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## Recent Exposure to Particle Radioactivity and Biomarkers of Oxidative Stress and Inflammation: The Framingham Heart Study

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### Abstract

**Background:** Decay products of radioactive materials may attach to ambient fine particles and form radioactive aerosol. Internal ionizing radiation source from inhaled radioactive aerosol may contribute to the fine particulate matter (PM<sub>2.5</sub>)-inflammation pathway. However, few studies in humans have examined the associations.

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**Objectives:** To examine the associations between particle radioactivity and biomarkers of oxidative stress and inflammation among participants from the Framingham Offspring and Third Generation cohorts.

**Methods:** We included 3,996 participants who were not current smokers and lived within 50 km from our central air pollution monitoring station. We estimated regional mean gross beta radioactivity from monitors in the northeastern U.S. as a surrogate for ambient radioactive particles, and calculated the 1- to 28-day moving averages. We used linear regression models for fibrinogen, tumor necrosis factor  $\alpha$ , interleukin-6, and myeloperoxidase which were measured once, and linear mixed effect models for 8-epi-prostaglandin  $F_{2\alpha}$ , C-reactive protein, intercellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), P-selectin, and tumor necrosis factor receptor-2 that were measured up to twice, adjusting for demographics, individual- and area-level socioeconomic positions, time, meteorology, and  $PM_{2.5}$ . We also examined whether the associations differed by median age, sex, diabetes status,  $PM_{2.5}$  levels, and black carbon levels.

**Results:** The mean age was 54 years and 54% were women. An interquartile range ( $3 \times 10^{-3}$  pCi/m<sup>3</sup>) higher beta radioactivity level at the 7-day moving average was associated with 5.09% (95% CI: 0.92, 9.43), 2.65% (1.10, 4.22), and 4.71% (95% CI: 3.01, 6.44) higher levels of interleukin-6, MCP-1, and P-selectin, but with 7.01% (95% CI: -11.64, -2.15) and 2.70% (95% CI: -3.97, -1.42) lower levels of 8-epi-prostaglandin  $F_{2\alpha}$  and ICAM-1, respectively.

**Conclusions:** Regional mean particle radioactivity was positively associated with interleukin-6, MCP-1, and P-selectin, but negatively with ICAM-1 and 8-epi-prostaglandin  $F_{2\alpha}$  among our study participants.

## Graphical Abstract

Associations between the 7-day moving average of regional mean gross beta radioactivity (per  $3 \times 10^{-3}$  pCi/m<sup>3</sup>) and levels of oxidative stress and inflammation biomarkers among participants from the Framingham Offspring and Third Generation cohorts.

## Keywords

gross beta radiation; particle radioactivity; epidemiology; environment; inflammation; oxidative stress

## 1. Introduction

Individuals are constantly exposed to naturally occurring radioactive materials, mainly contributed by decay products of radon ( $^{222}\text{Rn}$ ) and thoron ( $^{220}\text{Rn}$ ) (Amrane et al. 2014). The radioactive gaseous nuclides escape from the soil produce near ground and can attach to ambient particles forming a radioactive airborne particle mixture (radioactive aerosol). Studies have shown that the majority of this radioactivity is connected with suspended fine particles ( $PM_{2.5}$ ; particulate matter with aerodynamic diameter  $\leq 2.5 \mu\text{m}$ ) (Mohery et al. 2014; Moriizumi et al. 2014; Papastefanou 2009; Röbig et al. 1981). Compared to particles with larger aerodynamic diameter (e.g.  $PM_{2.5-10}$ ),  $PM_{2.5}$  has larger surface, higher pulmonary deposition efficiency, and can penetrate deeper into the lung. Once inhaled, the

radioactive aerosol may reach the alveoli and may be capable of inducing local oxidative stress and inflammation. In the indoor environment, the levels of radioactive aerosol may build up and have potential adverse health effects: higher exposure to indoor radon ( $^{222}\text{Rn}$ ) has been associated with elevated lung cancer risk (Field et al. 2006; IARC 1988). In the outdoor environment, the decay products of radon and thoron ( $^{220}\text{Rn}$ ) contribute to the majority of radioactive exposure (Akan et al. 2014) but at lower levels.

Exposure to ambient  $\text{PM}_{2.5}$  has been associated with cardiovascular and respiratory disease, with air pollution-induced oxidative stress and inflammation hypothesized as important underlying mechanisms. However, the contributions of  $\text{PM}_{2.5}$  constituents to these mechanisms are unclear. We, therefore, hypothesized that internal ionizing radiation source formed by inhaled ambient radioactive particles may contribute to the  $\text{PM}_{2.5}$ -inflammation pathway.

Beta particles are high-energy and high-speed electrons or positrons that are emitted during radioactive decay. In the current study, we measured regional gross beta radioactivity levels as a surrogate of particle radioactivity, and examined the associations of regional beta radioactivity with systemic biomarkers of oxidative stress and inflammation among participants from the Framingham Offspring and Third Generation cohorts, an ambulatory community-based sample residing in the Northeast U.S..

## 2. Material and methods

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Framingham Heart Study at <https://www.framinghamheartstudy.org/researchers/>.

### 2.1 Study sample

We included participants who attended the seventh (1998–2001) and eighth (2005–2008) examinations of the Framingham Offspring cohort and the first (2002–2005) and second (2008–2011) examinations of the Third Generation cohort. The details of study design and selection criteria of both cohorts have been described elsewhere (Kannel et al. 1979; Splansky et al. 2007). For the current study, we included 4,056 participants (6,963 observations) who were not current smokers (1,115 observations from 571 participants were excluded) and lived within 50 km from the Harvard Supersite air pollution monitoring station (Boston, MA, USA). We excluded current smokers because the likely elevated levels of inflammatory biomarkers among current smokers may interfere with our ability to estimate the expected small magnitude of changes in biomarker levels associated with particle radioactivity (Levitzky et al. 2008). We assigned “missing” to biomarker levels that were lower than the minimum detection limit (27 observations for C-reactive protein (CRP), 10 observations for interleukin-6, and 1 observation for tumor necrosis factor receptor-2 (TNFR-2)), or that were extremely high (1 observation with TNFR-2 level at 948,114 pg/ml). In total, we excluded 32 observations with no measurement of any biomarker, and 103 observations with missing data on body mass index, alcohol intake, and cigarette smoking pack-years. We additionally excluded 14 observations with no measurement of  $\text{PM}_{2.5}$  on the day before examination visit, because we adjusted for  $\text{PM}_{2.5}$  in the primary analyses, leaving

3,996 participants (6,814 observations) eligible for the present analyses. At each examination visit, physical exams were performed following standardized protocols, and we collected data on demographics, medication history, smoking history, and alcohol intake using publicly available questionnaires. All participants provided written informed consent at each examination, and the Institutional Review Boards at Beth Israel Deaconess Medical Center (CCI Protocol#: 2009-P-000224) and Boston University Medical Center approved the study.

## 2.2 Exposure assessment

Gross beta particle radioactivity, which measures beta radioactivity regardless of specific radionuclide source, was used as a surrogate for particle radioactivity in this study. The gross beta activity data was obtained from the U.S. Environmental Protection Agency's RadNet monitoring network (U.S. Environmental Protection Agency 2017). The RadNet network was established in 1973 and it consists of 135 sampling stations that collect airborne particulate samples. Each stationary air monitoring station is equipped with a Total Suspended Particle high volume air sampler that collects particles on filters that are replaced twice per week. The gross beta radioactivity was then measured in the field following a 5-hour period to permit decay of short-lived radon progenies (e.g.,  $^{214}\text{Pb}$ ,  $^{214}\text{Bi}$ ) that may be attached to the collected particles. Based on laboratory experiments, conducted at the Kuwait Institute of Scientific Research, we found that much of the beta radiation, after the short-lived radon progenies are decayed and in the absence of artificial radionuclides, is due to the  $^{212}\text{Pb}$ . This is a progeny of  $^{220}\text{Rn}$  (Thoron) and has a half-life of approximately 10 hr. We also found strong correlation between gross beta and gross alpha activities (adjusted  $R^2=0.98$ ). To determine the quantity of beta radioactivity on the filters, background radioactivity level was subtracted from the gross beta activity measurements.

Data from four monitoring sites (Boston, Massachusetts; Worcester, Massachusetts; Providence, Rhode Island; and Albany, New York) were used in the current study. Because the measurements were taken over several days (typically 5 to 7 days), the same mean gross beta radioactivity level was assigned to days within the same sampling period, and we then calculated moving averages based on daily values. Because data collected from each site did not cover the entire study period, we used measurements of gross beta radioactivity from the Albany site, which covered the majority days in the study period from 1998 to 2011, to impute missing levels of gross beta radioactivity in each of the other three sites separately. Briefly, for each site we regressed the available daily measurements on the corresponding data collected at the Albany site to estimate a slope and an intercept that we used to predict the missing gross beta radioactivity levels. The  $R^2$  values for the three calibration regressions ranged from 0.62 to 0.71. For the 83 noncontiguous days during the study period that the Albany site had no measurement, levels of gross beta radioactivity were first interpolated based on measured values at the site, and then were used to predict beta radioactivity levels in the other three sites. Last, we averaged the daily gross beta radioactivity levels from all three sites (Boston, Worcester, and Providence) to obtain the regional daily beta radioactivity level for the current study. Detailed assessment methods have been described elsewhere (Nyhan et al. 2018). We have provided a map showing the relative locations of the monitoring sites and the distributions of our study sample (Figure 1).

### 2.3 Ambient PM<sub>2.5</sub>, black carbon (BC), temperature, and relative humidity

We calculated daily PM<sub>2.5</sub> and BC concentrations based on hourly measurements from the Harvard Boston Supersite air pollution monitoring station. This monitoring station is located on the rooftop of the Francis A. Countway Library of Medicine (20 m above ground) and 50 m from the nearest street. PM<sub>2.5</sub> was measured using a tapered element oscillating microbalance (Model 1400A, Rupprecht & Patashnick Co., Inc.); BC was measured using an aethalometer (Model AE-16, Magee Scientific Corp.). The detailed measurement methods have been described previously (Kang et al. 2010). We obtained temperature and relative humidity data from Boston Logan International Airport Weather Station, located 12 km from the central site.

### 2.4 Biomarker assessment

The blood samples were collected in the morning after an overnight fast, and were stored at  $-80^{\circ}\text{C}$  until the biomarkers were assayed. The urine samples were collected and stored at  $-20^{\circ}\text{C}$  (for creatinine) or  $-80^{\circ}\text{C}$  (for 8-epi-prostaglandin F<sub>2 $\alpha$</sub>  (8-epi-PGF<sub>2 $\alpha$</sub> )) until the biomarkers were assayed. Plasma samples were analyzed for myeloperoxidase (MPO), P-selectin, TNF- $\alpha$ , TNFR-2, and fibrinogen, serum samples were assessed for CRP, interleukin-6, intercellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein-1 (MCP-1). CRP was measured in the Offspring cohort examination cycle 7 and Third Generation cohort examination cycle 1 using a Dade Behring BN 100 nephelometer; cycle 8 and Third Generation cohort examination cycle 2 used Roche Diagnostics Latex High Sensitivity Assay. Fibrinogen was measured in duplicate from citrated plasma using the Clauss method (Diagnostica Stago Reagents) in the Offspring cohort examination cycle 7 and Third Generation cohort examination cycle 1. MPO was measured in the Offspring cohort examination cycle 7 and 8-epi-PGF<sub>2 $\alpha$</sub>  were measured in examination cycles 7 and 8, both by enzyme immunoassay kit (OXIS Health Products and Cayman Chemical, respectively). Measured 8-epi-PGF<sub>2 $\alpha$</sub>  was adjusted for urinary creatinine to account for urine dilution. Commercially available ELISA kits (R&D Systems) were used to measure ICAM-1, interleukin-6, MCP-1, P-selectin, TNF- $\alpha$ , and TNFR-2. All intra-assay coefficients of variation were  $<10\%$ . Details regarding biomarker measurements have been reported elsewhere (Fontes et al. 2013; Keaney et al. 2003; McManus et al. 2013; Pou et al. 2007) and can also be found at the Framingham Heart Study website: <https://www.framinghamheartstudy.org/researchers/description-data/noninvasive-biomarker.php>.

### 2.5 Statistical methods

We calculated 1-, 7-, 14-, 21-, and 28-day moving averages of the regional mean beta radioactivity level, PM<sub>2.5</sub>, and BC prior to examination dates. We defined the 1-day moving average as the average value on the day before the examination. For each moving average, we fitted multivariable linear regression models for MPO, fibrinogen, TNF- $\alpha$ , and interleukin-6, and multivariable linear mixed effects models with subject-specific random intercepts for indexed 8epi-PGF<sub>2 $\alpha$</sub> , CRP, TNFR-2, ICAM-1, MCP-1, and P-selectin. We log<sub>e</sub>-transformed the levels of biomarkers so that the residuals approximated a normal distribution. In the statistical models we adjusted for demographic variables and individual- and area-level socioeconomic position variables: centered age and (centered age)<sup>2</sup>; sex; body

mass index; cigarette smoking status (former or never smoker); cigarette pack-years; alcohol intake (drinks/week; standardized to 15 mL alcohol/drink) (Elias et al. 1999); educational level (high school or less, some college, and college graduate); median household income in the participant's census tract from U.S. Census 2000 data. To account for seasonality and time, we adjusted for a linear term of examination date, day of week of examination date, and sine and cosine day of the year (calculated as  $\sin(2\pi \times (\text{day of year})/365.24)$  and  $\cos(2\pi \times (\text{day of year})/365.24)$ ). We also adjusted for temperature and relative humidity to account for meteorological conditions. In addition, we adjusted for  $\text{PM}_{2.5}$  in the model because the concentration of  $\text{PM}_{2.5}$  may affect measured radioactivity and is associated with levels of inflammation (Li et al. 2017). Last, we adjusted for an examination identifier if the biomarker was measured in multiple examinations. Because the percent of missingness in education attainment is very small ( $N=35$ ; 0.5%), we created a missing indicator for those participants.

For sensitivity analyses, we examined whether associations differed after including current smokers or after replacing  $\text{PM}_{2.5}$  with BC in the model. We also examined whether associations varied by median age (53 years), sex, diabetes, and  $\text{PM}_{2.5}$  and BC levels above or below the 75<sup>th</sup> percentile ( $12 \mu\text{g}/\text{m}^3$  for  $\text{PM}_{2.5}$  and  $1 \mu\text{g}/\text{m}^3$  for BC (Li et al. 2017)) by adding interaction terms.

Because adjusting for  $\text{PM}_{2.5}$ , temperature, and relative humidity in the primary analyses did not materially alter our results, we explored the associations among 5,709 eligible participants (9,957 observations) who were non-current smokers and lived in the northeast U.S. We removed  $\text{PM}_{2.5}$ , temperature, and relative humidity from that model.

Estimates were scaled to a  $3 \times 10^{-3}$  pCi/ $\text{m}^3$  increment, which approximated the interquartile range of the regional mean beta radioactivity level, and we reported estimated % difference with 95% confidence intervals (CIs). We focused on describing and highlighting association patterns that we considered consistent across multiple moving averages. 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

The characteristics of the study population are shown in Table 1. The mean age of the study population was 54 (standard deviation: 14) years old, and over half were women. On the day before the examination, the average regional mean gross beta radioactivity was 7.45 (standard deviation:  $2.26 \times 10^{-3}$  pCi/ $\text{m}^3$ ), and the average  $\text{PM}_{2.5}$  concentration was 9.68 (standard deviation:  $5.81 \mu\text{g}/\text{m}^3$ ). The characteristics of the 1-, 7-, 14-, 21- and 28-day moving averages of regional mean beta radioactivity level are shown in Table 2. As expected, correlations between moving averages were moderate to high. Histograms showing the distribution of the biomarkers are shown in Figure S1, numbers of participants in each examination are shown in Table S1, and the correlations between beta radioactivity,  $\text{PM}_{2.5}$ , and BC are shown in Table S2.

The results from our main analyses are shown in Figure 2. Exposure to higher levels of regional mean beta radioactivity was associated with higher levels of interleukin-6, MCP-1, and P-selectin across multiple moving averages. For example, a  $3 \times 10^{-3}$  pCi/m<sup>3</sup> increase in the 7-day moving average was associated with 5.09% (95% CI: 0.92, 9.43), 2.65% (95% CI: 1.10, 4.22), and 4.71% (95% CI: 3.01, 6.44) higher levels of interleukin-6, MCP-1, and P-selectin, respectively (Figures 2A, 2B, and 2C). The magnitude of the associations were similar between 7-day and 28-day moving averages. The 1-day moving average of regional mean particle beta radioactivity was associated with 2.97% (95% CI: -0.38, 6.44) higher CRP levels; however, the associations were attenuated for 7- to 28-day moving averages (Figure 2D). We unexpectedly found negative associations of regional mean particle beta radioactivity level with indexed 8-epi-PGF<sub>2α</sub> and ICAM-1 (Figures 2E and 2F): a  $3 \times 10^{-3}$  pCi/m<sup>3</sup> increase in the 7-day moving average of regional mean beta radioactivity level was associated with 7.01% (95% CI: -11.64, -2.15) and 2.70% (95% CI: -3.97, -1.42) lower levels of indexed 8-epi-PGF<sub>2α</sub> and ICAM-1. Longer moving averages of regional mean beta radioactivity level appeared to be negatively associated with fibrinogen (Figure 2G), however, the 95% CIs were wide and overlapped the null. The associations for MPO, TNF-α, and TNFR-2 were generally null. Detailed results are provided in Table S3.

Including current smokers or replacing PM<sub>2.5</sub> with BC did not alter our conclusion. Stronger associations between beta radioactivity and circulating ICAM-1 were observed for those who were older than 53 years old (median age). Although the regional mean beta radioactivity was not associated with TNFR-2 in our main analyses, the associations were positive among participants who were older (Figure 3A; Figure S2). The positive associations of regional mean beta radioactivity with P-selectin were stronger among men, while the negative associations with ICAM-1 were stronger among women (Figure S3). Furthermore, stronger positive associations were observed at longer moving averages with CRP and P-selectin among those who had type 2 diabetes than those without (Figures 3B and 3C; Figure S4). Last, we examined whether the associations differed by PM<sub>2.5</sub> levels and BC levels. The associations of longer moving averages of regional mean beta radioactivity with indexed 8-epi-PGF<sub>2α</sub>, CRP, and fibrinogen were negative among those who were exposed to PM<sub>2.5</sub> above the upper quartile (12 μg/m<sup>3</sup>), and the negative associations with ICAM-1 were stronger among those who were exposed to BC above the upper quartile (1 μg/m<sup>3</sup>).

Extending the analyses to all 5,709 eligible participants in the northeast U.S. led to attenuated associations for CRP, interleukin-6, MCP-1, and P-selectin. However, the positive associations of particle radioactivity with P-selectin and negative associations with ICAM-1 and fibrinogen remained.

#### 4. Discussion

Among participants from the Framingham Offspring and Third Generation cohorts, we observed that exposure to higher levels of regional mean beta radioactivity was associated with higher circulating levels of interleukin-6 and P-selectin, but lower levels of urinary 8-epi-PGF<sub>2α</sub> and serum ICAM-1 after adjusting for ambient PM<sub>2.5</sub> level. We further observed that the associations may differ by age, diabetes status, PM<sub>2.5</sub> level, or BC level. Although

we observed consistent positive associations with MCP-1 in the primary analyses, the association pattern was not observed after we extended analyses to a broader geographic region. Our study is among the first studies to examine the associations of exposure to ambient particle beta radioactivity with oxidative stress and inflammatory biomarkers.

We observed moderate associations of regional mean particle beta radioactivity with inflammatory biomarkers after adjusting for PM<sub>2.5</sub> concentrations; however, the underlying mechanisms are unclear. Radiation therapy administered at low dose, but much higher than ambient levels, has been reported to be associated with heightened immune response and systemic inflammation (Frey et al. 2015; Hekim et al. 2015). The current U.S. Environmental Protection Agency (EPA) recommendation on indoor radon level is <4 pCi/L (i.e., 4,000 pCi/m<sup>3</sup>) (U.S. Environmental Protection Agency 2016) and the current WHO recommendation is <2.7 pCi/L (World Health Organization 2009). However, the ambient particle beta radioactivity levels cannot be directly compared to indoor radon levels, and we measured particle beta radioactivity as a surrogate of the overall ambient particle radioactivity. According to the USEPA's RadNet database ([https://iaspub.epa.gov/enviro/erams\\_query\\_v2.simple\\_query](https://iaspub.epa.gov/enviro/erams_query_v2.simple_query)), between January, 2000 and August, 2018, the overall average level of gross beta activity in the U.S. was 0.01 pCi/m<sup>3</sup>, the average gross beta activity in Massachusetts between October, 2004 and August, 2018 was 6.86×10<sup>-3</sup> pCi/m<sup>3</sup> (range: 0.219×10<sup>-3</sup> pCi/m<sup>3</sup> to 35.2×10<sup>-3</sup> pCi/m<sup>3</sup>). Outside of the U.S., a study conducted in Malaga, Spain, found an average of 15.3×10<sup>-3</sup> pCi/m<sup>3</sup> for gross beta activity between 1992 and 1995 (Dueñas et al. 1999); meanwhile another study conducted in Tehran, Iran, observed an average of 6.02×10<sup>-3</sup> pCi/m<sup>3</sup> for gross beta activity between 2001 and 2004 (Arkian et al. 2008).

We unexpectedly observed negative associations of the regional mean beta radioactivity with indexed 8-epi-PGF<sub>2α</sub> and ICAM-1; however, the reasons for the negative associations are unclear. Because the associations between radiation exposure and inflammatory response are complicated and the exact biological mechanisms are unclear, further mechanistic research will be required to explain the observed negative associations.

Among participants of the Framingham Heart Study, we examined the associations between short-term exposure to ambient air pollution with biomarkers of oxidative stress and inflammation in our previous work (Li et al. 2017; Li et al. 2016). In those analyses, we observed positive associations of PM<sub>2.5</sub> and BC with levels of MPO, 8-epi-PGF<sub>2α</sub>, CRP, and TNFR-2, and negative associations between PM<sub>2.5</sub> and fibrinogen. In the current study, although we accounted for PM<sub>2.5</sub> in the analyses, we still observed negative associations between particle radioactivity and levels of 8-epi-PGF<sub>2α</sub>. Consistent with our previous study in which we examined the associations between ambient air pollution and inflammatory biomarkers, we observed stronger associations of radioactive particles with circulating levels of CRP and P-selectin among participants with type 2 diabetes than those without. The susceptibility may be attributable to chronic inflammation-induced endothelial dysfunction among these participants. We also found positive associations between regional mean beta radioactivity level and TNFR-2 only among participants who were older than the median age (53 years old), suggesting increased susceptibility among older individuals.



There are several limitations to our study. First, several sources may introduce non-differential measurement error to our exposure assessment. Because beta radioactivity levels were not available at all monitors on all days during the study period, we utilized a regression model to estimate the regional mean beta radioactivity level. However, the  $R^2$  value of the model ranged from 0.62 to 0.71 for the monitoring sites, and there were moderate correlations across sites ( $r=0.40$  to  $0.63$ ). Additionally, beta radioactivity levels at each site was assessed over 5 to 7 days, which limited our ability to examine the associations within shorter time frames. However, the beta radioactivity appeared to be stable over short periods of time. We also lack measures of absorbance dose, the indoor radiation exposures, and participants' radiation therapy history. However, participants in the Framingham Heart Study were generally healthy and the percentage of participants who received radiation therapy was expected to be small. Overall, because the beta radioactivity levels were measured independent of biomarker measurements, any measurement error is unlikely to be associated with participants' biomarker levels. Second, participants in the Framingham Heart Study were mostly middle-age individuals of European ancestry. Our results may not be generalizable to populations with different age distributions or of different ethnicity/ancestry. Third, we cannot rule out residual confounding and unmeasured confounding, and we cannot establish temporality. Thus, our findings preclude inference for causality.

Our study also has several strengths. First, the Framingham Heart Study is a well-characterized large community-based cohort. Participants were examined by physicians and nurses with standardized protocols. Second, the levels of ambient air pollution in the study region were relatively low, which reduced potential confounding from  $PM_{2.5}$ . Third, the assessment of beta radioactivity level and biomarker assessment were independent. Participants in the Framingham Heart Study scheduled their examination visits months in advance, which reduced potential differential exposure measurement error.

## 5. Conclusions

Our findings suggested positive associations between exposure to ambient particle radioactivity and several oxidative stress and inflammatory biomarkers after accounting for ambient  $PM_{2.5}$  concentrations, but not all. At the moment, we have very little information on the potential adverse health effects of ambient particle radioactivity as well as the underlying biological mechanism. Thus, our findings have limited public health implications until these associations are confirmed or refuted in future controlled animal studies and human epidemiological studies.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations:

<b>8-epi-PGF<sub>2α</sub></b>	8-epi-prostaglandin F <sub>2α</sub>
<b>BC</b>	Black carbon
<b>CRP</b>	C-reactive protein
<b>ICAM-1</b>	Intercellular adhesion molecule 1
<b>MCP-1</b>	Monocyte chemoattractant protein 1
<b>PM<sub>2.5</sub></b>	Fine particulate matter
<b>TNF-α</b>	Tumor necrosis factor α
<b>TNFR-2</b>	Tumor necrosis factor receptor 2

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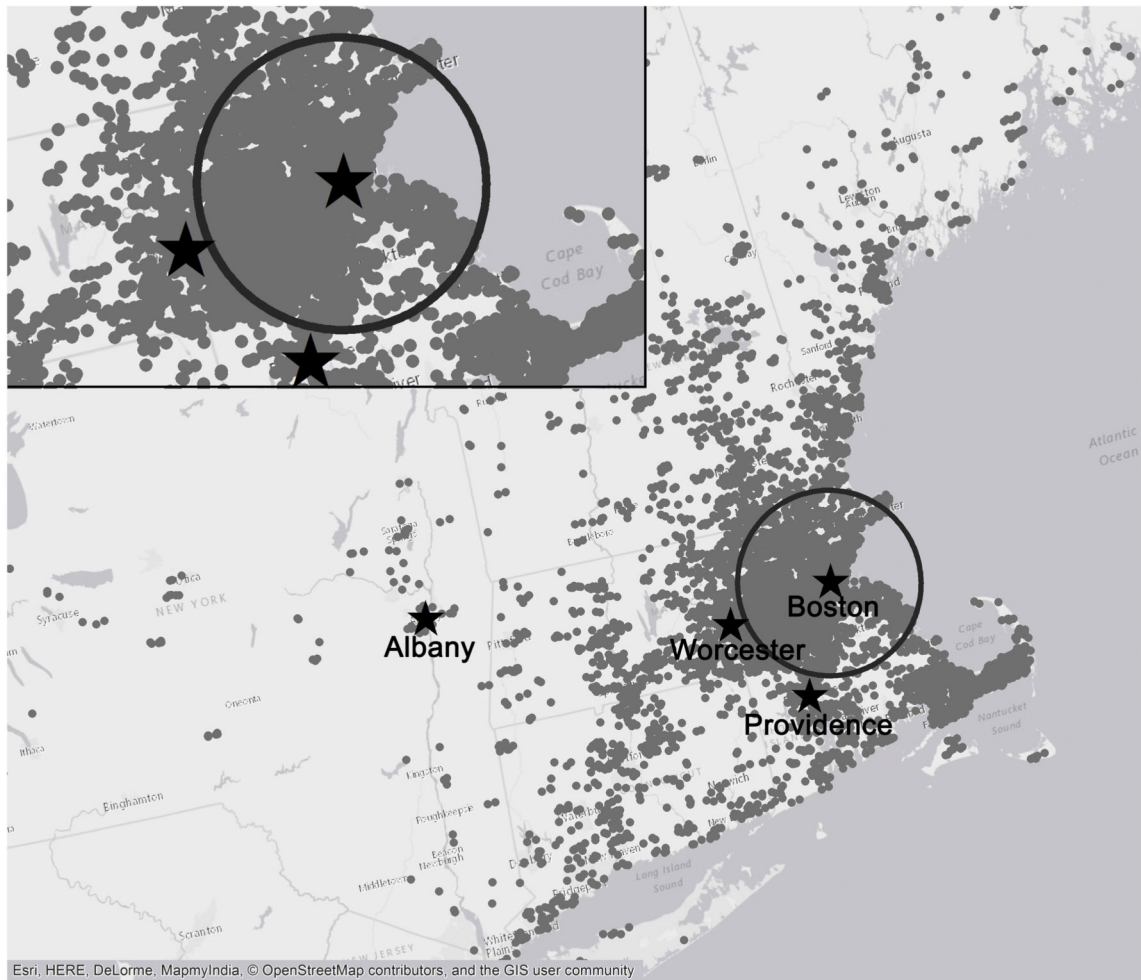
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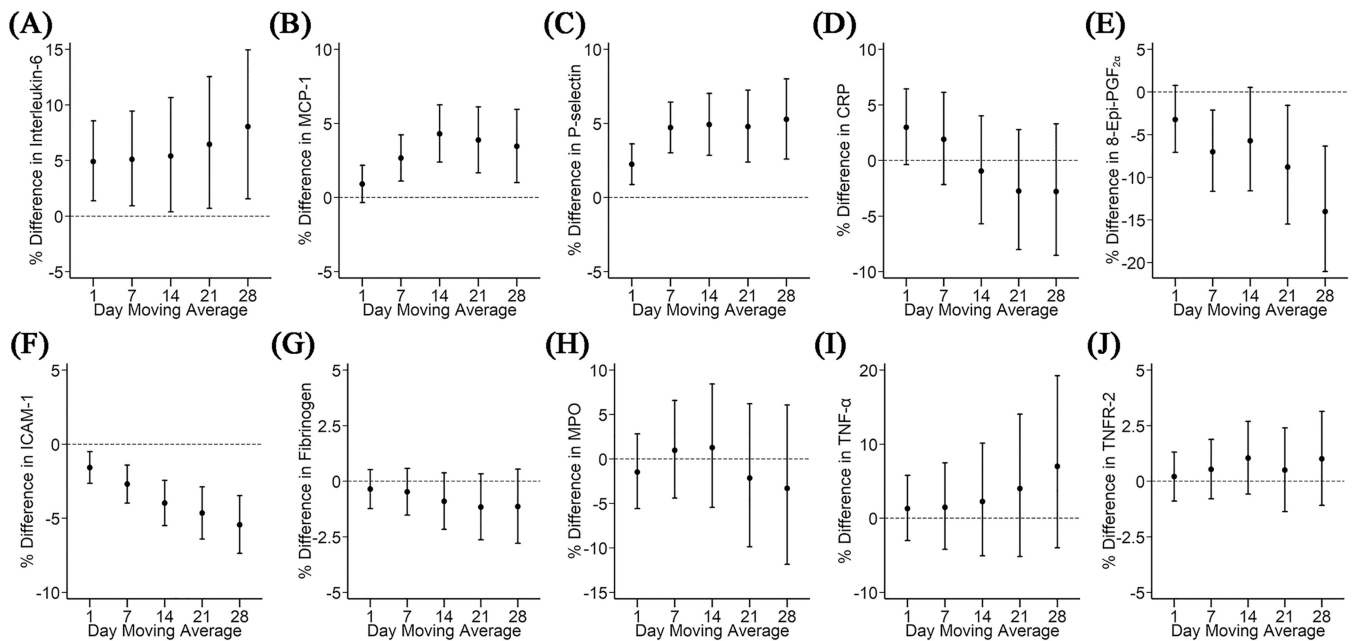
### Highlights

- Decay products of ambient radioactive materials can be attached to ambient particles
- Inhaled radioactive particles may form an ionizing radiation source in the lung
- Few studies studied the associations of particle radioactivity with inflammation
- Particle radioactivity was associated with inflammation adjusting for air pollution
- Associations differed by age, sex, diabetes status and ambient air pollution levels



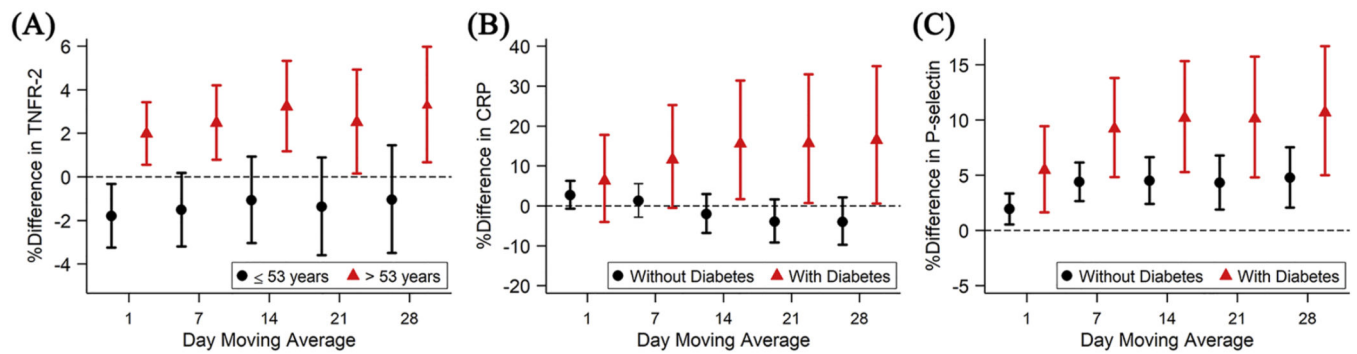
**Figure 1. Map of the study region showing the distribution of the study participants and the locations of monitors.**

To protect the confidentiality of the participants, the residential locations on the map were masked by altering the longitude and latitude by a small random amount. Thus, although these locations are representative of the distribution of participants' residential locations, none of them represent actual residential locations of the study participants. Circle indicates the 50 km radius from Supersite. Dots: residential locations of the study participants.



**Figure 2. Associations of 1- to 28-day moving averages of gross beta radioactivity with (A) interleukin-6, (B) MCP-1, (C) P-selectin, (D) CRP, (E) 8-epi-PGF<sub>2α</sub>, (F) ICAM-1, (G) fibrinogen, (H) MPO, (I) TNF-α, and (J) TNFR-2 from participants of the Framingham Offspring and Third Generation cohorts.**

Models were adjusted for centered age and (centered age)<sup>2</sup>; sex; body mass index; cigarette smoking status; cigarette pack-years; alcohol intake; educational level; median household income in the participant's census tract from U.S. Census 2000 data; linear term of examination date, day of week of examination date, and sine and cosine term of the examination date; temperature and relative humidity; and PM<sub>2.5</sub>. We added an examination identifier for 8-epi-PGF<sub>2α</sub>, CRP, fibrinogen, ICAM-1, interleukin-6, MCP-1, Pselectin, and TNFR-2. Results were scaled by  $3 \times 10^{-3}$  pCi/m<sup>3</sup>. Error bars indicate the 95% confidence intervals.



**Figure 3.**

Associations of 1- to 28-day moving averages of gross beta radioactivity with (A) TNFR-2 by **median age**, and of (B) CRP and (C) P-selectin by **diabetes status**. Models were adjusted for centered age and (centered age)<sup>2</sup>; sex; body mass index; cigarette smoking status; cigarette pack-years; alcohol intake; educational level; median household income in the participant's census tract from U.S. Census 2000 data; linear term of examination date, day of week of examination date, and sine and cosine term of the examination date; temperature and relative humidity; and PM<sub>2.5</sub>; and an exam identifier. Results were scaled by  $3 \times 10^{-3}$  pCi/m<sup>3</sup>. Error bars indicate the 95% confidence intervals.



**Table 1.**

Characteristics of 6,814 observations (3,996 participants) from the Framingham Offspring and Third Generation cohorts.

Characteristics <sup>a</sup>	Offspring cohort		Third Generation cohort		Overall
	Cycle 7	Cycle 8	Cycle 1	Cycle 2	
Number of participants	1,844	1,560	1,817	1,593	6,814
Age, years	61.6 ± 9.53	67.3 ± 9.15	40.1 ± 8.86	46.5 ± 8.55	53.6 ± 14.2
Women	985 (53.4%)	844 (54.1%)	968 (53.3%)	852 (53.5%)	3649 (53.6%)
Educational attainment <sup>b</sup>					
High school or less	665 (36.1%)	554 (35.5%)	265 (14.6%)	230 (14.4%)	1714 (25.2%)
College	562 (30.5%)	486 (31.2%)	575 (31.7%)	481 (30.2%)	2104 (30.9%)
Higher than college	587 (31.8%)	520 (33.3%)	973 (53.6%)	881 (55.3%)	2961 (43.5%)
Nonsmoker	793 (43.0%)	670 (43.0%)	1254 (69.0%)	1046 (65.7%)	3763 (55.2%)
Former smoker	1051 (57.0%)	890 (57.1%)	563 (31.0%)	547 (34.3%)	3051 (44.8%)
Pack years	14.0 ± 20.5	14.0 ± 20.5	3.51 ± 8.91	4.63 ± 10.2	9.02 ± 16.8
Alcohol intake, drink/week	4.49 ± 7.02	3.98 ± 6.65	4.28 ± 6.20	4.49 ± 6.13	4.32 ± 6.52
BMI, kg/m <sup>2</sup>	28.4 ± 5.33	28.6 ± 5.45	27.1 ± 5.62	28.2 ± 5.75	28.1 ± 5.57
MPO <sup>c</sup> , ng/mL	40.7 ± 22.6	-	-	-	40.7 ± 22.6
8-epi-PGF <sub>2α</sub> <sup>c</sup> , ng/mmol creatinine	111 ± 63.6	106 ± 74.9	-	-	109 ± 69.7
CRP <sup>c</sup> , mg/L	2.27 ± 2.53	1.68 ± 1.79	1.11 ± 1.38	1.40 ± 1.51	1.56 ± 1.82
Fibrinogen <sup>c</sup> , mg/dL	372 ± 71.9	-	331 ± 66.1	-	351 ± 72.0
ICAM-1 <sup>c</sup> , ng/mL	245 ± 58.0	291 ± 91.4	240 ± 57.8	-	256 ± 70.6
Interleukin-6 <sup>c</sup> , pg/mL	-	2.01 ± 1.50	1.37 ± 0.909	-	1.63 ± 1.19
MCP-1 <sup>c</sup> , pg/mL	312±104	374±116	331±110	-	336±113
P-selectin <sup>c</sup> , ng/mL	35.2 ± 13.3	39.1 ± 12.6	45.4 ± 16.8	-	39.7 ± 14.9
TNF-α <sup>c</sup> , pg/mL	1.28 ± 0.639	-	-	-	1.28 ± 0.639
TNFR-2 <sup>c</sup> , pg/mL	2082 ± 664	2555 ± 926	2180±524	-	2251±720
Gross beta radioactivity <sup>d</sup> , x10 <sup>-3</sup> pCi/m <sup>3</sup>	7.97 ± 2.23	6.60 ± 1.69	8.23 ± 2.45	6.80 ± 2.06	7.45 ± 2.26
PM <sub>2.5</sub> <sup>d</sup> , µg/m <sup>3</sup>	10.6 ± 5.26	9.10 ± 5.39	10.9 ± 7.10	7.83 ± 4.49	9.68 ± 5.81

Note: BMI, body mass index; MPO, myeloperoxidase; 8-epi-PGF<sub>2α</sub>, 8-epi-prostaglandin F<sub>2α</sub>; CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor receptor-α; TNFR-2, tumor necrosis factor receptor-2; PM<sub>2.5</sub>, fine particulate matter.

<sup>a</sup>Mean ± Standard Deviation or N (%).

<sup>b</sup>35 (0.5%) participants had no information on educational attainment.

<sup>c</sup>Geometric mean and standard deviation.

<sup>d</sup>Calculated based on the 1-day moving averages.

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**Table 2.**

Characteristics of the 1- to 28-day moving averages of gross beta radioactivity level.

Day moving average, $\times 10^{-3}$ pCi/m <sup>3</sup>	Mean $\pm$ SD	Interquartile Range	Pearson Correlation Coefficients			
			7-day	14-day	21-day	28-day
1-day	7.45 $\pm$ 2.26	2.93	0.82	0.68	0.61	0.58
7-day	7.46 $\pm$ 2.04	2.63		0.88	0.78	0.73
14-day	7.48 $\pm$ 1.81	2.42			0.94	0.87
21-day	7.48 $\pm$ 1.65	2.30				0.96
28-day	7.48 $\pm$ 1.56	2.23				

Note: SD, standard deviation.

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