen P, Andrich S, Beelen R, Brunekreef B, et al. 2015. Air pollution from road traffic and systemic inflammation in adults: a cross-sectional analysis in the European ESCAPE project. Environ Health Perspect 123(8):785–791, PMID: 25816055, https://doi.org/10.1289/ehp.1408224.
14. Dabass A, Talbott EO, Venkat A, Rager J, Marsh GM, Sharma RK, et al. 2016. Association of exposure to particulate matter (PM2.5) air pollution and biomarkers of cardiovascular disease risk in adult NHANES participants (2001–2008). Int J Hyg Environ Health 219(3):301–310, PMID: 26725170, https://doi.org/10.1016/j.ijheh.2015.12.002.
15. Bind M-A, Baccarelli A, Zanobetti A, Tarantini L, Suh H, Vokonas P, et al. 2012. Air pollution and markers of coagulation, inflammation, and endothelial function: associations and epigene-environment interactions in an elderly cohort. Epidemiology 23(2):332–340, PMID: 22237295, https://doi.org/10.1097/EDE.0b013e31824523f0.
16. Dadvand P, Nieuwenhuijsen MJ, Agustí À, de Batlle J, Benet M, Beelen R, et al. 2014. Air pollution and biomarkers of systemic inflammation and tissue repair in COPD patients. Eur Respir J 44(3):603–613, PMID: 24558180, https://doi.org/10.1183/09031936.00168813.
17. Strak M, Hoek G, Godri KJ, Gosens I, Mudway IS, van Oerle R, et al. 2013. Composition of PM affects acute vascular inflammatory and coagulative markers - the RAPTES project. PLoS One 8(3):e58944, PMID: 23516583, https://doi.org/10.1371/journal.pone.0058944.
18. O'Toole TE, Hellmann J, Wheat L, Haberzettl P, Lee J, Conklin DJ, et al. 2010. Episodic exposure to fine particulate air pollution decreases circulating levels of endothelial progenitor cells. Circ Res 107(2):200–203, PMID: 20595651, https://doi.org/10.1161/CIRCRESAHA.110.222679.
19. Huttunen K, Siponen T, Salonen I, Yli-Tuomi T, Aurela M, Dufva H, et al. 2012. Low-level exposure to ambient particulate matter is associated with systemic inflammation in ischemic heart disease patients. Environ Res 116:44–51, PMID: 22541720, https://doi.org/10.1016/j.envres.2012.04.004.
20. Rich DQ, Zareba W, Beckett W, Hopke PK, Oakes D, Frampton MW, et al. 2012. Are ambient ultrafine, accumulation mode, and fine particles associated with adverse cardiac responses in patients undergoing cardiac rehabilitation? Environ Health Perspect 120(8):1162–1169, PMID: 22542955, https://doi.org/10.1289/ehp.1104262.
21. Croft DP, Cameron SJ, Morrell CN, Lowenstein CJ, Ling F, Zareba W, et al. 2017. Associations between ambient wood smoke and other particulate pollutants and biomarkers of systemic inflammation, coagulation and thrombosis in cardiac patients. Environ Res 154:352–361, PMID: 28167447, https://doi.org/10.1016/j.envres.2017.01.027.
22. Liu L, Ruddy T, Dalipaj M, Poon R, Szyszkowicz M, You H, et al. 2009. Effects of indoor, outdoor, and personal exposure to particulate air pollution on cardiovascular physiology and systemic mediators in seniors. J Occup Environ Med 51(9):1088–1098, PMID: 19701101, https://doi.org/10.1097/JOM.0b013e3181b35144.
23. Karottki DG, Bekö G, Clausen G, Madsen AM, Andersen ZJ, Massling A, et al. 2014. Cardiovascular and lung function in relation to outdoor and indoor exposure to fine and ultrafine particulate matter in middle-aged subjects. Environ Int 73:372–381, PMID: 25233101, https://doi.org/10.1016/j.envint.2014.08.019.
24. Hertel S, Viehmann A, Moebus S, Mann K, Bröcker-Preuss M, Möhlenkamp S, et al. 2010. Influence of short-term exposure to ultrafine and fine particles on systemic inflammation. Eur J Epidemiol 25(8):581–592, PMID: 20559688, https://doi.org/10.1007/s10654-010-9477-x.
25. Tang H, Cheng Z, Li N, Mao S, Ma R, He H, et al. 2020. The short- and long-term associations of particulate matter with inflammation and blood coagulation markers: a meta-analysis. Environ Pollut 267:115630, PMID: 33254709, https://doi.org/10.1016/j.envpol.2020.115630.
26. Liu Q, Gu X, Deng F, Mu L, Baccarelli AA, Guo X, et al. 2019. Ambient particulate air pollution and circulating C-reactive protein level: a systematic review and meta-analysis. Int J Hyg Environ Health 222(5):756–764, PMID: 31103472, https://doi.org/10.1016/j.ijheh.2019.05.005.
27. Iyer HS, Hart JE, Fiffer MR, Elliott EG, Yanosky JD, Kaufman JD, et al. 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(pt 1):113810, PMID: 35798268, https://doi.org/10.1016/j.envres.2022.113810.
28. Forbes LJL, Patel MD, Rudnicka AR, Cook DG, Bush T, Stedman JR, et al. 2009. Chronic exposure to outdoor air pollution and markers of systemic inflammation. Epidemiology 20(2):245–253, PMID: 19234416, https://doi.org/10.1097/EDE.0b013e318190ea3f.
29. Adar SD, D'Souza J, Mendelsohn-Victor K, Jacobs DR, Cushman M, Sheppard L, et al. 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(6):541–548, PMID: 25616153, https://doi.org/10.1289/ehp.1308069.
30. Davis E, Malig B, Broadwin R, Ebisu K, Basu R, Gold EB, et al. 2020. Association between coarse particulate matter and inflammatory and hemostatic markers in a cohort of midlife women. Environ Health 19(1):111, PMID: 33153486, https://doi.org/10.1186/s12940-020-00663-1.
31. Wang C, Chen R, Zhao Z, Cai J, Lu J, Ha S, et al. 2015. Particulate air pollution and circulating biomarkers among type 2 diabetic mellitus patients: the roles of particle size and time windows of exposure. Environ Res 140:112–118, PMID: 25863184, https://doi.org/10.1016/j.envres.2015.03.026.
32. Wittkopp S, Staimer N, Tjoa T, Gillen D, Daher N, Shafer M, et al. 2013. Mitochondrial genetic background modifies the relationship between traffic-related air pollution exposure and systemic biomarkers of inflammation. PLoS One 8(5):e64444, PMID: 23717615, https://doi.org/10.1371/journal.pone.0064444.
33. Pozzi R, De Berardis B, Paoletti L, Guastadisegni C. 2003. Inflammatory mediators induced by coarse (PM2.5-10) and fine (PM2.5) urban air particles in RAW 264.7 cells. Toxicology 183(1–3):243–254, PMID: 12504355, https://doi.org/10.1016/s0300-483x(02)00545-0.
34. Becker S, Dailey LA, Soukup JM, Grambow SC, Devlin RB, Huang Y-CT. 2005. Seasonal variations in air pollution particle-induced inflammatory mediator release and oxidative stress. Environ Health Perspect 113(8):1032–1038, PMID: 16079075, https://doi.org/10.1289/ehp.7996.
35. Aztatzi-Aguilar OG, Uribe-Ramírez M, Arias-Montaño JA, Barbier O, De Vizcaya-Ruiz A. 2015. Acute and subchronic exposure to air particulate matter induces expression of angiotensin and bradykinin-related genes in the lungs and heart: angiotensin-II type-I receptor as a molecular target of particulate matter exposure. Part Fibre Toxicol 12:17, PMID: 26113123, https://doi.org/10.1186/s12989-015-0094-4.
36. Gerlofs-Nijland ME, Dormans JAMA, Bloemen HJT, Leseman DLAC, John A, Boere F, et al. 2007. Toxicity of coarse and fine particulate matter from sites with contrasting traffic profiles. Inhal Toxicol 19(13):1055–1069, PMID: 17957546, https://doi.org/10.1080/08958370701626261.
37. Gerlofs-Nijland ME, Rummelhard M, Boere AJF, Leseman DLAC, Duffin R, Schins RPF, et al. 2009. Particle induced toxicity in relation to transition metal and polycyclic aromatic hydrocarbon contents. Environ Sci Technol 43(13):4729–4736, PMID: 19673258, https://doi.org/10.1021/es803176k.
38. Zanobetti A, Schwartz J. 2009. The effect of fine and coarse particulate air pollution on mortality: a national analysis. Environ Health Perspect 117(6):898–903, PMID: 19590680, https://doi.org/10.1289/ehp.0800108.
39. Peng RD, Chang HH, Bell ML, McDermott A, Zeger SL, Samet JM, et al. 2008. Coarse particulate matter air pollution and hospital admissions for cardiovascular and respiratory diseases among Medicare patients. JAMA 299(18):2172–2179, PMID: 18477784, https://doi.org/10.1001/jama.299.18.2172.
40. Hart JE, Puett RC, Rexrode KM, Albert CM, Laden F. 2015. Effect modification of long-term air pollution exposures and the risk of incident cardiovascular disease in US women. J Am Heart Assoc 4(12):e002301, PMID: 26607712, https://doi.org/10.1161/JAHA.115.002301.
41. Stafoggia M, Samoli E, Alessandrini E, Cadum E, Ostro B, Berti G, et al. 2013. Short-term associations between fine and coarse particulate matter and hospitalizations in Southern Europe: results from the MED-PARTICLES project. Environ Health Perspect 121(9):1026–1033, PMID: 23777832, https://doi.org/10.1289/ehp.1206151.
42. Chen Y-C, Weng Y-H, Chiu Y-W, Yang C-Y. 2015. Short-term effects of coarse particulate matter on hospital admissions for cardiovascular diseases: a case-crossover study in a tropical city. J Toxicol Environ Health A 78(19):1241–1253, PMID: 26408041, https://doi.org/10.1080/15287394.2015.1083520.
43. Powell H, Krall JR, Wang Y, Bell ML, Peng RD. 2015. Ambient coarse particulate matter and hospital admissions in the Medicare Cohort Air Pollution Study, 1999–2010. Environ Health Perspect 123(11):1152–1158, PMID: 25872223, https://doi.org/10.1289/ehp.1408720.
44. Alessandrini ER, Stafoggia M, Faustini A, Gobbi GP, Forastiere F. 2013. Saharan dust and the association between particulate matter and daily hospitalisations in

Rome, Italy. Occup Environ Med 70(6):432–434, PMID: 23503419, https://doi.org/10.1136/oemed-2012-101182.
45. Dennekamp M, Akram M, Abramson MJ, Tonkin A, Sim MR, Fridman M, et al. 2010. Outdoor air pollution as a trigger for out-of-hospital cardiac arrests. Epidemiology 21(4):494–500, PMID: 20489649, https://doi.org/10.1097/EDE.0b013e3181e093db.
46. Wichmann J, Folke F, Torp-Pedersen C, Lippert F, Ketzel M, Ellermann T, et al. 2013. Out-of-hospital cardiac arrests and outdoor air pollution exposure in Copenhagen, Denmark. PLoS One 8(1):e53684, PMID: 23341975, https://doi.org/10.1371/journal.pone.0053684.
47. 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(3):258–274, PMID: 25152864, https://doi.org/10.1007/s40572-014-0022-z.
48. Huang F, Luo Y, Guo Y, Tao L, Xu Q, Wang C, et al. 2016. Particulate matter and hospital admissions for stroke in Beijing, China: modification effects by ambient temperature. J Am Heart Assoc 5(7):e003437, https://doi.org/10.1161/JAHA.116.003437.
49. Liu C, Cai J, Chen R, Sera F, Guo Y, Tong S, et al. 2022. Coarse particulate air pollution and daily mortality: a global study in 205 cities. Am J Respir Crit Care Med 206(8):999–1007, PMID: 35671471, https://doi.org/10.1164/rccm.202111-2657OC.
50. Zhang K, Larson TV, Gassett A, Szpiro AA, Daviglus M, Burke GL, et al. 2014. Characterizing spatial patterns of airborne coarse particulate (PM10-2.5) mass and chemical components in three cities: the Multi-Ethnic Study of Atherosclerosis. Environ Health Perspect 122(8):823–830, PMID: 24642481, https://doi.org/10.1289/ehp.1307287.
51. Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, et al. 2012. Development of land use regression models for PM(2.5), PM(2.5) absorbance, PM(10) and PM(coarse) in 20 European study areas; results of the ESCAPE project. Environ Sci Technol 46(20):11195–11205, PMID: 22963366, https://doi.org/10.1021/es301948k.
52. Pedde M, Kloog I, Szpiro A, Dorman M, Larson TV, Adar SD. 2022. Estimating long-term $PM_{10-2.5}$ concentrations in six US cities using satellite-based aerosol optical depth data. Atmos Environ 272:118945, https://doi.org/10.1016/j.atmosenv.2022.118945.
53. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. 2002. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 156(9):871–881, PMID: 12397006, https://doi.org/10.1093/aje/kwf113.
54. Kaufman JD, Adar SD, Allen RW, Barr RG, Budoff MJ, Burke GL, et al. 2012. Prospective study of particulate air pollution exposures, subclinical atherosclerosis, and clinical cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). Am J Epidemiol 176(9):825–837, PMID: 23043127, https://doi.org/10.1093/aje/kws169.
55. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. 1995. Laboratory methods and quality assurance in the cardiovascular health study. Clinical Chemistry 41(2):264–270, https://doi.org/10.1093/clinchem/41.2.264.
56. US EPA. 2009. Integrated Science Assessment (ISA) for Particulate Matter. (Final Report, Dec 2009). US Environmental Protection Agency, Washington, DC. EPA/600/R-08/139F. https://assessments.epa.gov/isa/document/&deid=216546 [accessed 12 September 2022].
57. Hajat A, Diez-Roux AV, Adar SD, Auchincloss AH, Lovasi GS, O'Neill MS, et al. 2013. Air pollution and individual and neighborhood socioeconomic status: evidence from the multi-ethnic study of atherosclerosis (MESA). Environ Health Perspect 121(11–12):1325–1333, PMID: 24076625, https://doi.org/10.1289/ehp.1206337.
58. Keller JP, Olives C, Kim S-Y, Sheppard L, Sampson PD, Szpiro AA, et al. 2015. A unified spatiotemporal modeling approach for predicting concentrations of multiple air pollutants in the multi-ethnic study of atherosclerosis and air pollution. Environ Health Perspect 123(4):301–309, PMID: 25398188, https://doi.org/10.1289/ehp.1408145.
59. Szpiro AA, Sampson PD, Sheppard L, Lumley T, Adar SD, Kaufman J. 2009. Predicting intra-urban variation in air pollution concentrations with complex spatio-temporal dependencies. Environmetrics 21(6):606–631, PMID: 24860253, https://doi.org/10.1002/env.1014.
60. Dubowsky SD, Suh H, Schwartz J, Coull BA, Gold DR. 2006. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. Environ Health Perspect 114(7):992–998, PMID: 16835049, https://doi.org/10.1289/ehp.8469.
61. Shang Y, Sun Q. 2018. Particulate air pollution: major research methods and applications in animal models. Environ Dis 3(3):57–62, PMID: 31549002, https://doi.org/10.4103/ed.ed_16_18.
62. Brown JS, Wilson WE, Grant LD. 2005. Dosimetric comparisons of particle deposition and retention in rats and humans. Inhal Toxicol 17(7–8):355–385, PMID: 16020034, https://doi.org/10.1080/08958370590929475.
63. Colmer J, Hardman I, Shimshack J, Voorheis J. 2020. Disparities in $PM_{2.5}$ air pollution in the United States. Science 369(6503):575–578, PMID: 32732425, https://doi.org/10.1126/science.aaz9353.
64. Rudnicka AR, Rumley A, Lowe GDO, Strachan DP. 2007. Diurnal, seasonal, and blood-processing patterns in levels of circulating fibrinogen, fibrin D-dimer, C-reactive protein, tissue plasminogen activator, and von Willebrand Factor in a 45-year-old population. Circ 115(8):996–1003, PMID: 17296859, https://doi.org/10.1161/CIRCULATIONAHA.106.635169.
65. Kloog I, Ridgway B, Koutrakis P, Coull BA, Schwartz JD. 2013. Long- and short-term exposure to PM2.5 and mortality using novel exposure models. Epidemiology 24(4):555–561, PMID: 23676266, https://doi.org/10.1097/EDE.0b013e318294beaa.
66. Kloog I, Coull BA, Zanobetti A, Koutrakis P, Schwartz JD. 2012. Acute and chronic effects of particles on hospital admissions in New-England. PLoS One 7(4):e34664, PMID: 22529923, https://doi.org/10.1371/journal.pone.0034664.