**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_2α (8-epi-PGF_2α) 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_2α were log transformed. We used linear regression models and linear mixed-effects models with random intercepts for myeloperoxidase and indexed 8-epi-PGF_{2α}, 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_{2α}. 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](http://jaha.ahajournals.org/))

**Key Words:** air pollution • isoprostanes • myeloperoxidase

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Increasing 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.2,5–7 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 particu-
late matter (diameter ≤2.5 μm [PM2.5]), black carbon (BC),
and nitrogen oxides (NOx) with myeloperoxidase were found in
a group of potentially genetically susceptible participants.14

8-Epi-prostaglandin F_{2α} (8-epi-PGF_{2α}) is formed from
peroxidation of arachidonic acid19 and is detectable in human
plasma and urine. The quantification of 8-epi-PGF_{2α} 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_{2α} sampled from exhaled
breath condensate in children, adolescents, and healthy
young adults22–25; however, few studies have assessed the
relationship between exposure to ambient air pollution and
urinary 8-epi-PGF_{2α}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,26 atrial fibrillation,27 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_{2α}, 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 crea-
tinine-indexed 8-epi-PGF_{2α} (3386 observations in total). At
each examination, physical examinations were performed
according to standardized protocols, and data on demograph-
ic, 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_{2α} (pg/mL) was measured in
duplicate with the Enzyme Immunoassay Kit (Cayman Chemi-
cal) in examinations 7 and 8. Measured 8-epi-PGF_{2α} was
adjusted for urinary creatinine and was expressed in
nanograms per millimole of creatinine. The levels of myeloper-
oxidase and indexed 8-epi-PGF_{2α} 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} (μg/m^{3}) was measured by using a tapered
element oscillating microbalance (Model 1400A; Rupprecht &
Patahsnick Co Inc), and BC (μg/m^{3}) was measured by using
an aethalometer (Model AE-16; Magee Scientific Corp). Ozone
(O_{3}, ppm) and NOx were estimated by averaging available data
from local state monitors within the greater Boston area. Daily
sulfate (SO_{4}^{2−}, μg/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 measure-
ments 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 multivari-
able linear mixed-effects models with subject-specific random
intercepts (for indexed urinary 8-epi-PGF_{2α}). 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 $\mu$g/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 $\mu$g/m$^3$ for PM$_{2.5}$, 0.4 $\mu$g/m$^3$ for BC, 2 $\mu$g/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.

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

| Characteristic                          | 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 (33.2%)         |
| 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].
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 | SO4\(^{2-}\) | NO\(_x\) | O\(_3\) |
|-----------|---------------------|-----------|-----|----|-------------|--------|--------|
| PM\(_{2.5}\) | 3380 | 9.86 (5.34) | 6.28 | 0.76 | 0.79 | 0.47 | –0.05 |
| BC, µg/m\(^3\) | 3376 | 0.84 (0.46) | 0.57 | — | 0.53 | 0.61 | –0.25 |
| SO4\(^{2-}\), µg/m\(^3\) | 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; SO4\(^{2-}\), 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 SO4\(^{2-}\) with urinary 8-epi-PGF\(_{2\alpha}\) across multiple moving averages. The association of BC and SO4\(^{2-}\) 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) loge transformed myeloperoxidase, (C) indexed 8-epi-prostaglandin F\(_{2\alpha}\) (8-epi-PGF\(_{2\alpha}\)), and (D) loge 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.
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

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**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.
short-term air pollution and plasma myeloperoxidase. Ruckerl et al found higher myeloperoxidase levels were associated with the BC, NO, NO₂, and PM2.5 within 5 days in a group of potentially genetically susceptible participants who were free of type 2 diabetes or impaired glucose tolerance. However, Deffino et al reported no association between measured air pollutants and myeloperoxidase among 29 nonsmoking elderly participants with a history of coronary artery disease.

Urinary 8-epi-PGF₂α is a reliable and stable biomarker of lipid peroxidation that may promote vasoconstriction and platelet activation. Prior studies have found increased 8-epi-PGF₂α in exhaled breath condensate after exposure to air pollutants. However, systemic oxidative stress may be

Figure 3. Associations of moving averages of air pollutants with (A) myeloperoxidase and (B) indexed 8-epi-prostaglandin F₂α (8-epi-PGF₂α). Scaled to 5 μg/m³ for fine particulate matter (PM₂.₅), 0.4 μg/m³ for black carbon (BC), 2 μg/m³ for sulfate (SO₄²⁻), and 0.01 ppm for nitrogen oxides (NOₓ) and ozone (O₃). 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-PGF₂α as the dependent variable. Error bars indicate the 95% CIs.

Figure 4. Associations of moving averages of air pollutants with (A) myeloperoxidase and (B) indexed 8-epi-prostaglandin F₂α (8-epi-PGF₂α) among participants with diabetes and those without (triangle, participants with diabetes; circle, participants without diabetes). Scaled to 5 μg/m³ for fine particulate matter (PM₂.₅), 0.4 μg/m³ for black carbon (BC), 2 μg/m³ for sulfate (SO₄²⁻), and 0.01 ppm for nitrogen oxides (NOₓ) and ozone (O₃). 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-PGF₂α 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$_{2\alpha}$ or other oxidative stress markers.\textsuperscript{37}

Prior studies of short-term ambient air pollution exposure with acute cardiovascular outcomes\textsuperscript{38–41} and markers of vascular reactivity\textsuperscript{42} and inflammation\textsuperscript{43} suggest that individuals with diabetes are more sensitive to air pollution, as a result of baseline chronic inflammation and endothelial dysfunction.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 temporal, rather than spatial, variability,\textsuperscript{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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