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Short-term Exposure to Ambient Air Pollution and Circulating Biomarkers of Endothelial Cell Activation: The Framingham Heart Study

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Abstract

Background: Short-term exposure to air pollution has been associated with cardiovascular events, potentially by promoting endothelial cell activation and inflammation. A few large-scale studies have examined the associations and have had mixed results.

Methods: We included 3820 non-current smoking participants (mean age 56 years, 54% women) from the Framingham Offspring cohort examinations 7 (1998–2001) and 8 (2005–2008), and Third Generation cohort examination 1 (2002–2005), who lived within 50 km of a central monitoring station. We calculated the 1- to 7-day moving averages of fine particulate matter (PM_{2.5}), black carbon (BC), sulfate (SO₄²⁻), nitrogen oxides (NO_x), and ozone before examination visits. We used linear mixed effect models for P-selectin, monocyte chemoattractant protein 1 (MCP-1),

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Declarations of interest:

None.

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intercellular adhesion molecule 1, lipoprotein-associated phospholipase A2 activity and mass, and osteoprotegerin that were measured up to twice, and linear regression models for CD40 ligand and interleukin-18 that were measured once, adjusting for demographics, life style and clinical factors, socioeconomic position, time, and meteorology.

Results: We found negative associations of PM_{2.5} and BC with P-selectin, of ozone with MCP-1, and of SO₄²⁻ and NO_x with osteoprotegerin. At the 5-day moving average, a 5 µg/m³ higher PM_{2.5} was associated with 1.6% (95% CI: -2.8, -0.3) lower levels of P-selectin; a 10 ppb higher ozone was associated with 1.7% (95% CI: -3.2, -0.1) lower levels of MCP-1; and a 20 ppb higher NO_x was associated with 2.0% (95% CI: -3.6, -0.4) lower levels of osteoprotegerin.

Conclusions: We did not find evidence of positive associations between short-term air pollution exposure and endothelial cell activation. On the contrary, short-term exposure to higher levels of ambient pollutants were associated with lower levels of P-selectin, MCP-1, and osteoprotegerin in the Framingham Heart Study.

Keywords

Air pollution; Endothelial dysfunction; Inflammation; Biomarker; Environment; Epidemiology

1. Introduction

Short-term exposure to ambient air pollution has been associated with acute cardiovascular events^{1, 2}. One of the hypothesized underlying mechanisms is air pollution-induced oxidative stress and inflammation. Higher levels of oxidative stress and inflammation in the vascular system promote platelet and endothelial cell activation, leading to increased tendency towards thrombosis and erosion and/or disruption of atherosclerotic plaque³⁻⁷. For example, CD40 ligand and P-selectin are released upon platelet activation and may enhance endothelial inflammation and upregulate expression of chemokines (such as monocyte chemoattractant protein 1 (MCP-1)) and adhesion molecules (such as intercellular adhesion molecule 1 (ICAM-1)), altering the properties of the endothelium and contributing to the formation of atherosclerotic plaque³⁻⁷. Increased vascular inflammation also stimulates secretion of biomarkers such as interleukin-18, lipoprotein-associated phospholipase A2 (LpPLA2), and osteoprotegerin. Higher levels of interleukin-18 and LpPLA2 are associated with plaque disruption and thrombosis^{8, 9}, and higher levels of osteoprotegerin are associated with vascular calcification in human studies¹⁰⁻¹². Figure 1 illustrates the involvement of these biomarkers.

Several prior studies have examined the associations between short-term exposure to air pollutants and the aforementioned biomarkers that are involved in endothelial cell activation¹³⁻³³. While some of these studies found positive associations between some air pollutants and CD40 ligand¹³⁻¹⁶, P-selectin¹⁴⁻¹⁸, MCP-1^{14, 31}, and ICAM-1^{29, 30}, the findings were generally inconsistent across different air pollutants or studies, possibly because most of these previous studies were conducted with small sample sizes, limited age range, or among participants with conditions that may predispose them to the adverse health effects of air pollution. Some other studies have found null associations with interleukin-18³¹, positive associations with LpPLA2 mass³², and negative associations with osteoprotegerin³³.

Among participants from the Framingham Heart Study, we have found associations between short-term exposure to ambient air pollution and biomarkers of oxidative stress³⁴ and systemic inflammation³⁵. However, the associations for biomarkers of endothelial cell activation and atherosclerotic plaque have not been examined.

We therefore hypothesized that short-term exposure to higher levels of ambient air pollution is associated with higher levels of biomarkers of endothelial cell activation. We investigated the associations among participants from the Framingham Heart Study.

2. Methods

2.1 Study sample

We included participants from the Framingham Offspring cohort examinations 7 (1998-2001) and 8 (2005-2008), and Third Generation cohort examination 1 (2002-2005). The study design and selection criteria of the two cohorts have been described elsewhere^{36, 37}. We restricted our analyses to 4540 participants (6192 observations) who lived within 50 km from the Harvard Supersite air pollution monitor in Boston, Massachusetts. Interleukin-18 levels that were under the minimum detection limit (128 pg/ml) were treated as missing (N=162). We then excluded 879 observations contributed by current smokers because levels of inflammatory biomarkers may be influenced by smoking and may interfere with our ability to assess the relatively small variation in these biomarkers that can be attributed to ambient air pollution³⁸. Last, we excluded 97 observations where data on body mass index, alcohol intake, or pack years of smoking were missing, leaving 3820 participants (5216 observations) in the final dataset. At each examination visit, physical examinations were performed following standardized protocols, and data on demographics, medication history, smoking history, and alcohol intake were collected using standardized questionnaires. All participants provided written informed consent at each examination, and the Institutional Review Boards at Beth Israel Deaconess Medical Center, Harvard T.H. Chan School of Public Health, and Boston University Medical Center approved the study.

2.2 Air pollution and meteorology assessment

We calculated 1-, 2-, 3-, 5-, and 7-day moving averages of the air pollutants prior to the date of examination visit, based on measures of fine particulate matter (particles with diameters $2.5 \mu\text{m}$; $\text{PM}_{2.5}$), black carbon (BC), and sulfate (SO_4^{2-}) from the Boston Harvard Supersite air pollution monitoring station, and measures of nitrogen oxides (NO_x) and ozone (O_3) from local state monitors within the Greater Boston area (three for NO_x and two for O_3)^{39, 40}. The 1-day moving average (lag 0) was calculated as the average from 9:00 am on the day before examination date to 9:00 am on the day of examination visit. The 2-day moving average was calculated as the mean of lag 0 and lag 1. If more than 25% of the days for a moving average were missing, we assigned “missing” to that moving average.

The Supersite monitor is located on the rooftop of the Francis A. Countway Library of Medicine (5 stories above ground level) and 50 m from the nearest street. $\text{PM}_{2.5}$ was measured using a tapered element oscillating microbalance (Model 1400A, Rupprecht & Patashnick Co., Inc.); BC was measured using an aethalometer (Model AE16, Magee

Scientific Corp.); and SO_4^{2-} was measured from elemental sulfur that was measured by X-Ray Fluorescence analysis of the $\text{PM}_{2.5}$ filter samples. On days when SO_4^{2-} X-Ray Fluorescence data were not available, we used an SO_4^{2-} analyzer (Model 5020, Thermo Electron Corp.). Hourly temperature and relative humidity were assessed at the Boston Logan International Airport Weather Station, located 12 km from the Supersite ⁴¹.

2.3 Biomarker assessment

All blood samples were obtained after an overnight fast, typically between 7 and 9 am. Blood specimens were stored at -80°C until assay. Commercially available enzyme-linked immunoassay kits were used to assess P-selectin, MCP-1, ICAM-1 (R&D Systems, Minneapolis, MN); CD40 ligand (Bender MedSystems, Vienna, Austria); interleukin-18 (MBL, Woburn, MA); and osteoprotegerin (BioMedica Incorporate, San Diego, CA). LpPLA2 activity was measured using a colorimetric activity method (diaDexus CAM Kit, Inc., San Francisco, CA).

LpPLA2 mass was measured using a commercially available sandwich enzyme immunoassay (diaDexus PLAC Test, Inc., San Francisco, CA). Details regarding biomarker measurements have been reported elsewhere ⁴²⁻⁴⁴ and can also be found at the Framingham Heart Study website (<https://www.framinghamheartstudy.org>).

2.4 Statistical methods

Because P-selectin, MCP-1, ICAM-1, LpPLA2 activity, LpPLA2 mass, and osteoprotegerin were measured in both Offspring cohort examination 7 (1998-2001) and 8 (2005-2008), we used multivariable linear mixed effects models with participant-specific random intercepts. We used multivariable linear regression models for CD40 ligand and interleukin-18 that were measured only once in the Offspring cohort examination 7. Levels of the biomarkers were loge transformed to meet the model assumptions, assessed by residual plots.

For each moving average, the model was adjusted for demographic variables, individual-level socioeconomic position, census tract-level socioeconomic position, lifestyle factors, clinical factors, time, and meteorology. The covariates were selected because of their role as potential confounders or predictors of the outcome. The demographic variables included centered age at the time of examination visit, (centered age)², and sex. For individual-level socioeconomic position, we adjusted for educational attainment (high school or less, some college, and college graduate) and usual occupation (laborer; sales/homemaker/clerical; professional/executive/supervisory/technical; and unspecified) ^{35, 45}. For census tract-level socioeconomic position, we adjusted for median household income (continuous), median value of owner-occupied housing units (continuous), and population density (people/km², continuous), from U.S. Census 2000 data. For lifestyle factors, we included body mass index, alcohol intake (drinks/week; standardized to 15 ml alcohol/drink, continuous), pack years of smoking (continuous), smoking status (never or former smoker), and tertiles of physical activity index ⁴⁶. For clinical factors, we adjusted for cardiovascular disease status, use of antihypertensive medications, and use of statins, all as binary variables. We adjusted for time by including a linear term of examination date, for seasonality by including sine and cosine terms of the examination date, and for meteorology by adding temperature and

relative humidity. Last, we added an examination cycle identifier for biomarkers that were measured in multiple examinations to account for potential batch effects. We created missing indicators for participants with missing data on educational attainment (34 observations) or physical activity (88 observations).

We conducted a sensitivity analysis restricting analyses to participants who lived within 40 km (4456 observations, 85%) from the central site. We also examined whether associations differed by age (> 65 years old), sex, and diabetes status. Due to the moderate negative correlation between NO_x and O_3 ($r=-0.55$), we conducted a post-hoc sensitivity analysis and included both pollutants in the same model. Last, we examined the associations between moving averages of daily maximum 8-hour O_3 and the levels of measured biomarkers.

Parameter estimates (β s) were scaled by a factor close to the interquartile range of the 1-day moving average: $5 \mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, $0.5 \mu\text{g}/\text{m}^3$ for BC, $2 \mu\text{g}/\text{m}^3$ for SO_4^{2-} , 20 ppb for NO_x , and 10 ppb for O_3 .

We reported percent difference ($(e^{(\text{scaled } \beta)} - 1) \times 100\%$) with 95% confidence intervals (CIs). In interpreting the results, we focused on describing and highlighting association patterns that were consistently observed across multiple moving averages of the pollutants. Analyses were performed using PROC GLM and PROC MIXED in SAS 9.4 (SAS Institute, Inc., Cary, NC). Figures were plotted using Stata 13 (StataCorp LP, College Station, TX).

3. Results

Of the 5216 observations, the mean age was 56 years old (standard deviation (SD): 15) and 2794 (54%) were from women (Table 1). The mean level of the 1-day moving average $\text{PM}_{2.5}$ was $10.2 \mu\text{g}/\text{m}^3$ (SD: 6.1). As expected, the correlations between $\text{PM}_{2.5}$, BC, and SO_4^{2-} were moderate to high, and NO_x was negatively correlated with O_3 (Table 2). The distribution of measured pollutants are shown in Supplemental Figure 1.

Higher levels of exposure to $\text{PM}_{2.5}$ and BC were associated with lower levels of P-selectin: a $5 \mu\text{g}/\text{m}^3$ higher 5-day moving average of $\text{PM}_{2.5}$ and a $0.5 \mu\text{g}/\text{m}^3$ higher 5-day moving average of BC were associated with 1.6% ($-2.8, -0.3$) and 1.8% ($-3.7, 0.1$) lower levels of P-selectin, respectively (Figure 2B). Exposure to higher levels of 1- to 5-day moving averages of O_3 before exam visit was associated with lower levels of MCP-1: a 10 ppb higher 5-day moving average of O_3 was associated with 1.7% ($-3.2, -0.1$) lower levels of MCP-1 (Figure 2C). We also found that higher levels of exposure to SO_4^{2-} and NO_x were associated with lower levels of osteoprotegerin: for the 5-day moving average, a $2 \mu\text{g}/\text{m}^3$ higher SO_4^{2-} and a 20 ppb higher NO_x were associated with 1.1% ($-2.3, 0.2$) and 2.0% ($-3.6, -0.4$) lower levels of osteoprotegerin, respectively (Figure 2E). Higher exposure to O_3 at longer moving averages were associated with higher levels of interleukin-18 (Figure 2F) and LpPLA2 mass (Figure 2G). The associations otherwise appeared to be generally null.

Restricting the study sample to participants who lived within 40 km from the Supersite, or replacing daily 24-hour average O_3 with daily maximum 8-hour O_3 did not alter our results materially (Supplemental Figures 2 and 3). In analyses where we included both NO_x and O_3 in the same model, both NO_x and O_3 appeared to be positively associated with

interleukin-18 across multiple moving averages (Supplemental Figure 4). Among participants with diabetes, we observed consistent and positive associations of $PM_{2.5}$, BC, and SO_4^{2-} with ICAM-1 over multiple moving averages (Figures 3A). We also observed positive associations of BC with MCP-1 among participants with diabetes, and of SO_4^{2-} with MCP-1 among participants younger than 65 years old (Figures 3B and 3C). However, the differing association pattern was not observed between other pollutants and MCP-1. The associations otherwise did not differ by age of 65 years old, sex, or diabetes status (Supplemental Figures 5-7).

4. Discussion

Among participants from the Framingham Offspring and Third Generation cohorts, we found negative associations of $PM_{2.5}$ and BC with P-selectin, of O_3 with MCP-1, and of SO_4^{2-} and NO_x with osteoprotegerin; the associations otherwise appeared to be null. There was no consistent association for ICAM-1 in the overall study sample, however, higher levels of exposure to $PM_{2.5}$, BC, and SO_4^{2-} were associated with higher levels of ICAM-1 among participants with diabetes.

The current study adds to our previous work in the Framingham Heart Study^{34, 35}, in which we found short-term exposure to higher levels of ambient air pollution was associated with higher levels of myeloperoxidase, indexed 8-epi-PGF_{2α}³⁴, C-reactive protein (CRP), interleukin-6, and tumor necrosis factor receptor 2 (TNFR2), but not with fibrinogen or TNFα³⁵. Together we have provided a comprehensive coverage of the associations between short-term exposure to ambient air pollution and biomarkers of oxidative stress, systemic inflammation, and endothelial cell activation among participants from the community-based Framingham Heart Study. Because the magnitude of observed negative associations were rather small and the associations observed were likely transient, the interpretation of our findings may not be suitable for clinical interpretation.

Both CD40 ligand and P-selectin are released upon platelet and endothelial cell activation, and induce the production of reactive oxygen species, adhesion molecules, chemokines, and other inflammatory biomarkers^{4, 5, 7}. Some studies have found positive associations of short-term exposure to air pollution with CD40 ligand¹³⁻¹⁶ and P-selectin¹⁴⁻¹⁸, but not all^{13, 19-21, 31}. Moreover, one of the studies found a negative association for CD40 ligand³¹. However, these studies were all conducted among a relatively small number of participants^{13, 31}, and many were conducted in regions with higher levels of air pollution than the current study^{14-17, 21}.

In the current study, we found generally null associations between $PM_{2.5}$ and MCP-1 and ICAM-1, except that among potentially susceptible participants who had type 2 diabetes, we found positive associations between $PM_{2.5}$ and ICAM-1. Expression of both MCP-1 and ICAM-1 by endothelial cells are upregulated upon stimulation by pro-inflammatory cytokines^{4, 5}. Prior studies of the associations between $PM_{2.5}$ and MCP-1 have had inconsistent results; two studies reported positive associations^{14, 31}, but the association appeared to be null in another study¹⁵.

The association between PM_{2.5} and ICAM-1 has been examined in a larger number of studies^{14, 15, 22-31} and several of them had a relatively large sample size²⁷⁻³⁰; however, the findings were not consistent across studies. For example, in the Multi-Ethnic Study of Atherosclerosis (MESA), Hajat *et al.* found negative associations between the 3- to 5-day moving averages of PM_{2.5} and ICAM-1 among 2865 participants (4007 observations in total), and reasons for this negative association were unclear²⁷. Moreover, PM_{2.5} was positively associated with ICAM-1 in two reports from the Normative Aging Study^{29, 30}.

Sustained baseline inflammation among participants with diabetes may upregulate the inflammatory response to air pollutants⁴⁷, and in our previous work we found a larger magnitude of the associations of short-term air pollution with C-reactive protein and interleukin-6 among participants with diabetes than those without³⁵. In the current study, we found positive associations of PM_{2.5}, BC, and SO₄²⁻ with ICAM-1 across multiple moving averages among participants with diabetes, suggesting potentially higher susceptibility to air pollution among individuals with diabetes.

Both interleukin-18 and LpPLA2 are highly expressed in atherosclerotic plaque, and may result in increased risk of plaque disruption and thrombosis^{7, 8}. LpPLA2 is an enzyme that hydrolyses oxidized phospholipids and generates oxidized free fatty acids and lysophosphatidylcholine, promoting atherogenesis and plaque formation^{8, 9}. Previous small-scale studies have found null associations of PM_{2.5} with interleukin-18 among 72 healthy young participants³¹, but positive associations with LpPLA2 mass among 200 myocardial infarction survivors³². The associations were generally null in the current study. It is possible that the different study sample characteristics contributed to the discrepancies between the current study and previous studies; the study participants in the current study were middle-aged and older, and were generally healthy with relatively low prevalence of cardiovascular disease and diabetes.

The exact role of osteoprotegerin in vascular biology is not clear. In controlled animal studies, osteoprotegerin was found to be a protective factor against atherosclerotic calcification¹⁰⁻¹². However, in human studies, osteoprotegerin was positively associated with vascular calcification and coronary heart disease⁴⁸⁻⁵⁴. It has been proposed that the elevated osteoprotegerin level was the result of a compensatory mechanism¹¹. We found negative associations of SO₄²⁻ and NO_x with osteoprotegerin, similar to the previous study where negative associations were observed between indoor PM_{2.5} from burning of biomass and osteoprotegerin³³.

In summary, in the current study we examined the associations between short-term exposure to ambient air pollution and several biomarkers of endothelial cell activation, and found that the associations were generally null or negative, except for longer moving averages of O₃ with interleukin-18 and LpPLA2 mass. This divergent associations may represent different underlying biological pathways: while P-selectin and MCP-1 are related to platelet activation and stimulation from pro-inflammatory cytokines, and osteoprotegerin is potentially related to vascular calcification, interleukin-18 and LpPLA2 are potentially related to existing plaques. However, the exact biological mechanism remains unclear. As we mentioned before, not many large-scale studies have examined the associations between

short-term exposure to air pollution and the biomarkers that were measured in the current study. Thus, future large-scale studies are needed to examine these associations.

There are several limitations in the current study. First, we measured levels of air pollution at a central air pollution monitor. Previous studies in the Boston region have found moderate correlations between central site measured $\text{PM}_{2.5}$ and SO_4^{2-} and personal exposure levels (regression slope was 0.3 in winter and 0.8-0.9 in summer for $\text{PM}_{2.5}$; and was 0.4-0.6 in winter and 0.7 in summer for SO_4^{2-})^{55, 56}, which supports the rationale of exposure assignment. Moreover, this potential exposure measurement error was likely non-differential. Second, participants from the Framingham Heart Study are mostly middle-aged and older adults of European ancestry; our findings may not be generalizable to different age groups or races/ethnicities. Last, although we adjusted for many potential confounders, we cannot rule out residual or unmeasured confounding, and cannot ascertain temporality in the current study. Thus, the observed associations should not be used to infer causality.

There are also several strengths of the current study. The current study is among a few large-scale studies that included participants from a community-based cohort and examined the associations between ambient air pollution and biomarkers of endothelial cell activation. The Framingham Heart Study utilized standardized protocols for physical examinations and biomarkers assessments. We adjusted for a robust set of potential confounders, including demographic characteristics, lifestyle, individual- and area-level socioeconomic position, meteorology, and time in our analyses. Additionally, levels of air pollutants and biomarkers were measured separately so that any measurement error was likely non-differential. Last, because the differences in air pollution levels between participants were mostly determined by the dates of participants' examination visits and the participants could schedule their examination visit in advance and spread over the year, the possibility of strong residual confounding by examination date is unlikely.

5. Conclusions

Our findings do not support the hypothesis that short-term exposure to ambient air pollution is associated with higher levels of circulating biomarkers of endothelial cell activation among generally healthy adults. Rather, in this region with relatively low levels of ambient air pollution, we found negative associations of several air pollutants with these biomarkers, including P-selectin, MCP-1, and osteoprotegerin. Furthermore, among participants with diabetes, the associations for ICAM-1 appeared to be positive. Future longitudinal studies with large sample sizes and larger variations in air pollution levels are needed to confirm or refute our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BC	Black carbon
ICAM-1	Intercellular adhesion molecule 1
LpPLA2	Lipoprotein-associated phospholipase A2
MCP-1	Monocyte chemoattractant protein 1
NO_x	Nitrogen oxides
O₃	Ozone
PM_{2.5}	Fine particulate matter
SO₄²⁻	Sulfate

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Highlights

- Higher PM_{2.5} and BC were associated with lower P-selectin levels
- Higher ozone was associated with lower MCP-1 levels
- Higher SO₄²⁻ and NO_x were associated with lower osteoprotegerin levels
- Participants with type 2 diabetes may be more susceptible

Fig. 1.

Involvement of CD40 ligand, P-selectin, chemoattractant protein 1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), interleukin-18, lipoprotein-associated phospholipase A2 (LpPLA2), and osteoprotegerin in endothelial cell activation.

Fig. 2.

Associations of 1- to 7-day moving averages of air pollutants with A) CD40 ligand; B) P-selectin; C) monocyte chemoattractant protein 1 (MCP-1); D) intercellular adhesion molecule 1 (ICAM-1); E) osteoprotegerin; F) interleukin-18; G) lipoprotein-associated phospholipase A2 (LpPLA2) mass; and H) LpPLA2 activity. Models were adjusted for centered age, (centered age)², sex, body mass index, smoking status, pack years, alcohol intake, educational attainment, usual occupations, tertiles of physical activity index, census tract median household income, census tract population density, census tract median value of owner-occupied housing unit, cardiovascular disease, use of antihypertensives, use of statins, date of examination visit, sine and cosine season, day of week, temperature, and relative humidity. An exam identifier was added for P-selectin, MCP-1, ICAM-1, osteoprotegerin, LpPLA2 mass, and LpPLA2 activity. Results were scaled to 5 µg/m³ for PM_{2.5}, 0.5 µg/m³ for BC, 2 µg/m³ for SO₄²⁻, 20 ppb for NO_x, and 10 ppb for O₃. Error bars indicate the 95% confidence intervals.

Fig. 3.

Associations of 1- to 7-day moving averages of air pollutants with A) ICAM-1 and B) MCP-1 by **diabetes status**, and with C) MCP-1 by **age of 65 years old**. Models were adjusted for centered age, (centered age)², sex, body mass index, smoking status, pack years, alcohol intake, educational attainment, usual occupations, tertiles of physical activity index, census tract median household income, census tract population density, census tract median value of owner-occupied housing unit, cardiovascular disease, use of antihypertensives, use of statins, date of examination visit, sine and cosine season, day of week, temperature, relative humidity, and an examination identifier. Results were scaled to 5 $\mu\text{g}/\text{m}^3$ for PM_{2.5}, 0.5 $\mu\text{g}/\text{m}^3$ for BC, 2 $\mu\text{g}/\text{m}^3$ for SO₄²⁻, 20 ppb for NO_x, and 10 ppb for O₃. Error bars indicate the 95% confidence intervals.

Table 1.

Characteristics of the 3820 participants (5216 observations) from the Framingham Offspring and Third Generation cohorts.

Characteristics	Offspring Cohort Mean(SD) or N[%]		Third Generation Cohort Mean(SD) or N[%]	Overall Mean(SD) or N[%]
	Cycle 7	Cycle 8	Cycle 1	
Number of observations	1846	1549	1821	5216
Age, years	61.7 (9.5)	67.3 (9.1)	40.1 (8.9)	55.8 (14.9)
Women	987 [53.5]	836 [54.0]	971 [53.3]	2794 [53.6]
Body mass index, kg/m ²	28.4 (5.3)	28.6 (5.4)	27.0 (5.6)	28.0 (5.5)
Alcohol, drinks/week	4.5 (7.0)	4.0 (6.7)	4.3 (6.2)	4.3 (6.6)
Smoking status				
Non-smoker	792 [42.9]	665 [42.9]	1255 [68.9]	2712 [52.0]
Former smoker	1054 [57.1]	884 [57.1]	566 [31.1]	2504 [48.0]
Pack year	14.1 (20.6)	14.1 (20.6)	3.5 (9.0)	10.4 (18.2)
Educational attainment ^a				
High school or less	667 [36.1]	549 [35.4]	266 [14.6]	1482 [28.4]
Some college	563 [30.5]	483 [31.2]	575 [31.6]	1621 [31.1]
College graduate	586 [31.7]	517 [33.4]	976 [53.6]	2079 [39.9]
Diabetes	245 [13.3]	288 [18.6]	55 [3.0]	588 [11.3]
Cardiovascular disease	240 [13.0]	263 [17.0]	28 [1.5]	531 [10.2]
Antihypertensive use	681 [36.9]	920 [59.4]	186 [10.2]	1787 [34.3]
Statins use	422 [22.9]	661 [42.7]	124 [6.8]	1207 [23.1]
CD40 ligand ^b , ng/ml	1.6 (2.0)	-	-	1.6 (2.0)
ICAM-1 ^{b,c} , ng/ml	244.8 (57.9)	291.3 (91.4)	240.1 (57.8)	255.8 (70.5)
Interleukin-18 ^b , pg/ml	250.8 (94.6)	-	-	250.8 (94.6)
LpPLA2 activity ^{b,c} , nmol/min/ml	138.2 (34.4)	134.2 (34.8)	160.8 (36.6)	144.5 (37.2)
LpPLA2 mass ^{b,c} , ng/ml	282.5 (89.8)	192.5 (51.4)	225.8 (46.2)	233.2 (72.2)
MCP-1 ^{b,c} , pg/ml	312.4 (104.4)	374.4 (116.2)	331.1 (109.9)	336.3 (112.6)
P-selectin ^{b,c} , ng/ml	35.3 (13.3)	39.1 (12.6)	45.4 (16.8)	39.7 (14.9)
Osteoprotegerin ^{b,c} , pmol/l	5.4 (1.7)	4.8 (1.6)	-	5.1 (1.7)

Abbreviation: SD, standard deviation; ICAM-1, intercellular adhesion molecule 1; LpPLA2, lipoprotein-associated phospholipase A2; MCP-1, monocyte chemoattractant protein 1.

^a30 (1.6%) and 4 (0.2%) participants in examination cycle 7 and 1, respectively, were missing educational attainment data and were assigned missing indicators.

^bGeometric mean and standard deviation.

^c1352 participants had two measurements of ICAM-1, 1376 participants had two measurements of LpPLA2 activity and LpPLA2 mass, 1328 participants had two measurements of MCP-1, 1395 participants had two measurements of P-selectin, and 1392 participants had two measurements of osteoprotegerin.

Table 2.

Characteristics and the Spearman correlation coefficients between the 1-day moving averages of measured ambient air pollutants.

Pollutant	Number of observations	Mean (SD)	Interquartile Range	Spearman Correlation Coefficients			
				BC	SO ₄ ²⁻	NO _x	O ₃
PM _{2.5} , µg/m ³	5206	10.2 (6.1)	6.4	0.73	0.82	0.41	0.00
BC, µg/m ³	5205	0.8 (0.5)	0.5		0.53	0.57	-0.25
SO ₄ ²⁻ , µg/m ³	4461	3.2 (2.5)	2.4			0.28	0.11
NO _x , ppb	4912	39.1 (21.0)	19.7				-0.55
O ₃ , ppb	5207	23.2 (11.2)	15.4				

Abbreviation: PM_{2.5}, fine particulate matter; BC, black carbon; SO₄²⁻, sulfate; NO_x, nitrogen oxides; O₃, ozone.