



HHS Public Access

Author manuscript

Arterioscler Thromb Vasc Biol. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Arterioscler Thromb Vasc Biol. 2017 September ; 37(9): 1793–1800. doi:10.1161/ATVBAHA.117.309799.

Short-term Exposure to Ambient Air Pollution and Biomarkers of Systemic Inflammation: The Framingham Heart Study

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Abstract

Objective—To examine associations between short-term exposure to ambient air pollution and circulating biomarkers of systemic inflammation in participants from the Framingham Offspring and Third Generation cohorts in the Greater Boston area.

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Disclosures

WL, KSD, MBR, PLL, JDS, BAC, PK, DRG, JFK, RSV, EJB, and MAM declare no conflicts of interest. EHW received non-financial support from Servier.

Approach and Results—We included 3,996 non-current smoking participants (mean age 53.6 years, 54% women) who lived within 50 km from a central air pollution monitoring site in Boston, Massachusetts, and calculated the 1- to 7-day moving averages of fine particulate matter (PM_{2.5}), black carbon (BC), sulfate, nitrogen oxides (NO_x), and ozone prior to the examination visits. We used linear mixed effects models for C-reactive protein (CRP) and tumor necrosis factor receptor 2 (TNFR2) which were measured up to twice for each participant; we used linear regression models for interleukin-6, fibrinogen, and tumor necrosis factor α (TNFα) which were measured once. We adjusted for demographics, socioeconomic position, lifestyle, time, and weather. The 3- to 7-day moving averages of PM_{2.5} and sulfate were positively associated with CRP concentrations. A 5 μg/m³ higher 5-day moving average PM_{2.5} was associated with 4.2% (95% CI: 0.8, 7.6) higher circulating CRP. Positive associations were also observed for NO_x with interleukin-6, and for BC, sulfate, and ozone with TNFR2. However, BC, sulfate, and NO_x were negatively associated with fibrinogen, and sulfate was negatively associated with TNFα.

Conclusions—Higher short-term exposure to relatively low levels of ambient air pollution was associated with higher levels of CRP, interleukin-6, and TNFR2, but not fibrinogen or TNFα, in individuals residing in the Greater Boston area.

Keywords

Air Pollution; Inflammation; Epidemiology; Biomarkers

Subject Terms

Epidemiology; Inflammation; Risk factor

Introduction

Air pollution-induced systemic inflammation is hypothesized to be one of the underlying mechanisms linking ambient air pollution exposure to the risk of cardiovascular disease.^{1, 2} Elevated short-term exposure to ambient fine particulate matter (PM_{2.5}, diameter < 2.5 μm) and gaseous pollutants, such as ozone (O₃), have been associated with higher levels of biomarkers of systemic inflammation in controlled animal studies.^{3–5} However, the majority of human studies that have explored these associations had relatively small sample sizes or had participants with conditions that may predispose them to the health effects of air pollution.^{6–16} Moreover, results from larger-scale epidemiological studies on the associations between air pollution and inflammatory response have yielded mixed results.^{17–23} For example, in the Multi-Ethnic Study of Atherosclerosis with over 6,000 participants, exposure to higher levels of PM_{2.5} on the day of the blood draw was only weakly associated with higher blood levels of C-reactive protein (CRP), however, the association was not observed for circulating interleukin-6 or fibrinogen.²² In the Tel-Aviv Medical Center Inflammation Survey, Steinvil *et al.* found negative associations of sulfur dioxide and nitrogen dioxide with fibrinogen across multiple lags only among male participants (N=2,203), and the associations for CRP were generally null.¹⁷ In contrast, Bind *et al.* reported positive associations of 28-day moving averages of PM_{2.5}, BC, and particle

number with circulating concentrations of CRP in 1,112 participants (3,615 visits in total) in the Normative Aging Study.²⁴

Studies conducted in the Greater Boston area have reported positive associations between short-term exposure to ambient air pollutants and acute cardiovascular events,^{24–26} and our group previously has observed positive associations between short-term exposure to higher levels of ambient air pollution and biomarkers of oxidative stress (myeloperoxidase and 8-epi-prostaglandin F_{2α}) among participants from the Framingham Heart Study.²⁷ However, the associations for circulating biomarkers of systemic inflammation among the participants have not been studied.

We therefore, examined the associations of short-term exposure to ambient air pollutants, measured at central and local air pollution monitors, with circulating concentrations of several biomarkers of systemic inflammation, including CRP, fibrinogen, interleukin-6, tumor necrosis factor α (TNFα), and TNF receptor 2 (TNFR2) among participants from the Framingham Offspring and Third Generation cohorts.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Results

The mean age of our study sample was 53.6 years old (standard deviation: 14.2) and 54% of the observations were in women (Table 1). The characteristics of measured biomarkers are shown in Table 1. The average levels of 1-day moving average PM_{2.5} was 9.7 μg/m³ (Table 2). As expected, BC and SO₄²⁻ were highly correlated with PM_{2.5} (r=0.73 and 0.82, respectively), and O₃ was negatively correlated with NO_x (Table 2). Descriptive statistics and correlation matrix of the 1- to 7-day moving averages of the air pollutants are shown in Supplemental Table I and II. The distributions of measured air pollutants are shown in Supplemental Figure I and the distributions of measured inflammatory biomarkers are shown in Supplemental Figure II.

Higher levels of 3- to 7-day moving averages of PM_{2.5} and SO₄²⁻ were associated with higher CRP levels (Figure 1A): a 5 μg/m³ higher 5-day moving average PM_{2.5} was associated with 4.2% (95% CI: 0.8, 7.6) higher circulating CRP, and a 2 μg/m³ higher 5-day moving average SO₄²⁻ was associated with 2.9% (95% CI: -0.3, 6.3) higher circulating CRP (Figure 1A). A 0.5 μg/m³ higher 5-day moving average BC was associated with 5.8% (95% CI: 0.5, 11.4) higher CRP, however, the associations with other moving averages were generally null. NO_x was consistently and positively associated with interleukin-6 across multiple moving averages (Figure 1B); and BC, SO₄²⁻, and O₃ were positively associated with TNFR2 (Figure 1C). We unexpectedly observed a pattern of negative associations of BC, SO₄²⁻, and NO_x with fibrinogen (Figure 1D), and of 5- and 7-day moving averages of SO₄²⁻ with TNFα (Figure 1E). Overall, the magnitude of the associations appeared larger at longer moving averages, and associations otherwise were generally null.

In sensitivity analyses, we examined the associations under the following conditions separately and together, our results were not materially changed: excluding observations that had a daily average PM_{2.5} concentration >35 µg/m³ in any one of the 7 days prior to the examination date, including current smokers in the analyses, restricting study participants to those who lived within 40 km from the central monitoring site, restricting analyses to the same participants across multiple moving averages for each pollutant, and adjusting for additional individual- and area-level socioeconomic position variables and clinical factors. The results are shown in Supplemental Figure III–VII.

The association between PM_{2.5}, BC, and SO₄²⁻ and TNFR2 was stronger among participants older than 53 years old than those who were younger (Figure 2A). Among participants with diabetes, we found a pattern of stronger associations between BC and NO_x and CRP, and between BC and interleukin-6 across multiple moving averages compared with participants without diabetes (Figure 2B and 2C). Additionally, associations between longer moving averages of PM_{2.5} and CRP were stronger among participants with diabetes than those without (Figure 2B). Furthermore, we observed some evidence of stronger associations of air pollutants with TNFR2 among participants with cardiovascular disease or those who were using statins (Figure 2D and 2E). Although there was no overall association between NO_x and TNFR2, there was an apparent negative association in the warm seasons (April–September) with longer moving averages (Figure 2F). Associations otherwise did not differ by median age, sex, educational attainment, diabetes status, cardiovascular disease status, statins use, anti-hypertensives use, or season (Supplemental Figure VIII–XV). We separately examined the associations between air pollutants and the biomarkers among participants from each cohort and have included the results as Supplemental Figure XVI and XVII.

Because BC and SO₄²⁻ were moderately correlated (r=0.55), we conducted a sensitivity analysis where we put both pollutants (of the same day moving average) in the same model: the associations for both BC and SO₄²⁻ were attenuated, however, SO₄²⁻ was still positively associated with TNFR2 and negatively associated with TNFα, and BC was still negatively associated with fibrinogen (Figure 3C, 3D, and 3E).

Discussion

Among participants from the community-based Framingham Offspring and Third Generation cohorts living in the greater Boston area, we observed positive associations of PM_{2.5} and SO₄²⁻ with blood levels of CRP, of NO_x with serum interleukin-6, and of BC, SO₄²⁻ and O₃ with plasma TNFR2 concentrations. We also observed negative associations between BC, SO₄²⁻, and NO_x with plasma fibrinogen and between SO₄²⁻ and TNFα. Stronger associations were mostly found with longer moving averages. We further showed that the observed associations for CRP were stronger among participants who had diabetes mellitus, and the observed associations for TNFR2 were stronger among those who were older than 53 years at the time of their examination visits.

Acute inflammation may initiate increased secretion of pro-inflammatory cytokines such as interleukin-6 and TNFα, and further stimulate and mediate hepatic production of acute

phase proteins, such as CRP and fibrinogen.^{28, 29} The levels of these biomarkers would increase within a few days after initiation of inflammatory response.^{29, 30} Results from studies *in vivo* suggested a downmodulating role of TNFR2 in TNF α -induced inflammatory responses.^{31–34} Moreover, TNF receptor plays an important role in mediating O₃-induced pulmonary inflammation and hyperreactivity.³⁵ Our work in the Framingham Offspring cohort showed that higher short-term exposures to ambient air pollutants measured at the central site was associated with higher levels of oxidative stress biomarkers.²⁷ Thus, it is reasonable to expect that higher levels of air pollution may also be associated with higher levels of inflammatory response among the participants. The magnitude of the associations in our findings were rather small. Thus, the interpretation of this likely transient change may not be suitable for clinical interpretation. From a physiological perspective, however, this transient but small difference may still contribute to the associations between air pollution and acute cardiovascular events, as air pollution-induced oxidative stress and inflammation was considered as one of the underlying mechanisms.

In the current study, we observed positive associations of PM_{2.5}, BC, and SO₄²⁻ with serum CRP at longer moving averages of these pollutants. Past studies reported mixed associations between acute exposures to ambient air pollutants and CRP, interleukin-6, TNF α , or TNFR2.^{8–13, 22, 23} In the Multi-Ethnic Study of Atherosclerosis, higher levels of PM_{2.5} on the day of blood draw was associated with higher CRP concentrations (1% difference in CRP for each 5 $\mu\text{g}/\text{m}^3$ difference in PM_{2.5}, 95% CI: 0–3%), but this positive association was not found with longer moving averages.^{22, 23} The discrepancy may be due to different population characteristics or different compositions of ambient PM_{2.5}. We did not find positive associations for TNF α , however, O₃ was positively associated with TNFR2. It is possible that higher levels of TNFR2 masked the associations for TNF α . However, given the observational design of our study, we cannot rule out residual confounding or unmeasured confounding.

The associations of PM_{2.5} with fibrinogen in our current study were generally null, but we observed negative associations of BC, SO₄²⁻, and NO_x with fibrinogen. Prior studies have not found consistent associations between ambient air pollutants and fibrinogen.^{6, 7, 13–15, 17–22} For example, in the Normative Aging Study, a cohort of elderly men, short-term exposure to BC and NO_x were associated with higher blood levels of fibrinogen.⁶ Among 2,086 women, Green *et al.* reported null associations between 1-day average PM_{2.5} and O₃ with plasma fibrinogen.¹⁹ In another study conducted in Italy with 1,218 healthy participants, the 7-day moving average of O₃ was negatively associated with plasma fibrinogen.²¹ The reasons for the observed negative associations between BC, SO₄²⁻, and NO_x and fibrinogen were unclear and we do not have a plausible explanation; it could be a chance finding, however, we cannot rule out residual confounding or unmeasured confounding.

We observed consistently stronger associations of PM_{2.5}, BC, and SO₄²⁻ with TNFR2 among older participants. Older populations are generally considered particularly susceptible to the adverse health effects of air pollution on cardiovascular disease morbidity and mortality.^{36–38} Although air pollution-induced inflammation may be one of the underlying pathways linking air pollution exposure to acute cardiovascular events, few

studies have examined whether age modifies the association between air pollution and inflammation, and have had mixed results.^{13, 23} Our findings of stronger associations of PM_{2.5}, BC, and SO₄²⁻ with TNFR2 among older participants adds some supportive new evidence to the literature. Our findings further suggest that the relatively higher prevalence of cardiovascular disease, diabetes, and indication for medication use may contribute to the susceptibility. Sustained baseline inflammation may induce endothelial dysfunction and dysregulation of cytokine secretion, which may exaggerate inflammatory response among participants with diabetes.¹⁰ Similar to our previous report of stronger associations between higher levels of ambient air pollution and biomarkers of oxidative stress in the Framingham Heart Study participants who had diabetes,²⁷ we observed some evidence of a larger magnitude of the associations of PM_{2.5}, BC, and NO_x with CRP, and of BC with interleukin-6 among participants with diabetes than those without. The wide 95% CIs indicate a loss of statistical power that may be due to the relatively low prevalence of diabetes in our study sample. Lastly, the observed differing associations between air pollutants and TNFR2 between the Offspring and Third Generation cohorts were likely driven by the uneven distribution of age and clinical factors such as cardiovascular disease and indication for statins use.

In our study region, ambient air pollution is from both regional emissions and local sources such as traffic and residential heating.³⁹ In this region, BC and NO_x were viewed as correlates of local traffic, and SO₄²⁻ is primarily transported from coal-fired power plants and to a lesser extent is generated from diesel exhaust.⁴⁰ In our sensitivity analysis, adjusting for both BC and SO₄²⁻ in the models led to attenuated associations but the positive associations between SO₄²⁻ and TNFR2 and the negative associations between SO₄²⁻ and TNF α remained, suggesting a possibly stronger role of transported air pollutants in these associations.

Our study has several limitations that should be noted. The exposures were measured at central air pollution monitoring stations and were assigned to each participant. This may induce potential exposure measurement error, likely non-differential, which may decrease our statistical power and attenuate our results. Previous studies in the Boston region compared air pollutants measured by personal monitor and the central site, and showed moderate correlations between PM_{2.5} and SO₄²⁻ measured at this central site and personal exposure levels (slope for PM_{2.5} was 0.3 in winter and 0.8–0.9 in summer; slope for SO₄²⁻ was 0.4–0.6 in winter and 0.7 in summer),^{41, 42} which provided support and rationale for the exposure assignment. Additionally, most of the short-term variability in exposure within our region is related to temporal (day to day) variability, rather than spatial variability.⁴³ Moreover, the levels of air pollutants were related to the date that participants came for their examination appointment. Since participants scheduled their appointments months earlier, it is unlikely that the choice of date would be related to the air pollution levels before the pre-scheduled appointment. Thus, we expect the exposure measurement error due to assignment to be non-differential, leading to attenuated point estimates and wider confidence intervals. The study participants were predominantly middle-aged and older adults of European ancestry, which limits the generalizability of our results to populations of different ethnicities or age groups. Last, we cannot exclude the possibility of residual confounding,

unmeasured confounding, thus, the observed associations should not be used to infer causality.

There are also several strengths worth noting. First, we had a relatively large study sample from two community-based cohorts with standardized protocols for physical examinations and high-quality biomarker assessments. Second, we adjusted for demographic characteristics, lifestyle, individual- and area-level of socioeconomic position, meteorology, and time in our analyses. Third, assessments of air pollutants and biomarkers were performed separately in our study (blinded to the results of each other), and the participants scheduled their examination visit months in advance.

In conclusion, our findings suggest that in a region in compliance with current air quality standards, elevated exposure to ambient air pollutants over a few days was associated with higher levels of biomarkers of systemic inflammation. Together with our previous work on biomarkers of oxidative stress, we have provided suggestive evidence for potential pathways that may partly explain the link between short-term air pollution exposures and acute cardiovascular events in our study region.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the Framingham Offspring and Third Generation Study Participants.

Sources of Funding

This publication was made possible by USEPA grant numbers RD-834798 and RD-835872. Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the USEPA. Further, USEPA does not endorse the purchase of any commercial products or services mentioned in the publication. This work was further supported by the National Heart, Lung, and Blood Institute (NHLBI) contracts and grants HHSN268201500001I, N01-HC 25195, 1R01HL64753, R01HL076784, 1R01AG028321, 1R01HL128914, 1P50HL120163, and T32HL007575, and National Institute of Environmental Health Sciences (NIEHS) grants P01ES09825, K23ES026204, R00ES022243, and P30ES000002.

Nonstandard Abbreviations and Acronyms

PM_{2.5}	Fine particulate matter
BC	Black carbon
SO₄²⁻	Sulfate
NO_x	Nitrogen oxides
O₃	Ozone
CRP	C-reactive protein
TNFα	Tumor necrosis factor α
TNFR2	Tumor necrosis factor receptor 2

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Highlights

- Air pollution-induced systemic inflammation may partially explain the link between short-term exposure to higher levels of air pollution and acute cardiovascular events, however, results from prior large-scale epidemiological studies on the associations between short-term exposure to air pollution and systemic inflammation are mixed.
- We found positive associations of short-term exposure to fine particulate matter and sulfate with C-reactive protein, of nitrogen oxides with interleukin-6, and of black carbon, sulfate, and ozone with tumor necrosis factor receptor 2 in a large sample of generally healthy participants in a region with relatively low levels of air pollution.
- We unexpectedly observed negative associations of black carbon, sulfate, and nitrogen oxides with fibrinogen.
- Older people and individuals with type 2 diabetes might be more susceptible to a pro-inflammatory response to high air pollution exposure.

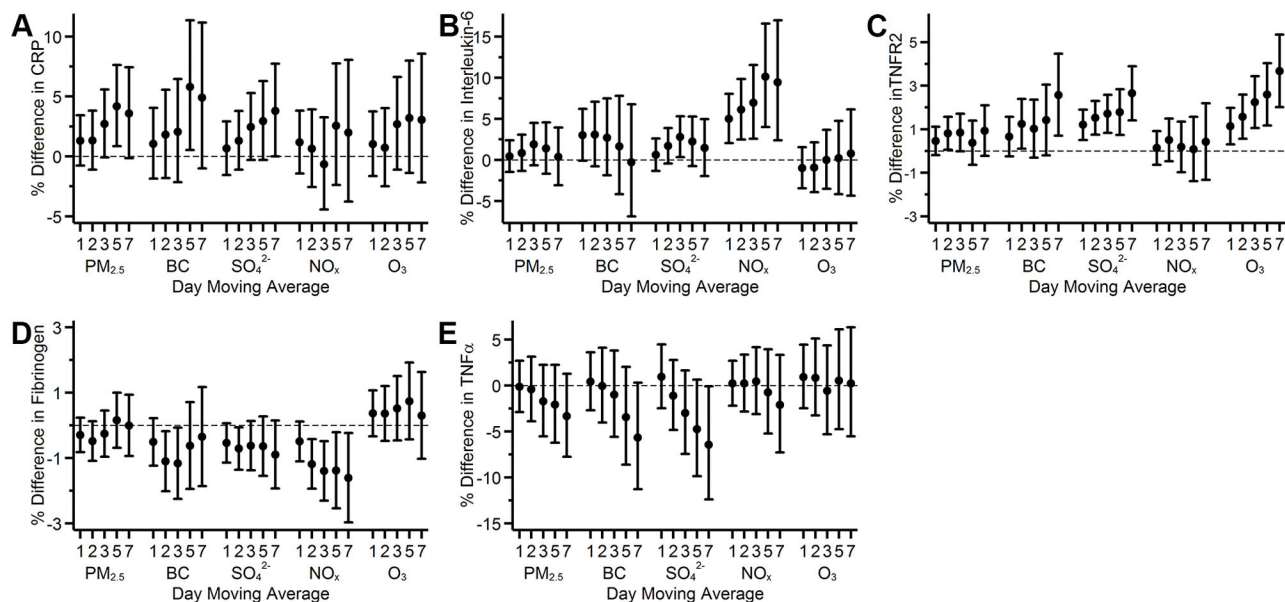


Figure 1.

Associations of 1- to 7-day moving averages of air pollutants with A) \log_e C-reactive protein (CRP); B) \log_e interleukin-6; C) \log_e tumor necrosis factor receptor 2 (TNFR2); D) \log_e fibrinogen; and E) \log_e TNF α among participants from the Framingham Offspring cohort examination 7 (1998–2001), examination 8 (2005–2008), Third Generation cohort examination 1 (2002–2005), and examination 2 (2008–2011). Models were adjusted for centered age, (centered age)², sex, body mass index, smoking status, pack years, alcohol intake, educational attainment, census tract median household income, date of examination visit, sine and cosine season, day of week, temperature, and relative humidity. An exam identifier was added for CRP, interleukin-6, TNFR2, and fibrinogen. Results were scaled to 5 $\mu\text{g}/\text{m}^3$ for fine particulate matter (PM_{2.5}), 0.5 $\mu\text{g}/\text{m}^3$ for black carbon (BC), 2 $\mu\text{g}/\text{m}^3$ for sulfate (SO₄²⁻), 20 ppb for nitrogen oxides (NO_x), and 10 ppb for ozone (O₃). Error bars indicate the 95% confidence intervals.

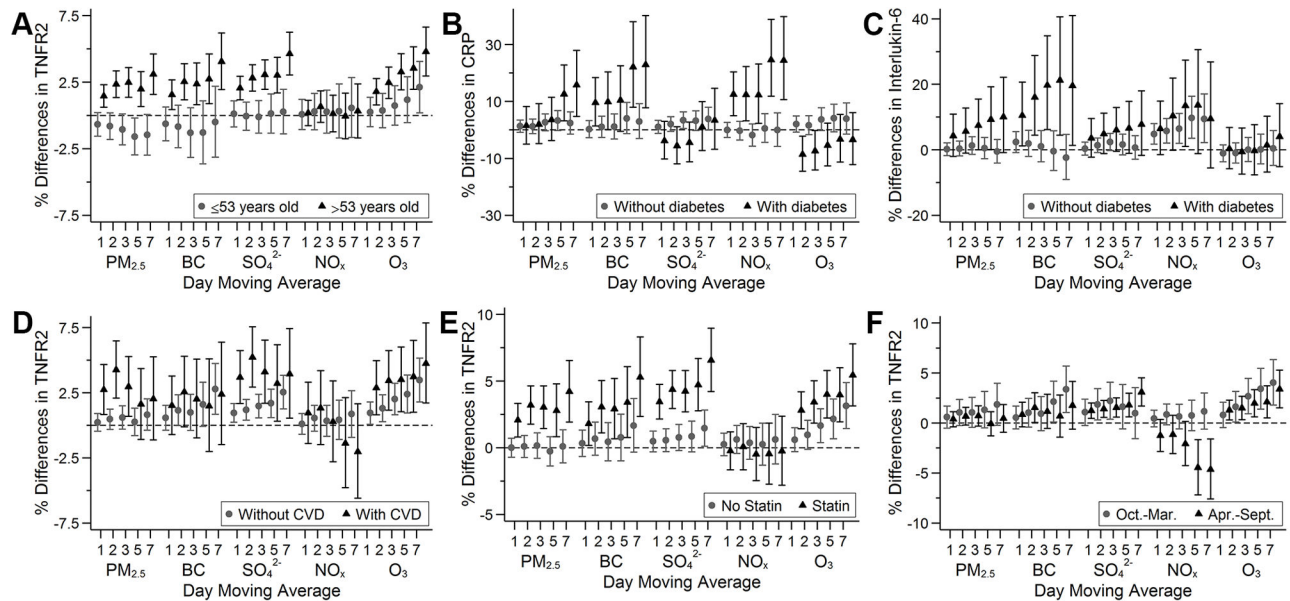


Figure 2.

Associations of 1- to 7-day moving averages of air pollutants with TNFR2 stratified by median age (A); with C-reactive protein (CRP) and interleukin-6 stratified by diabetes status (B and C); and with TNFR2 stratified by season (D) among participants from the Framingham Offspring cohort examination 7 (1998–2001), examination 8 (2005–2008), Third Generation cohort examination 1 (2002–2005), and examination 2 (2008–2011). Models were adjusted for centered age, (centered age)², sex, body mass index, smoking status, pack years, alcohol intake, educational attainment, census tract median household income, date of examination visit, sine and cosine season, day of week, temperature, and relative humidity. An exam identifier was added for CRP, interleukin-6, TNFR2, and fibrinogen. Results were scaled to 5 $\mu\text{g}/\text{m}^3$ for fine particulate matter (PM_{2.5}), 0.5 $\mu\text{g}/\text{m}^3$ for black carbon (BC), 2 $\mu\text{g}/\text{m}^3$ for sulfate (SO₄²⁻), 20 ppb for nitrogen oxides (NO_x), and 10 ppb for ozone (O₃). Error bars indicate the 95% confidence intervals.

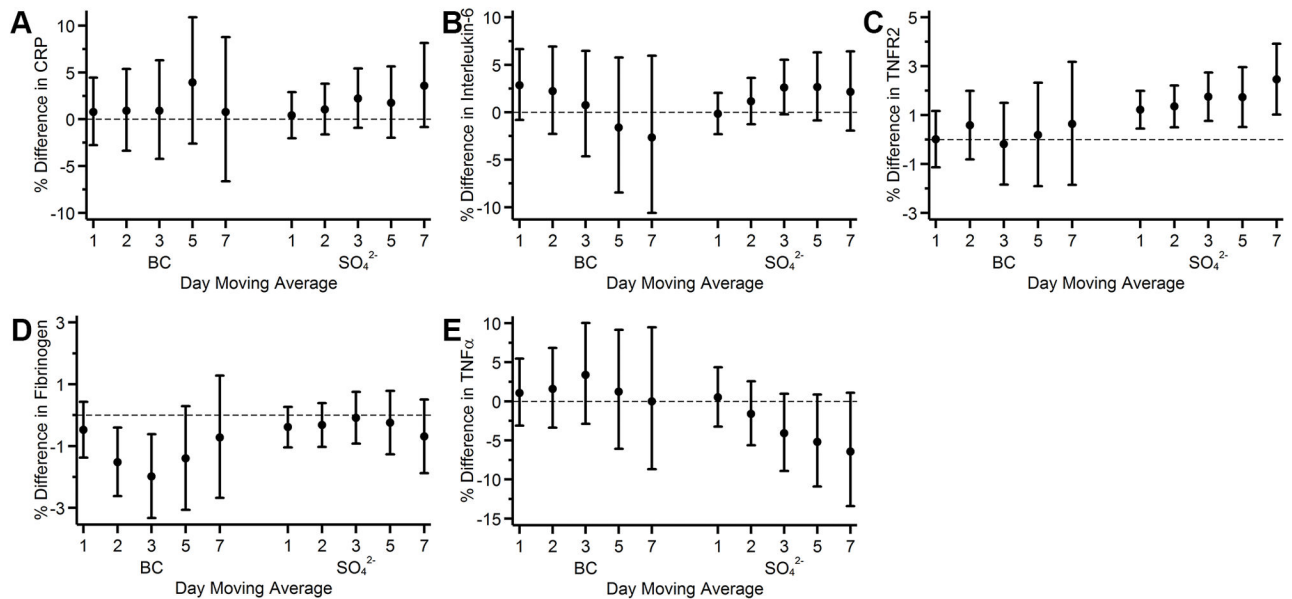


Figure 3.

Associations of 1- to 7-day moving averages of black carbon (BC) and sulfate (SO₄²⁻) with A) log_e C-reactive protein (CRP); B) log_e interleukin-6; C) log_e tumor necrosis factor receptor 2 (TNFR2); D) log_e fibrinogen; and E) log_e TNFα among participants from the Framingham Offspring cohort examination 7 (1998–2001), examination 8 (2005–2008), Third Generation cohort examination 1 (2002–2005), and examination 2 (2008–2011). Models were adjusted for same-day moving averages of BC and SO₄²⁻. Covariates included in the models were centered age, (centered age)², sex, body mass index, smoking status, pack years, alcohol intake, educational attainment, census tract median household income, date of examination visit, sine and cosine season, day of week, temperature, and relative humidity. An exam identifier was added for TNFR2 and fibrinogen. Results were scaled to 5 μg/m³ for fine particulate matter (PM_{2.5}), 0.5 μg/m³ for BC, 2 μg/m³ for SO₄²⁻, 20 ppb for nitrogen oxides (NO_x), and 10 ppb for ozone (O₃). Error bars indicate the 95% confidence intervals.

Table 1

Characteristics of the 6,814 observations from 3,996 participants in the Framingham Offspring cohort examination 7 (1998–2001), examination 8 (2005–2008), Third Generation cohort examination 1 (2002–2005), and examination 2 (2008–2011).

Characteristics	Offspring cohort* (N=1,999)	Third Generation cohort* (N=1,997)	Overall* (N=3,996)
Number of observations	3,396	3,418	6,814
Age, years	64.2 [9.8]	43.1 [9.3]	53.6 [14.2]
Women	1,823 (54%)	1,825 (53%)	3,648 (54%)
Body mass index, kg/m ²	28.5 [5.4]	27.6 [5.7]	28.1 [5.6]
Alcohol, drinks/week	4.3 [6.9]	4.4 [6.2]	4.3 [6.5]
Former Smoker	1,938 (57%)	1,114 (33%)	3,052 (45%)
Education [†]			
High school or less	1,217 (36%)	496 (15%)	1,713 (25%)
Some college	1,046 (31%)	1,059 (31%)	2,105 (31%)
College graduate	1,103 (32%)	1,858 (54%)	2,961 (43%)
Antihypertensive medication use	1,602 (47%)	507 (15%)	2,109 (31%)
Statins use	1,083 (32%)	386 (11%)	1,469 (22%)
Cardiovascular disease	504 (15%)	66 (2%)	570 (8%)
Diabetes	534 (16%)	143 (4%)	677 (10%)
CRP [‡] , mg/l	2.0 [2.2]	1.2 [1.5]	1.6 [1.8]
Fibrinogen [‡] , mg/100 ml	372 [72]	331 [66]	351 [72]
Interleukin-6 [‡] , pg/ml	2.0 [1.5]	1.4 [0.9]	1.6 [1.2]
TNF α [‡] , pg/ml	1.3 [0.6]		1.3 [0.6]
TNFR2 [‡] , pg/ml	2289 [812]	2,180 [524]	2,250 [720]

Abbreviation: SD, standard deviation; CRP, C-reactive protein; TNFR2, tumor necrosis factor receptor 2; TNF α : tumor necrosis factor α .

* Mean [SD] or N (%).

[†] There were 35 observations where educational attainment information were missing.

[‡] Geometric mean [standard deviation of the geometric mean].

Characteristics of air pollutants 1 day prior to the examination date in the study sample.

Table 2

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	6,800	9.7 (5.8)	5.7	0.73	0.82	0.43	0.02
BC, µg/m ³	6,793	0.8 (0.4)	0.5		0.55	0.58	-0.25
SO ₄ ²⁻ , µg/m ³	5,921	2.9 (2.4)	2.2			0.32	0.12
NO _x , ppb	6,510	36.5 (20.0)	19.0				-0.54
O ₃ , ppb	6,805	23.7 (10.9)	14.4				

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