Short-Term Exposure to Air Pollution and Biomarkers of Oxidative Stress: The Framingham Heart Study

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Background—Short-term exposure to elevated air pollution has been associated with higher risk of acute cardiovascular diseases, with systemic oxidative stress induced by air pollution hypothesized as an important underlying mechanism. However, few community-based studies have assessed this association.

Methods and Results—Two thousand thirty-five Framingham Offspring Cohort participants living within 50 km of the Harvard Boston Supersite who were not current smokers were included. We assessed circulating biomarkers of oxidative stress including blood myeloperoxidase at the seventh examination (1998–2001) and urinary creatinine-indexed 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-PGF$_{2\alpha}$) at the seventh and eighth (2005–2008) examinations. We measured fine particulate matter (PM$_{2.5}$), black carbon, sulfate, nitrogen oxides, and ozone at the Supersite and calculated 1-, 2-, 3-, 5-, and 7-day moving averages of each pollutant. Measured myeloperoxidase and 8-epi-PGF$_{2\alpha}$ were log$_e$ transformed. We used linear regression models and linear mixed-effects models with random intercepts for myeloperoxidase and indexed 8-epi-PGF$_{2\alpha}$, respectively. Models were adjusted for demographic variables, individual- and area-level measures of socioeconomic position, clinical and lifestyle factors, weather, and temporal trend. We found positive associations of PM$_{2.5}$ and black carbon with myeloperoxidase across multiple moving averages. Additionally, 2- to 7-day moving averages of PM$_{2.5}$ and sulfate were consistently positively associated with 8-epi-PGF$_{2\alpha}$. Stronger positive associations of black carbon and sulfate with myeloperoxidase were observed among participants with diabetes than in those without.

Conclusions—Our community-based investigation supports an association of select markers of ambient air pollution with circulating biomarkers of oxidative stress. (***J Am Heart Assoc***. 2016;5:e002742 doi: 10.1161/JAHA.115.002742)

Key Words: air pollution • isoprostanes • myeloperoxidase

I ncreasing evidence indicates that short-term exposure to elevated air pollution is associated with higher risk of incident ischemic stroke, myocardial infarction, and other acute cardiovascular events.[1–3] Oxidative stress, an imbalance between the production of the reactive oxygen species and the human body's antioxidant defense mechanism,[4] has been proposed as an important underlying biological mechanism mediating this association.[3,5–7] Increased oxidative stress may induce endothelial dysfunction, which is characterized by increased endothelial permeability, altered vascular tone, platelet adhesion and aggregation, and enhanced thrombogenicity.[8,9]

Myeloperoxidase is an enzyme that is abundantly stored in inflammatory cells such as neutrophils, macrophages, and

monocytes and is involved in a wide range of activities that generate reactive oxygen and nitrogen species.[10–13] Prior studies have yielded mixed results.[14–18] In a recent study, positive associations of short-term exposure to fine particulate matter (diameter ≤2.5 µm [$PM_{2.5}$]), black carbon (BC), and nitrogen oxides (NO_x) with myeloperoxidase were found in a group of potentially genetically susceptible participants.[14]

8-Epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) is formed from peroxidation of arachidonic acid[19] and is detectable in human plasma and urine. The quantification of 8-epi-$PGF_{2\alpha}$ has been widely used as a noninvasive method to assess lipid peroxidation.[20,21] Higher short-term air pollution has been associated with higher 8-epi-$PGF_{2\alpha}$ sampled from exhaled breath condensate in children, adolescents, and healthy young adults[22–25]; however, few studies have assessed the relationship between exposure to ambient air pollution and urinary 8-epi-$PGF_{2\alpha}$[26,27] or in older populations at increased risk of cardiovascular events.

Epidemiologic studies conducted in the Boston area have reported positive associations of short-term exposure to air pollution with acute stroke onset,[28] atrial fibrillation,[29] and myocardial infarction onset.[30] In the present study, we evaluated whether short-term (1–7 days) ambient air pollution exposure is associated with systemic levels of oxidative stress, measured by plasma myeloperoxidase and urinary creatinine-indexed 8-epi-$PGF_{2\alpha}$, in the community-based Framingham Heart Study. Our study catchment region and study period largely overlap with the above-mentioned studies, and a closer look at the relationship may enable us to elucidate underlying biologic pathways that could in part explain previous findings.

Methods

Study Sample

The study participants were from the Framingham Heart Study Offspring cohort living within 50 km of the Harvard Supersite air pollution monitor in Boston, Massachusetts.[31] The study design and selection criteria of the Framingham Offspring cohort has been described elsewhere.[32] We included 2035 participants from the Offspring cohort seventh examination (1998–2001) and/or eighth examination (2005–2008) who were not current smokers and had at least one valid measurement of plasma myeloperoxidase or urinary creatinine-indexed 8-epi-$PGF_{2\alpha}$ (3386 observations in total). At each examination, physical examinations were performed according to standardized protocols, and data on demographics, medication history, smoking history, and alcohol intake were collected via questionnaires. All participants provided written informed consent for the Framingham Heart Study examinations, and institutional review boards at Beth Israel

Deaconess Medical Center and Boston University Medical Center approved the study.

Biomarkers of Oxidative Stress

Fasting morning plasma samples and urine samples were collected at the examination visits. Plasma myeloperoxidase (ng/mL) was measured in duplicate in examination 7 by using the commercially available Enzyme Immunoassay Kit (OXIS Health Products), and 8-epi-$PGF_{2\alpha}$ (pg/mL) was measured in duplicate with the Enzyme Immunoassay Kit (Cayman Chemical) in examinations 7 and 8. Measured 8-epi-$PGF_{2\alpha}$ was adjusted for urinary creatinine and was expressed in nanograms per millimole of creatinine. The levels of myeloperoxidase and indexed 8-epi-$PGF_{2\alpha}$ were $\log_e$ transformed.

Air Pollution and Meteorological Variables

Air pollution levels were measured at the Harvard Supersite, located on the rooftop of the Francis A. Countway Library of Medicine (5 stories above ground level) and 50 m from the nearest street. Measurement methods have been described previously.[31] $PM_{2.5}$ ($\mu g/m^3$) was measured by using a tapered element oscillating microbalance (Model 1400A; Rupprecht & Patashnick Co Inc), and BC ($\mu g/m^3$) was measured by using an aethalometer (Model AE-16; Magee Scientific Corp). Ozone (O_3, ppm) and NO_x were estimated by averaging available data from local state monitors within the greater Boston area. Daily sulfate (SO_4^{2-}, $\mu g/m^3$) was calculated from elemental sulfur measured with x-ray fluorescence analysis of the $PM_{2.5}$ filter samples. On days when SO_4^{2-} x-ray fluorescence measurements were not available, an SO_4^{2-} analyzer (Model 5020; Thermo Electron Corp) was used. Temperature and relative humidity were monitored at the Boston Logan International Airport Weather Station, located 12 km from the Supersite.

Statistical Methods

We calculated 1-, 2-, 3-, 5-, and 7-day moving averages for measured pollutants based on the daily means. For each moving average of a pollutant, we fit multivariable linear regression models (for plasma myeloperoxidase) and multivariable linear mixed-effects models with subject-specific random intercepts (for indexed urinary 8-epi-$PGF_{2\alpha}$). We adjusted for individual- and area-level covariates in the models, including centered age, and (centered age)^2; sex; body mass index; smoking status (former or never smoker); pack years; alcohol intake; educational level; and the quartile of median household income in the participant's census tract from the 2000 US Census. An examination identifier (examination 7 or 8) was added to the linear mixed models. We additionally adjusted for season, linear time trend, temperature, and relative humidity.

In secondary analyses, we explored the associations within current US Environmental Protection Agency (EPA) National Ambient Air Quality Standards by excluding observations with any of the 7 days before the examination date that had a 24-hour $PM_{2.5}$ >35 µg/m^3. We also explored whether associations differed when we included current smokers. Additionally, we repeated our analyses after restricting the study population to participants who lived within 40 km of the Harvard Supersite air pollution monitor. Further, we examined whether associations varied by age (>65/≤65 years), sex, obesity (31.8%), diabetes (16.8%), cardiovascular disease (15.0%), antihypertensive medication use (46.8%), statin use (31.5%), and season (warm [April to September] versus cold [October to March]) by adding an interaction term to these models.

Analyses were scaled to 5 µg/m^3 for $PM_{2.5}$, 0.4 µg/m^3 for BC, 2 µg/m^3 for SO_4^{2-}, and 0.01 ppm for NO_x and O_3, which approximated the IQR.

Estimated percent changes were reported with 95% CIs. For primary analyses, we focused on describing the association patterns between pollutants and the biomarkers. For sensitivity analyses in which effect modification was explored, the 2-tailed *P*-value from the Wald test of the interaction term was used to decide whether the observed association differed between subgroups; however, only consistent association patterns were considered important and highlighted. A 2-tailed *P*<0.05 value was considered statistically significant in these analyses. Primary analyses were performed using PROC GLM and PROC Mixed in SAS 9.4 (SAS Institute, Inc). Figures were plotted using Stata 13 (StataCorp LP).

Results

Table 1 shows the population characteristics. $PM_{2.5}$ was strongly correlated with BC and SO_4^{2-}. NO_x was moderately correlated with BC and negatively correlated with O_3 (Table 2). The correlation structure was similar for longer-term moving averages. Figure 1 shows the distributions of myeloperoxidase and indexed urinary 8-epi-PGF$_{2\alpha}$, and Figure 2 shows the distribution of the daily concentrations of each air pollutant.

We found positive associations of $PM_{2.5}$ and BC with plasma myeloperoxidase across multiple moving averages (Figure 3A). Additionally, 3- to 7-day moving averages of SO_4^{2-} were weakly associated with plasma myeloperoxidase; however, 95% CIs were rather wide.

We also observed consistent positive associations for $PM_{2.5}$ and SO_4^{2-} with indexed urinary 8-epi-PGF$_{2\alpha}$, with stronger associations appearing in 3- to 7-day moving averages of $PM_{2.5}$ and 2- to 7-day moving averages of SO_4^{2-} (Figure 3B). Similar but weaker positive associations were observed for 2- to 7-day moving averages of BC.

Table 1. Characteristics of the 3386 Observations From the Framingham Offspring Cohort Examination 7 (1998–2001) and/or 8 (2005–2008) Participants

	No. (%) or Mean [SD]
Examination cycle 7	1878 (55.5%)
Age, y	64.1 [9.7]
Women	1789 (52.8%)
BMI, kg/m^2	28.5 [5.4]
Alcohol, drinks/wk	4.2 [6.9]
Diabetes	569 (16.8%)
Former smoker	2018 (59.6%)
Education	
<High school	161 (4.8%)
High School	1051 (31.0%)
Some college	1050 (31.0%)
College graduate	1094 (32.3%)
Antihypertensive medication use	1583 (46.8%)
Statins	1066 (31.5%)
Plasma myeloperoxidase*, ng/mL	40.6 [22.5]
Urinary 8-epi-PGF$_{2\alpha}$*, pg/mL	897.9 [842.3]
Urine creatinine, mg/100 mL	115.2 [69.1]
Indexed urinary 8-epi-PGF$_{2\alpha}$*, ng/mmol creatinine	108.7 [69.6]

BMI indicates body mass index; 8-epi-PGF$_{2\alpha}$, 8-epi-prostaglandin F$_{2\alpha}$.
*Geometric mean [SD of the geometric mean].

Excluding observations with any 24-hour average $PM_{2.5}$ above the EPA National Ambient Air Quality Standards (19 observations for plasma myeloperoxidase and 38 observations for urinary 8-epi-PGF$_{2\alpha}$) did not change our findings substantially. As before, 3- to 7-day moving averages of $PM_{2.5}$ and 2- to 7-day moving averages of SO_4^{2-} were positively associated with indexed urinary 8-epi-PGF$_{2\alpha}$ with 95% CIs that did not overlap the null. Results were not materially altered after we included current smokers and adjusted for smoking status and pack years in the primary analyses or after we restricted study participants to those who lived within 40 km of the Harvard Supersite air pollution monitor. We tested the robustness of our results by including BC and SO_4^{2-} simultaneously; the associations were slightly attenuated but without any substantial change.

There was no consistent evidence of differing associations between pollutants and either biomarker by age, sex, obesity, cardiovascular disease, antihypertensive medication use, statin use, or season. However, stronger associations of BC and SO_4^{2-} with plasma myeloperoxidase were observed among participants with diabetes than those without (Figure 4A).

Table 2. Characteristics of the 1-Day Moving Averages of Air Pollutants Previous to the Examination Date in the Study Population (1998–2001, 2005–2008)

Pollutant	No. of Observations	Mean (SD)	IQR	BC	SO_4^{2-}	NO_x	O_3
$PM_{2.5}$, µg/m³	3380	9.86 (5.34)	6.28	0.76	0.79	0.47	−0.05
BC, µg/m³	3376	0.84 (0.46)	0.57	—	0.53	0.61	−0.25
SO_4^{2-}, µg/m³	2758	2.98 (2.25)	2.22	—	—	0.33	0.05
NO_x, ppm	3081	0.04 (0.02)	0.02	—	—	—	−0.52
O_3, ppm	3377	0.02 (0.01)	0.01	—	—	—	—

BC indicates black carbon; NO_x, nitrogen oxides; O_3, ozone; $PM_{2.5}$, fine particulate matter; SO_4^{2-}, sulfate.

Discussion

In our community-based study, we found positive associations of $PM_{2.5}$ and BC with plasma myeloperoxidase and of $PM_{2.5}$ and SO_4^{2-} with urinary 8-epi-$PGF_{2\alpha}$ across multiple moving averages. The association of BC and SO_4^{2-} with plasma myeloperoxidase appeared to be stronger among participants with diabetes. To our knowledge, we report the largest community-based study to date on the association of short-term ambient air pollution with oxidative stress biomarkers.
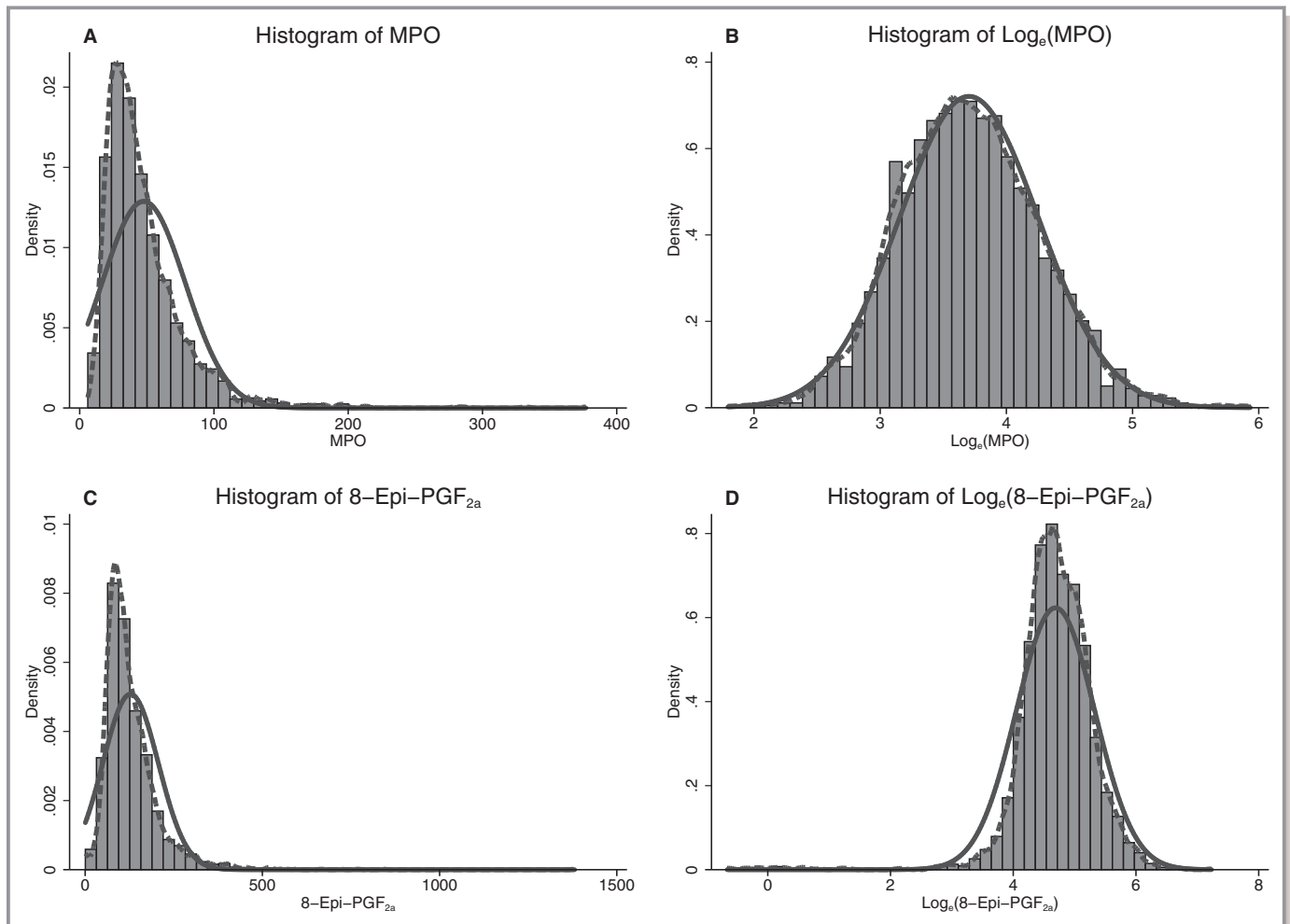

Figure 1. Histograms of (A) myeloperoxidase, (B) log_e transformed myeloperoxidase, (C) indexed 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$), and (D) log_e transformed indexed 8-epi-$PGF_{2\alpha}$ among the Framingham Offspring cohort examination 7 (1998–2001) and/or 8 (2005–2008) participants. Solid line indicates the normal-density plot; dashed line indicates the kernel-density plot.
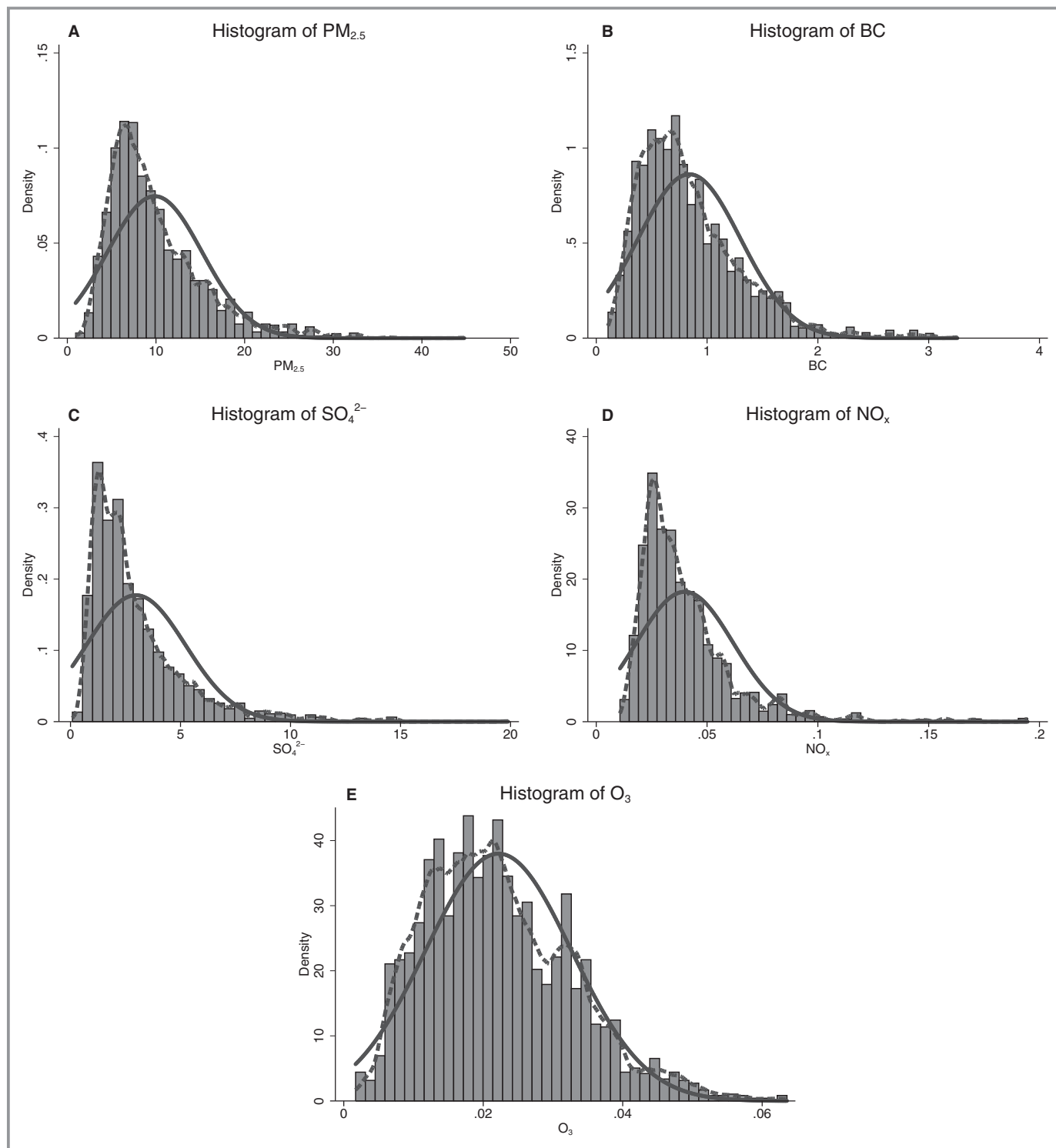
Figure 2. Histograms of the 1-day moving average concentrations of air pollutants previous to the examination date in the study population (1998–2001, 2005–2008): (A) fine particulate matter ($PM_{2.5}$), (B) black carbon (BC), (C) sulfate (SO_4^{2-}), (D) nitrogen oxides (NO_x), and (E) ozone (O_3). Solid line indicates the normal-density plot; dashed line indicates the kernel-density plot.

Myeloperoxidase can be involved in diverse oxidation reactions, including lipid peroxidation by acting as an enzyme in generating multiple reactive oxygen and nitrogen species, and may promote endothelial dysfunction.[10] Accumulation of lipid peroxidation products in vascular walls promotes disruption of vulnerable plaques,[33,34] which likely contributes to the risk of acute cardiovascular events. Some,[14–16] but not all,[17,18] prior studies have found an association between
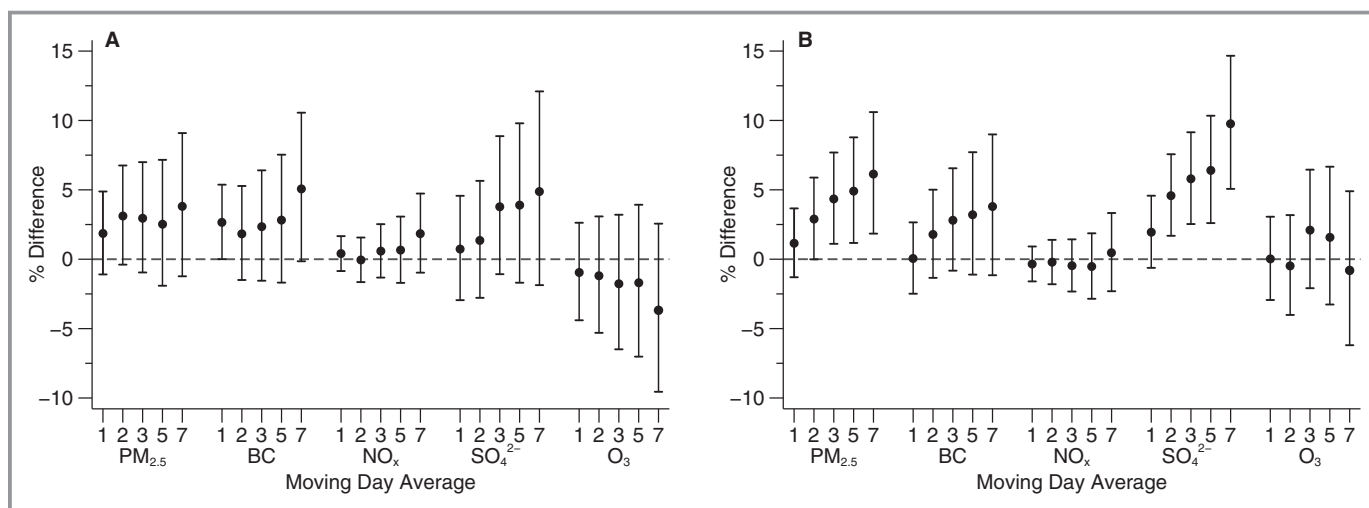
Figure 3. Associations of moving averages of air pollutants with (A) myeloperoxidase and (B) indexed 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-PGF$_{2\alpha}$). Scaled to 5 $\mu g/m^3$ for fine particulate matter (PM$_{2.5}$), 0.4 $\mu g/m^3$ for black carbon (BC), 2 $\mu g/m^3$ for sulfate (SO$_4^{2-}$), and 0.01 ppm for nitrogen oxides (NO$_x$) and ozone (O$_3$). Models are adjusted for centered age, (centered age)^2, sex, body mass index, smoking status, pack years, alcohol intake, education level, quartile of median household income in the participants' census tracts from the 2000 US Census, sine and cosine of the day of year, examination date, day of the week, temperature, and relative humidity, and an examination identifier is added to models with indexed 8-epi-PGF$_{2\alpha}$ as the dependent variable. Error bars indicate the 95% CIs.

short-term air pollution and plasma myeloperoxidase. Ruckerl et al found higher myeloperoxidase levels were associated with the BC, NO, NO$_2$, and PM$_{2.5}$ within 5 days in a group of potentially genetically susceptible participants who were free of type 2 diabetes or impaired glucose tolerance.[14] However, Delfino et al reported no association between measured air pollutants and myeloperoxidase among 29 nonsmoking

elderly participants with a history of coronary artery disease.[17]

Urinary 8-epi-PGF$_{2\alpha}$ is a reliable and stable biomarker of lipid peroxidation that may promote vasoconstriction and platelet activation.[20] Prior studies have found increased 8-epi-PGF$_{2\alpha}$ in exhaled breath condensate after exposure to air pollutants.[22,24,25] However, systemic oxidative stress may be
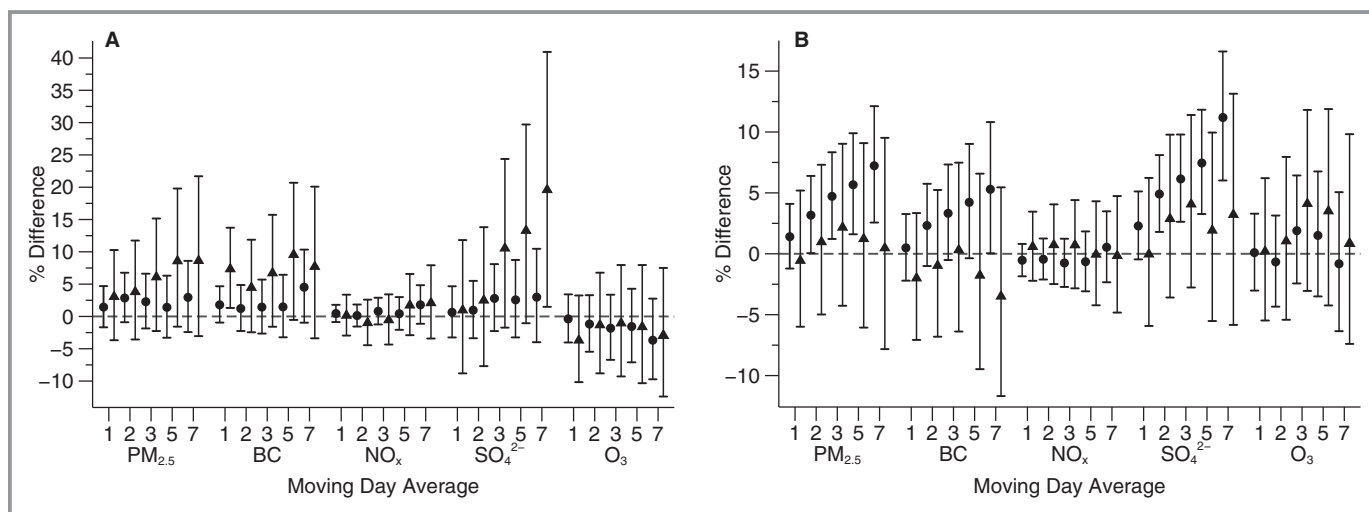

Figure 4. Associations of moving averages of air pollutants with (A) myeloperoxidase and (B) indexed 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-PGF$_{2\alpha}$) among participants with diabetes and those without (triangle, participants with diabetes; circle, participants without diabetes). Scaled to 5 $\mu g/m^3$ for fine particulate matter (PM$_{2.5}$), 0.4 $\mu g/m^3$ for black carbon (BC), 2 $\mu g/m^3$ for sulfate (SO$_4^{2-}$), and 0.01 ppm for nitrogen oxides (NO$_x$) and ozone (O$_3$). Models are adjusted for centered age, (centered age)^2, sex, bpdy mass index, smoking status, pack years, alcohol intake, education level, quartile of median household income in the participants' census tracts from the 2000 US Census, sine and cosine of the day of year, examination date, day of the week, temperature, and relative humidity, and an examination identifier is added to models with indexed 8-epi-PGF$_{2\alpha}$ as the dependent variable. Error bars indicate the 95% CIs.

better reflected by 8-epi-PGF$_{2\alpha}$ measured in plasma or urine. Mixed results have been seen between air pollution and 8-epi-PGF$_{2\alpha}$[26,35,36] or other oxidative stress markers.[37]

Prior studies of short-term ambient air pollution exposure with acute cardiovascular outcomes[38–41] and markers of vascular reactivity[42] and inflammation[43] suggest that individuals with diabetes are more sensitive to air pollution, as a result of baseline chronic inflammation and endothelial dysfunction.[44] We observed tendencies for participants with diabetes to have higher levels of myeloperoxidase in relation to BC and SO$_4^{2-}$. There was no evidence suggesting differing associations between pollutants and 8-epi-PGF$_{2\alpha}$.

In this study region, local traffic sources and regional pollution both contribute to PM$_{2.5}$ mass concentrations.[45] Locally emitted or transported BC is a product of incomplete combustion and is associated with different sources such as traffic, residential heating and cooking, and biomass burning. SO$_4^{2-}$ is primarily from regional sulfur-related pollution sources such as coal-fired power plants, and some is generated from local diesel exhaust.[46] When we included both BC and SO$_4^{2-}$ in the models, we observed potential positive association between BC and myeloperoxidase but not SO$_4^{2-}$, suggesting that local sources may play an important role, whereas for 8-epi-PGF$_{2\alpha}$, the stronger association with SO$_4^{2-}$ suggests that the transported pollutants may play a stronger role, consistent with the finding of Ren et al.[47]

There are several limitations that should be noted. We assigned the ambient air pollution level measured by a central monitoring site to all participants, which may decrease precision of our estimates and induce exposure measurement error. Prior studies in our region have demonstrated moderate correlation between PM$_{2.5}$ measured at the Supersite and personal exposure level.[48] In daily time series, most of the variability in exposure within the study region is related to temporal, rather than spatial, variability,[45] which supports assigning regional average concentrations to study participants. In the present investigation, the distribution of exposure of the participants was primarily related to the date that participants came for their examination appointment. Thus, we expect the exposure measurement error caused by assignment to be nondifferential, leading to attenuated point estimates and wider CIs. The participants of the Framingham Offspring Study were predominantly white individuals of European ancestry and middle-aged to older adults, which limits the generalizability of our findings to other ethnicities and to age groups not studied. We acknowledge that we cannot exclude the possibility of residual confounding and that we cannot prove causal relations.

There are also several strengths. First, our study sample was from a large community-based cohort with standardized protocols for physical examinations and biomarker assessments. Second, we adjusted for demographic characteristics, lifestyle, individual- and area-level of socioeconomic position, weather, and temporal trend. Third, assessments of air pollutants and biomarkers were performed separately. Fourth, we conducted the study in a region that has pollution levels in compliance with current air quality standards, and our findings still suggested adverse associations. Future studies in regions with higher levels of ambient air pollution are needed to determine if these associations are stronger in such regions. Additionally, participants of the Framingham Heart Study scheduled the date of their examination visit months in advance, and this was not likely related to the air pollution level on the days leading up to that prescheduled appointment.

Conclusions

Our findings suggest positive associations of short-term exposure to PM$_{2.5}$ and BC with plasma myeloperoxidase and of short-term exposure to PM$_{2.5}$ and SO$_4^{2-}$ with urinary 8-epi-PGF$_{2\alpha}$. The associations of BC and SO$_4^{2-}$ with plasma myeloperoxidase appear stronger among participants with diabetes. Our findings provide evidence suggesting potential intermediate biological mechanisms that may in part explain the observed associations between transiently higher air pollution levels and the increase of acute cardiovascular events.

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Disclosures

None.

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