Effect modification of ambient particle mortality by radon: A time series analysis in 108 U.S. cities


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ABSTRACT
Numerous studies have reported a positive association between ambient fine particles and daily mortality, but little is known about the particle properties or environmental factors that may contribute to these effects. This study assessed potential modification of radon on PM$_{2.5}$ (particulate matter with an aerodynamic diameter <2.5 μm)-associated daily mortality in 108 U.S. cities using a two-stage statistical approach. First, city- and season-specific PM$_{2.5}$ mortality risks were estimated using over-dispersed Poisson regression models. These PM$_{2.5}$ effect estimates were then regressed against mean city-level residential radon concentrations to estimate overall PM$_{2.5}$ effects and potential modification by radon. Radon exposure estimates based on measured short-term basement concentrations and modeled long-term living-area concentrations were both assessed. Exposure to PM$_{2.5}$ was associated with total, cardiovascular, and respiratory mortality in both the spring and the fall. In addition, higher mean city-level radon concentrations increased PM$_{2.5}$-associated mortality in the spring and fall. For example, a 10 μg/m$^3$ increase in PM$_{2.5}$ in the spring at the 10th percentile of city-averaged short-term radon concentrations (21.1 Bq/m$^3$) was associated with a 1.92% increase in total mortality (95% CI: 1.29, 2.55), whereas the same PM$_{2.5}$ exposure at the 90th radon percentile (234.2 Bq/m$^3$) was associated with a 3.73% increase in total mortality (95% CI: 2.87, 4.59). Results were robust to adjustment for spatial confounders, including average planetary boundary height, population age, percent poverty and tobacco use. While additional research is necessary, this study suggests that radon enhances PM$_{2.5}$ mortality. This is of significant regulatory importance, as effective regulation should consider the increased risk for particle mortality in cities with higher radon levels. 

Implications: In this large national study, city-averaged indoor radon concentration was a significant effect modifier of PM$_{2.5}$-associated total, cardiovascular, and respiratory mortality risk in the spring and fall. These results suggest that radon may enhance PM$_{2.5}$-associated mortality. In addition, local radon concentrations partially explain the significant variability in PM$_{2.5}$ effect estimates across U.S. cities, noted in this and previous studies. Although the concept of PM as a vector for radon progeny is feasible, additional research is needed on the noncancer health effects of radon and its potential interaction with PM. Future air quality regulations may need to consider the increased risk for particle mortality in cities with higher radon levels.

Introduction
Decades of research have established a significant association between ambient particulate matter (PM) and increased risk of death (Dockery et al. 1993; Lelieveld et al. 2015). Additional research has assessed potential mechanisms underlying the PM-mortality association by investigating the effects of physical and chemical properties of PM, such as particle size and chemical components (Atkinson et al. 2015; Cassee et al. 2013; Kelly and Fussell 2012). However, the properties of particles responsible for their toxicity are still not fully understood. Although there is a general consensus that PM causes inflammation and oxidative stress, the exact mechanisms are still unknown (Brook et al. 2010; Landrigan et al. 2017). Improving our understanding of the toxicogenic properties of PM is critical to developing cost-effective air quality regulations and ultimately protecting public health.

We propose a new hypothesis to explain the toxicity of ambient particles, suggesting that particle toxicity may be
mediated by local radon concentrations. Radon, a naturally occurring gas, is a product of the radioactive decay of trace elements found in the soil. Once radon is emitted, it migrates upward, accumulates in homes, and decays to radioactive progeny. These freshly generated progeny react with water vapor and atmospheric gases to form highly mobile clusters, which then rapidly attach to airborne aerosols (Porstendörfer 1994, 2001). The fraction of attached progeny increases with increasing ambient aerosol concentrations (Porstendörfer 1994). The attached fraction usually composes 90% or more of total radon progeny in a typical room (Guo, Zhang, and Guo 2016; Porstendörfer 1994; Reineking and Porstendörfer 1990). Respirable air pollution particles then act as vectors of the attached radon progeny, which continue to decay and emit radiation after inhalation and deposition on the bronchial epithelium. Significant research has documented the cellular and biochemical damage induced by exposure to radon and alpha-emitting particles. The inhalation of radon gas and alpha-emitting radioisotopes has been demonstrated to cause pulmonary inflammation and oxidative damage in both animal models and human cells (Chauhan et al. 2012; Li and Tong 2007; Narayanan, Goodwin, and Lehnert 1997; Nie et al. 2012). Once inhaled, radioisotopes may also be translocated into systemic circulation and cause systemic effects (Marsh and Bailey 2013).

Exposure to radon is a well-documented cause of lung cancer at both occupational and environmental levels (Darby et al. 2005; Krewski et al. 2005; Tirmarche et al. 2010). There is also some limited evidence for noncancer effects of radon and other low-level radiation exposures, including circulatory disease (Little et al. 2012), chronic obstructive pulmonary disease (COPD) mortality (Turner et al. 2012), and COPD hospital admissions (Barbosa-Lorenzo et al. 2017). However, our hypothesis is unique in that it focuses on PM$_{2.5}$ (PM with an aerodynamic diameter <2.5 μm) toxicity and its potential modification by radon. Although we know of one study that considered traffic exhaust as a potential modifier of radon-associated cancer risk (Bräuner et al. 2010), we are not aware of any studies that have examined radon as a potential modifier of PM-associated risks. We previously studied the combined effects of ambient radiation and PM$_{2.5}$ and found effects on increased blood pressure in an elderly community-based cohort (Nyhan et al. 2018). This existing experimental and epidemiological evidence provides the scientific premise for our current study. To test our hypothesis, we conducted a national epidemiological study investigating whether the acute effects of PM$_{2.5}$ on total and cause-specific mortality varied by average local radon concentrations.

**Methods**

Our study encompasses daily data from 108 U.S. cities. Cities were included if they had at least 265 days of data per year (including PM$_{2.5}$, weather, and mortality data) for at least two consecutive years between 1999 and 2013. The geographic location of the cities is shown in Figure 1. A list of included cities and their respective years of data are included in the supplemental material as Table S1.

**Environmental data**

Daily PM$_{2.5}$ concentrations were obtained from the U.S. Environmental Protection Agency (EPA) Air Quality System Technology Transfer Network (EPA, 2016). PM$_{2.5}$ monitors for each city were selected based on the county of each city. For cities with more than one sampling site, daily values were calculated using a method previously described and explained here briefly (Zanobetti and Schwartz 2009). For each city, we (1) calculated daily deviations from the annual mean for each monitor; (2) standardized each monitor’s daily deviations by dividing by its annual standard deviation; (3) calculated mean daily standardized deviations for each city by averaging the daily standardized deviations for all monitors assigned to the city; (4) multiplied this mean daily deviation value by the standard deviation of all monitors within the city; and (5) added back the annual mean of all monitors within the city. This method standardizes daily measurements for all monitors within a city boundary and prevents missing days from one monitor from adding false variability to the daily value.

Weather data, including daily temperature and dew point temperature, were obtained from the National Oceanic Atmospheric Administration’s (NOAA) National Climatic Data Center and were used to calculate relative humidity. Each city was assigned to a weather station within a 60 km radius using a weighted selection criterion, which was calculated as the number of days with weather data divided by the distance between the city center and weather station.

We used two measures of radon exposures in our analysis. The first, the State/EPA Residential Radon Survey (SRRS), collected over 63,000 measurements from 1987 to 1992 to estimate short-term county-level mean indoor radon levels (Phillips, Marcinowski, and Macnaughay 1992; U.S. EPA, 1993). The majority of state-level surveys were conducted by the EPA using short-term charcoal canister samplers in the winter. Canisters were exposed for approximately 7 days in the lowest livable level of
each sampled residence (White et al. 1992). Eight states conducted independent surveys, which were also included in our analysis. Our second measure of radon concentrations was modeled by the Lawrence Berkeley National Laboratory (LBL), where Price and his colleagues estimated long-term average indoor living area radon concentrations using the SRRS short-term measurements, an additional survey of long-term U.S. indoor radon measurements, and additional regional characteristics, including geologic and housing characteristics (Price 1997; Price and Nero 1996a). Each city included in this analysis was assigned its county mean radon concentration from both the SRRS and LBL data sets. County radon concentrations are shown in Figure 1.

Monthly long-term averages of the planetary boundary layer (PBL) height are available from NOAA’s National Center for Atmospheric Prediction at a resolution of 32 km (Mesinger et al. 2006; NOAA Earth System Research Laboratory Physical Sciences Division 2016). These values were used to calculate a long-term annual mean PBL heights. Each city was assigned to the PBL estimate closest to the city center.

Health and demographic data
Daily mortality data through 2006 were obtained from the National Center for Health Statistics (NCHS), and data after 2006 were acquired from individual state departments of public health. We analyzed nonaccidental

**Figure 1.** Study city locations and mean county radon levels (a) measured by the EPA SRRS survey and (b) modeled by the Lawrence Berkeley Laboratory.
deaths due to all causes and specific diseases among individuals who resided in the city where they died. Outcomes were classified by the International statistical Classification of Disease, 10th revision (ICD-10), codes as follows: all causes (A00–R99), cardiovascular diseases (I01–I59), and respiratory diseases (J00–J99) (World Health Organization 2004). The proportion of residents over age 65 was obtained from the 2014 American Community Survey (U.S. Census Bureau 2016b), as was the percentage of all people whose income is below the poverty level (U.S. Census Bureau 2016a). Current cigarette use among adults was obtained from the 2016 Behavior Risk Factor Surveillance System (BRFSS) survey data for the year 2016 (Centers for Disease Control and Prevention [CDC] 2018).

Statistical analysis

We used a two-stage statistical approach in our analysis. First, we estimated city-specific and season-stratified mortality risk from exposure to averaged same-day and previous-day PM$_{2.5}$ concentrations, using a generalized additive model (GAM) with a quasi-Poisson link function to account for overdispersion. We stratified the analysis by season because previous studies have found seasonal variation in effects of PM$_{2.5}$ (Zanobetti and Schwartz 2009). Seasons were defined as follows: winter (December–February), spring (March–May), summer (June–August), and fall (September–November). The model controlled for long-term time using a natural spline (s) with 1.5 degrees of freedom (df) per season per year and for day of week (dow) as an indicator variable. We also controlled for potential confounding due to weather by including smooth functions of daily temperature (temp), lag-1 temperature (temp-lag1), and relative humidity (RH), each with 3 df per year. This model can be represented as

$$
\log(E(Y_i)) = \alpha + \beta \text{PM}_{2.5\ i-1\ t} + s(\text{temp}, \ df = 3) + s(\text{temp} - \text{lag1}, \ df = 3) + s(\text{RH}, \ df = 3) + s(\text{time}, \ df = 1.5 \text{ per season} - \text{year}) + \sum_{k=2}^7 \delta_k I(\text{dow}_t = k)
$$

(1)

where for each city and season, $E(Y_i)$ is the expected mortality count at day $t$, $\alpha$ is the intercept, $\text{PM}_{2.5\ i-1\ t}$ is the 2-day averaged PM$_{2.5}$ concentration, $\beta$ is the main effect of PM$_{2.5}$, $s$ is the natural smoothing spline function, $\text{dow}_t$ is a vector of indicator variables reflecting the day of week at time $t$, and $\delta$ is its corresponding vector of coefficients. $\hat{\beta}_i$ was estimated for each city and season and was standardized for a 10 µg/m$^3$ increase in PM$_{2.5}$ concentration.

In the second stage, we used a three-level mixed-effects meta-regression model to estimate the association between city-season-specific PM$_{2.5}$ mortality effect estimates and city-specific average radon levels for each season. In this model, random variation in the PM$_{2.5}$ effect estimates $\hat{\beta}_{i,s}$ are divided into three parts: (i) within-season uncertainty for a given city, (ii) between-season variation within a given city, and (iii) between-city variation. This properly accounts for potential correlation of seasonal effect estimates within each city. The model can be written as

$$
\hat{\beta}_{i,s} = \beta_0 + \sum_{s=2}^4 \beta_s I(\text{season} = s) + \sum_{s=1}^4 \beta_s^R \ln(\text{radon}_i) * I(\text{season} = s) + u_i + v_{i,s} + r_{i,s}
$$

(2)

where $\hat{\beta}_{i,s}$ is the estimated PM$_{2.5}$ coefficient for city $i$ in season $s$ obtained in the first stage, $\beta^S$ is a vector of coefficients for each season indicator variable, and $\beta^R$ is a vector of season-specific coefficients for the natural log of radon, where $\ln(\text{radon})$ is centered at its median value. The city-specific random effects are represented by $u_i$, which satisfies $u_i \sim N(0, \sigma_u^2)$; the season-specific random effects for each city are represented by $v_{i,s}$ which satisfies $v_{i,s} \sim N(0, \sigma_v^2)$, and the random deviation in within-season city estimates are represented by $r_{i,s}$, which satisfies $r_{i,s} \sim N(0, \sigma_r^2)$ (Van den Noortgate et al. 2015). We allowed the modifying effect of radon on PM$_{2.5}$ to vary by season because this effect may vary due to weather, home ventilation, and other seasonal patterns. We used a log-transformation of radon because this provided the best fit for the observed exposure-response curve between PM$_{2.5}$ slopes and radon, as judged by Akaike information criterion (AIC) values among several model alternatives.

PM$_{2.5}$ effect estimates are presented as the percent change in mortality associated with a 10 µg/m$^3$ increase in daily PM$_{2.5}$ at the study’s median radon value. The effects of radon on mortality are presented as the predicted PM$_{2.5}$ effects at the 10th and 90th percentiles of radon across cities. We assessed the significance of any remaining heterogeneity in PM$_{2.5}$ effect estimates among cities using the $Q_L$ test for residual heterogeneity.

As a sensitivity analysis, we assessed whether effect modification by radon changed after adjusting for spatially varying city characteristics. We ran a series of
second-stage meta-regression models, each including our basic model and an additional term for a potential confounder. We adjusted for the following city-averaged variables: average annual temperature, average annual planetary boundary layer height, the percentage of population over age 65, and the poverty rate. We also adjusted for state estimates of current tobacco smoking.

## Results

Our study included 108 cities and over 215,000 days with mortality and air pollution data. The mean daily total mortality rate was 27 deaths/day, with winter having the highest rate (30 deaths/day) and summer having the lowest (25 deaths/day). The mean 2-day averaged PM$_{2.5}$ was 12.7 μg/m$^3$, with the highest seasonal average levels in summer (14.4 μg/m$^3$) and lowest in spring (11.3 μg/m$^3$). Summary statistics are presented in Table 1.

Radon levels varied significantly across the United States, with the highest values found in the Northeast and Upper Midwest (Figure 1). Based on the SRRS data, the maximum radon concentration among the cities included in our analysis was 844 Bq/m$^3$ (Harrisburg, Pennsylvania) and the minimum concentration was 11.1 Bq/m$^3$ (Jacksonville, Florida; New Orleans, Louisiana; Port Arthur, Texas; and Riverside, California). LBL radon concentrations were lower and had less variability than SRRS concentrations, but the two measures were strongly correlated ($r = 0.87$). A Spearman test for correlation found that radon concentrations did not correlate significantly with mean city PM$_{2.5}$ concentrations ($r = 0.11$ and $r = 0.08$ for the SRRS and LBL data, respectively).

Table 2 presents the estimated percent increases in mortality for a 10 μg/m$^3$ increase in PM$_{2.5}$ calculated at the median radon level (74 Bq/m$^3$ based on the SRRS data). We found significant associations ($P < 0.05$) between PM$_{2.5}$ and total, cardiovascular, and respiratory mortality in both the spring and fall, as well as significant associations between PM$_{2.5}$ and total mortality in the summer. For example, a 10 μg/m$^3$ increase in PM$_{2.5}$ at the median radon level was associated with a 2.86% (95% confidence interval [CI]: 2.40, 3.33) increase in all-cause mortality in the spring, as compared with a 0.29% (95% CI: −0.08, 0.67) increase in the winter. Forest plots of city- and season-specific PM$_{2.5}$ effect estimates are included in the supplemental material as Figure S1.

Radon modified the PM$_{2.5}$ associations for total, cardiovascular, and respiratory deaths, with the strongest modification observed in the spring and fall. We estimated the PM$_{2.5}$-related mortality risk by season at the 10th and 90th percentiles of radon. The modifying effect of radon on PM$_{2.5}$-associated mortality was most significant in the spring and fall, the two seasons where the PM$_{2.5}$ effect was also the strongest. The greatest modification was seen in the spring. For example, using the SRRS data (based on short-term sampling), a 10 μg/m$^3$ increase in PM$_{2.5}$ in the spring at the 10th percentile of radon (21.1 Bq/m$^3$) was associated with a 1.92% increase in total mortality (95% CI: 1.29, 2.55), whereas the same increase in PM$_{2.5}$ at the 90th percentile of radon (234.2 Bq/m$^3$) was associated with a 3.73% increase in total mortality (95% CI: 2.87, 4.59). Similarly, a 10 μg/m$^3$ increase in PM$_{2.5}$ in the spring at the 10th percentile of radon was associated with a 2.13% increase in respiratory mortality (95% CI: 0.24, 4.07), whereas a 10 μg/m$^3$ increase in PM$_{2.5}$ at the 90th percentile of radon was associated with an increase of 9.14% in respiratory mortality (95% CI: 6.45, 11.9).

Although the radon interaction term was significant for some outcomes in winter, the main association between PM$_{2.5}$ and mortality in winter was small and

### Table 1. Summary (mean, SD) of daily mortality counts and environmental parameters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Winter</th>
<th>Spring</th>
<th>Summer</th>
<th>Fall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily mortality (deaths/day)</td>
<td>27 (31)</td>
<td>30 (34)</td>
<td>28 (31)</td>
<td>25 (29)</td>
<td>26 (30)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>9 (11)</td>
<td>10 (13)</td>
<td>9 (11)</td>
<td>8 (10)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>3 (3)</td>
<td>3 (4)</td>
<td>3 (3)</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>14.7 (9.7)</td>
<td>4.7 (7.9)</td>
<td>14.0 (7.5)</td>
<td>24.1 (4.1)</td>
<td>15.6 (7.3)</td>
</tr>
<tr>
<td>Relative humidity (%)</td>
<td>65.6 (16.6)</td>
<td>67.4 (16.6)</td>
<td>62.1 (17.3)</td>
<td>65.8 (15.9)</td>
<td>67.2 (16)</td>
</tr>
<tr>
<td>2-Day average PM$_{2.5}$ (μg/m$^3$)</td>
<td>12.7 (7.1)</td>
<td>13.1 (7.4)</td>
<td>11.3 (5.7)</td>
<td>14.4 (7.7)</td>
<td>12.3 (7.3)</td>
</tr>
<tr>
<td>Rn (Bq/m$^3$), SRRS$^a$</td>
<td>111.4 (125.9)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rn (Bq/m$^3$), LBL$^a$</td>
<td>51.8 (42)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Notes. $^a$In this paper, we use the international units for radon concentration, Bq/m$^3$. The EPA still uses the conventional units of pCi/L.

### Table 2. Estimated percent increases in mortality (95% CI) associated with a 10 μg/m$^3$ increase in PM$_{2.5}$ at the median SRRS radon level (74 Bq/m$^3$).

<table>
<thead>
<tr>
<th>Season</th>
<th>Total</th>
<th>Cardiovascular</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter</td>
<td>0.29 (−0.08, 0.67)</td>
<td>−0.19 (−0.85, 0.47)</td>
<td>0.32 (−0.79, 1.43)</td>
</tr>
<tr>
<td>Spring</td>
<td>2.86 (2.40, 3.33)</td>
<td>2.97 (2.16, 3.79)</td>
<td>5.74 (4.30, 7.19)</td>
</tr>
<tr>
<td>Summer</td>
<td>0.70 (0.30, 1.11)</td>
<td>0.41 (−0.31, 1.15)</td>
<td>1.27 (−0.04, 2.60)</td>
</tr>
<tr>
<td>Fall</td>
<td>1.49 (1.11, 1.87)</td>
<td>1.26 (0.57, 1.95)</td>
<td>2.76 (1.53, 3.99)</td>
</tr>
</tbody>
</table>
not significant, reducing our ability to meaningfully assess effect modification. Conducting the second-stage meta-regression using LBL radon concentrations (based on long-term living area estimates) yielded similar results for respiratory mortality that remained significant in the spring and fall. Results for total and cardiovascular mortality were similar but attenuated in magnitude and significance. Results for both radon exposures are shown in Figure 2 and in the supplemental material as Table S2.

We found significant remaining heterogeneity in our meta-regression models. Meta-regression models that controlled for both SRRS radon and season instead of just season reduced total remaining heterogeneity by 52%, 42%, and 32% in models for total, respiratory, and cardiovascular mortality, respectively. Meta-regression models that controlled for both LBL radon and season reduced total remaining heterogeneity by 19%, 19%, and 13% in models for total, respiratory, and cardiovascular mortality.

Our results were robust to adjustment for spatially varying city characteristics. Radon-season interaction terms remained significant and relatively unchanged after adjustment for the city-specific percentage of the population over age 65, percentage of population below the poverty line, and mean planetary boundary height, as well as statewide smoking rates. Results also remained similar after adjustment for city-mean temperature, although significance for the interaction term between radon and winter in the model of PM$_{2.5}$-associated cardiovascular mortality changed from significant to marginally significant. A presentation of the meta-regression results with and without adjustment for these additional spatial characteristics is included in the supplemental material as Figure S2.

**Discussion**

It is well established that radon and its decay products cause lung cancer (Darby et al. 2005; Tirmarche et al. 2010). However, little is known about the noncancer effects of radon exposure, especially in nonoccupational environments. In this large national study with almost 6 million deaths, we found that city-specific estimates of average indoor radon were associated with PM$_{2.5}$-related total, cardiovascular, and respiratory mortality risk.

The estimated PM$_{2.5}$ health effects from our study are similar in magnitude to previous national studies. For example, a national study based on 112 U.S. cities estimated the percent increases in all-cause mortality associated with a 10 µg/m$^3$ increase in 2-day averaged PM$_{2.5}$ to be 2.57 (95% CI: 1.96, 3.19), 0.25 (−0.13, 0.63), 0.95 (0.56, 1.34), and 0.56 (0.17, 0.94) in the spring, summer, fall, and winter, respectively (Zanobetti and Schwartz 2009). Although our estimated PM$_{2.5}$ effects

**Figure 2.** Estimated percent changes in mortality associated with a 10 µg/m$^3$ increase in PM$_{2.5}$ at the 10th and 90th percentiles of radon (SRRS: 21.1 and 234.2 Bq/m$^3$; LBL: 18.1 and 108.0 Bq/m$^3$). Significance for the ln(radon) term: *P < 0.05; **P < 0.001.
are somewhat higher in the fall than this earlier study, they follow a similar pattern, with greatest effects seen in the spring and fall. This increased risk in the spring and fall may be due to an increased indoor-outdoor air exchange rates during the milder months, where windows are more likely to be open.

We observed stronger mortality effects of PM$_{2.5}$ in cities with high average indoor radon concentrations, with the most significant effects in the spring and fall. This radon-season interaction may reflect seasonal variation in radon levels, as both indoor and outdoor radon levels vary seasonally (Miles and Algar 1988). Although most studies have found indoor radon levels to be highest in the winter, many factors can influence seasonal trends (Miles and Algar 1988). These factors include soil moisture, indoor and outdoor temperatures, wind speed, and building characteristics. These characteristics vary regionally and can cause regional differences in seasonal radon trends (Arvela, Holmgren, and Hanninen 2016). In addition, some studies have found an association between heating type and radon concentrations, and one EPA study found that heating in the winter lowers indoor concentrations of radon progeny (Hans and Lyon 1986). Additional research is needed to determine whether temporal trends in concentrations of radon and its progeny could explain the observed seasonal variation in our interaction effect estimates.

When we used the modeled radon concentrations obtained from the Lawrence Berkeley Laboratory rather than the measured EPA SRRS concentrations, our interaction effects for radon remained consistent for respiratory mortality but were of decreased magnitude and significance for total and cardiovascular mortality. This change is not unexpected. The two radon data sets are estimates of exposures during different time frames (short-term versus long-term) and locations in the home (lowest living area versus a living-area average), and the LBL estimates have significantly less variation across cities. In addition, the LBL estimates use sparse long-term measurements from 125 counties to predict long-term radon concentrations for all U.S. counties (Price and Nero 1996a). As has been demonstrated in other studies of spatially misaligned environmental exposure estimates, this can induce both classical and Berkson measurement errors and may introduce bias when used in our model (Gryparis et al. 2008; Peng and Bell 2010; Szpiro, Sheppard, and Lumley 2011). Any model misspecification in the LBL models may cause additional downward bias in our effect estimates (Alexeeff, Carroll, and Coull 2016).

It must be noted that the SRRS radon measurements are also subject to both classical and Berkson errors (Heid et al. 2004). Although EPA has based its approach to mitigating cancer risk on short-term lower living area measurements, these measurements of radon do not always reflect true long-term means and may not be a good surrogate for overall radon concentrations (Lubin, Samet, and Weinberg 1990). However, in light of the limitations posed by both sets of radon concentrations, we are encouraged by the close similarities in our results.

Radon effects remained significant even after adjusting for other spatially varying potential confounders. PBL height was considered as a potential confounder because ground-level radon concentrations are known to change due to changes in PBL height (Sesana, Caprioli, and Marcazzan 2003). Other potential confounders, including temperature, smoking, and population age, could indicate greater regional susceptibility to PM$_{2.5}$ effects. None of these potential confounders were significant when they were included in the meta-regression, and their inclusion did not impact the significance of interaction effects between radon and PM$_{2.5}$ effect estimates. This suggests that the observed interaction effect is robust to spatially varying variables.

An interaction between environmental radon levels and PM toxicity is biologically plausible. Particles may serve as vectors for radon progeny, which continue to emit alpha, beta, and gamma radiation after inhalation and deposition in the lungs. Alpha radiation causes considerably more biological damage than equivalent activities of beta and gamma radiation but cannot penetrate the epidermis. Therefore, inhalation of PM is a critical route of exposure to alpha radiation (United Nations Scientific Committee on the Effects of Atomic Radiation [UNSCEAR] 2012). Occupational and environmental health studies have shown that chronic inhalation of radionuclides emitting alpha radiation, primarily radon and its progeny, is an important risk factor for lung cancer even at the levels typically found in residential housing (Darby et al. 2005; Tirmarche et al. 2010). In addition, there is limited epidemiological evidence for noncancer effects of low-level radiation. Using the LBL estimates, radon exposure was found to be associated with chronic COPD mortality in the American Cancer Society Prevention Study II (Turner et al. 2012). An ecological study in Galicia, Spain, found a positive association between municipal residential radon levels and COPD hospital admissions (Barbosa-Lorenzo et al. 2017). Some epidemiological studies have suggested excess relative risk for circulatory disease at low levels of ionizing radiation (Little et al. 2012), and a recent study found that environmental particle radioactivity measured as beta radiation on ambient air pollution samples was associated with an increase in both diastolic and systolic blood pressures in the Normative Aging Study cohort (Nyhan et al.
Finally, there is support for acute effects from low-dose radiation exposure in both animal models and in human cells. Inhalation of radon by rats induced bronchoalveolar fluid (BALF) inflammation and interleukin-6 (IL-6) mRNA expression in both BALF and peripheral white blood cells (Li and Tong 2007). There is also evidence that radon causes oxidative damage, as radon exposure in rats resulted in a dose-dependent increase in 8-hydroxy-2-deoxyguanosine (8-OHdG) levels in lung tissue and an increase in reactive oxygen species (ROS) in BALF (Nie et al. 2012). Human fibroblasts exposed to alpha-emitting particles had increases in ROS production (Narayanan, Goodwin, and Lehnert 1997), and human pulmonary epithelial cells exposed to alpha-emitting particles demonstrated up-regulation of gene pathways that included those associated with inflammatory and respiratory diseases (Chauhan et al. 2012). However, it is important to stress that all previous studies have examined environmental radiation independently of PM exposures, whereas our analysis focuses primarily on PM
dust toxicity and its modification by radon. Toxicological studies could further investigate the presence of interaction between PM
dust and radon exposures by conducting a two-factorial experiment in mice and assessing known biomarkers.

Our findings, if true, have important scientific and regulatory implications. First, regional differences in radon levels may partially explain the spatial variability in PM
dust effect estimates across the United States found in many previous studies (Bell et al. 2008; Dominici et al. 2003, 2006). Second, considering that the amount of attached radionuclides is expected to be a function of PM surface area, our hypothesis provides an explanation for why PM mass (or volume) is the most reproducible predictor of PM toxicity compared with PM components (Health Effects Institute [HEI] 2013). Third, under typical atmospheric air pollution conditions, most of the freshly generated ultrafine radon progeny attach to the PM accumulation mode, which has an approximate size of 0.1–1 μm. Thus, our hypothesis may explain why PM
dust is, in general, more toxic than coarse particles (Peng et al. 2008). Finally, the radon effect on PM
dust risk justifies the lack of threshold in the PM exposure-response relationship (Di et al. 2017), as even low levels of PM can deliver sufficient alpha-emitting radionuclides into the human body.

**Strengths and limitations**

Our analysis utilizes data from a large number of cities and applies well-established statistical methods. In addition, our hypothesis about modification of PM toxicity is biologically plausible, since the adverse effects of alpha radiation have been previously demonstrated. However, our analysis has several limitations. A major limitation of our study is that it relies on county-level radon estimates and does not include any information on seasonal variability in radon, which may be driving some of the patterns seen in our results. Both sets of radon concentrations are subject to potential measurement error and spatial misalignment, as discussed above. In addition, the radon concentrations used in this study were collected before the study period began. However, because long-term average indoor radon concentrations depend largely on geologic parameters and housing characteristics (Nazaroff 1992), we expect long-term radon to remain relatively consistent. We would expect individual, current estimates of radon exposure based on measurements of particle-bound radon progeny to strengthen the observed associations. In addition, our ecological study design uses PM
dust concentrations measured at one or several central sites in each city instead of individual measurements of PM
dust exposures. This assumes that the monitor value for each city represents the true average ambient concentration for all individuals within a study. Any resulting measurement error may reduce efficiency and induce some downward bias on our estimated effect of PM
dust (Dominici, Zeger, and Samet 2000; Zeger et al. 2000). Future studies could use a prospective cohort design with individual measurements of radon and air pollution exposures to help overcome these limitations. Finally, we assume that there is no unmeasured confounding that could explain the effect modification of PM
dust on mortality by radon. Causality still needs to be demonstrated.

**Conclusion**

Radon is a ubiquitous natural pollutant, with over 7 million U.S. homes having radon concentrations exceeding the EPA mitigation level of 148 Bq/m³ (4 pCi/L) (Angell 2008). This level has been established based on lung cancer risk. However, our research suggests that radon, through its interaction with PM, is also associated with all-cause, cardiovascular, and respiratory mortality. Future efforts should focus on investigating the noncancer effects of radon. Furthermore, elucidating mechanisms responsible for PM toxicity, especially those related to a pollutant of natural origin such as radon, is of paramount importance to environmental and public health policies. Specifically, our findings suggest that it may be more effective to develop regional rather than national PM air quality standards. Given the significant regional
variation in radon, a national PM$_{2.5}$ standard may not adequately protect individuals living in areas with high radon exposures.

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