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Effect Modification of Ambient Particle Mortality by Radon: A Time Series Analysis in 108 U.S. Cities

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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. While 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 toxigenic 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 upwards, 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 (Porstendörfer, 1994, Reineking and Porstendörfer, 1990, Guo et al., 2016). Respirable air pollution particles then act as vectors of the attached

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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 (Li and Tong, 2007, Nie et al., 2012, Narayanan et al., 1997, Chauhan 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 non-cancer effects of radon and other low-level radiation exposures, including circulatory disease (Little et al., 2012), 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 $PM_{2.5}$ toxicity and its potential modification by radon. While 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 epidemiologic 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 $PM_{2.5}$ (PM with an aerodynamic diameter ≤ 2.5 μm) 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 as Table S1 in the supplemental material.

Environmental data

Daily $PM_{2.5}$ concentrations were obtained from the U.S. EPA Air Quality System Technology Transfer Network (U.S. EPA, 2016). $PM_{2.5}$ monitors for each city were selected based on the county(ies) 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

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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 criteria, 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 1987–1992 to estimate short-term county-level mean indoor radon levels (Phillips et al., 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 are also included in our analysis. Our second measure of radon concentrations were 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;b). Each city included in this analysis was assigned its county mean radon concentration from both the SRRS and LBL datasets. 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 ESRL PSD, 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 non-accidental 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, 10^{th} revision codes as follows: all causes (ICD-10, A00-R99), cardiovascular diseases (ICD-10, I01-I59), and respiratory diseases (ICD-10, 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 percent 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 (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 $PM_{2.5}$

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concentrations, using a generalized additive model (GAM) with a quasi-Poisson link function to account for over-dispersion. 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 penalized spline (s) with 1.5 degrees of freedom (df) per season per year and for day of week 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:

$$log[E(Y_t)] = \alpha + \beta\, PM_{2.5\,t-1,t} + s(temp,\ \ df = 3) + s(temp - lag1, df = 3) + s(RH, df = 3) + s(time, df = 1.5\ per\ season - year) + \sum_{k=2}^{7} \delta_k\, I(dow_t = k) \quad (1)$$

where for each city and season, $E(Y_t)$ is the expected mortality count at day t, α is the intercept, $PM_{2.5\,t}$ is the two-day averaged $PM_{2.5}$ concentration, β is the main effect of $PM_{2.5}$, $s()$ is the penalized smoothing spline function, dow_t is a vector of indicator variables reflecting the day of week at time t, and δ is its corresponding vector of coefficients. $\widehat{\beta}$ was estimated for each city and season and was standardized for a 10 $\mu g/m^3$ 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 $\widehat{\beta}_{i,s}$ 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:

$$\widehat{\beta}_{i,s} = \beta_0 + \sum_{s=2}^{4} \beta_s^S I(season = s) + \sum_{s=1}^{4} \beta_s^R \ln(radon_i) * I(season = s) + u_i + v_{i,s} + r_{i,s} \quad (2)$$

where $\widehat{\beta}_{i,s}$ is the estimated $PM_{2.5}$ coefficient for city i in season s obtained in the first stage, β^S is a vector of coefficients for each season indicator variable, and β^R is a vector of season-specific coefficients for the natural-log of radon, where ln(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

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$r_{i,s}$, which satisfies $r_{i,s} \sim N(0, \sigma^2_{r_{i,s}})$ (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 percentile of radon across cities. We assessed the significance of any remaining heterogeneity in $PM_{2.5}$ effect estimates among cities using the Q_E 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 percent 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 U.S., 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, PA) and the minimum concentration was 11.1 Bq/m^3 (Jacksonville, FL; New Orleans, LA; Port Arthur, TX; and Riverside, CA). 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 increase 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% CI: 2.40, 3.33) increase in all-cause mortality in the spring, as compared to a 0.29% (95% CI: −0.08, 0.67) increase in the winter. Forest

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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 10^{th} and 90^{th} percentile 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 $\mu g/m^3$ increase in $PM_{2.5}$ in the spring at the 10^{th} percentile of radon (21.1 Bq/m^3) was associated with a 1.92% increase in total mortality (95% CI: 1.29, 2.55), while the same increase in $PM_{2.5}$ at the 90^{th} 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 $\mu g/m^3$ increase in $PM_{2.5}$ in the spring at the 10^{th} percentile of radon was associated with a 2.13% increase in respiratory mortality (95% CI: 0.24, 4.07), while a 10 $\mu g/m^3$ increase in $PM_{2.5}$ at the 90^{th} percentile of radon was associated with an increase of 9.14% in respiratory mortality (95% CI: 6.45, 11.9). While 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 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 percent of the population over age 65, percent population below the poverty line, and mean planetary boundary height, as well as state-wide 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 as Figure S2 in the supplemental material.

DISCUSSION

It is well established that radon and its decay products cause lung cancer (Tirmarche et al., 2010, Darby et al., 2005). However, little is known about the non-cancer effects of radon

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exposure, especially in non-occupational environments. In this large national study with almost six 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 increase in all-cause mortality associated with a 10 $\mu g/m^3$ increase in two-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). While our estimated $PM_{2.5}$ effects 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). While 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 temperature, wind speed, and building characteristics. These characteristics vary regionally and can cause regional differences in seasonal radon trends (Arvela et al., 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 lab 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 datasets are estimates of exposures during different timeframes (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 1996). As has been demonstrated in other studies of spatially misaligned environmental exposure estimates, this can induce both Berkson and classical measurement errors and may introduce bias when used in our model (Szpiro et al., 2011, Peng and Bell, 2010, Gryparis et al., 2008). Any model misspecification in the LBL models may cause additional downward bias in our effect estimates (Alexeeff et al., 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 et al., 1990). However, in light of the limitations posed

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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 et al., 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 (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 (Tirmarche et al., 2010, Darby et al., 2005). In addition, there is limited epidemiological evidence for non-cancer 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 pressure in the Normative Aging Study cohort (Nyhan et al., 2018). 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 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-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 et al., 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 $PM_{2.5}$ toxicity and its modification by radon. Toxicological studies could further investigate the presence of interaction between $PM_{2.5}$ and radon exposures by conducting a two-factorial experiment in mice and assessing known biomarkers.

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Our findings, if true, have important scientific and regulatory implications. First, regional differences in radon levels may partially explain the spatial variability in $PM_{2.5}$ effect estimates across the U.S. found in many previous studies (Dominici et al., 2003, Dominici et al., 2006, Bell et al., 2008). 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 to PM components (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 $PM_{2.5}$ is, in general, more toxic than coarse particles (Peng et al., 2008). Finally, the radon effect on $PM_{2.5}$ 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 $PM_{2.5}$ concentrations measured at one or several central sites in each city instead of individual measurements of $PM_{2.5}$ 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 $PM_{2.5}$ (Zeger et al., 2000, Dominici 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 $PM_{2.5}$ on mortality by radon. Causality still needs to be demonstrated.

CONCLUSIONS

Radon is a ubiquitous natural pollutant, with over 7 million U.S. homes having radon concentrations exceeding the EPA mitigation level of 148 Bq/m^3 (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 non-cancer effects

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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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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. While the concept of PM as a vector for radon progeny is feasible, additional research is needed on the non-cancer 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.

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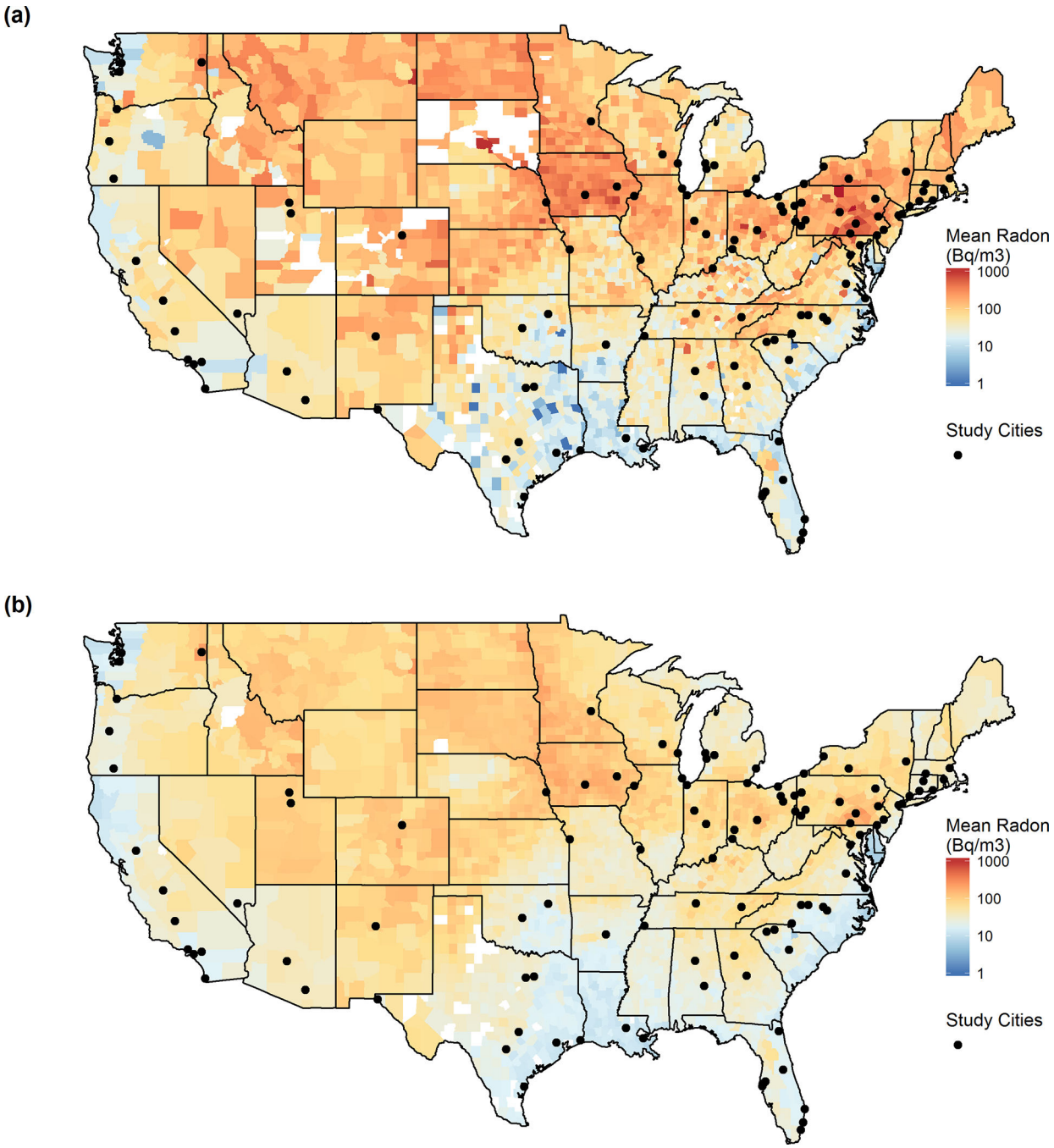

Figure 1:
Study city locations and mean county radon levels (a) measured by the EPA SRRS survey and (b) modeled by the Lawrence Berkeley Laboratory.

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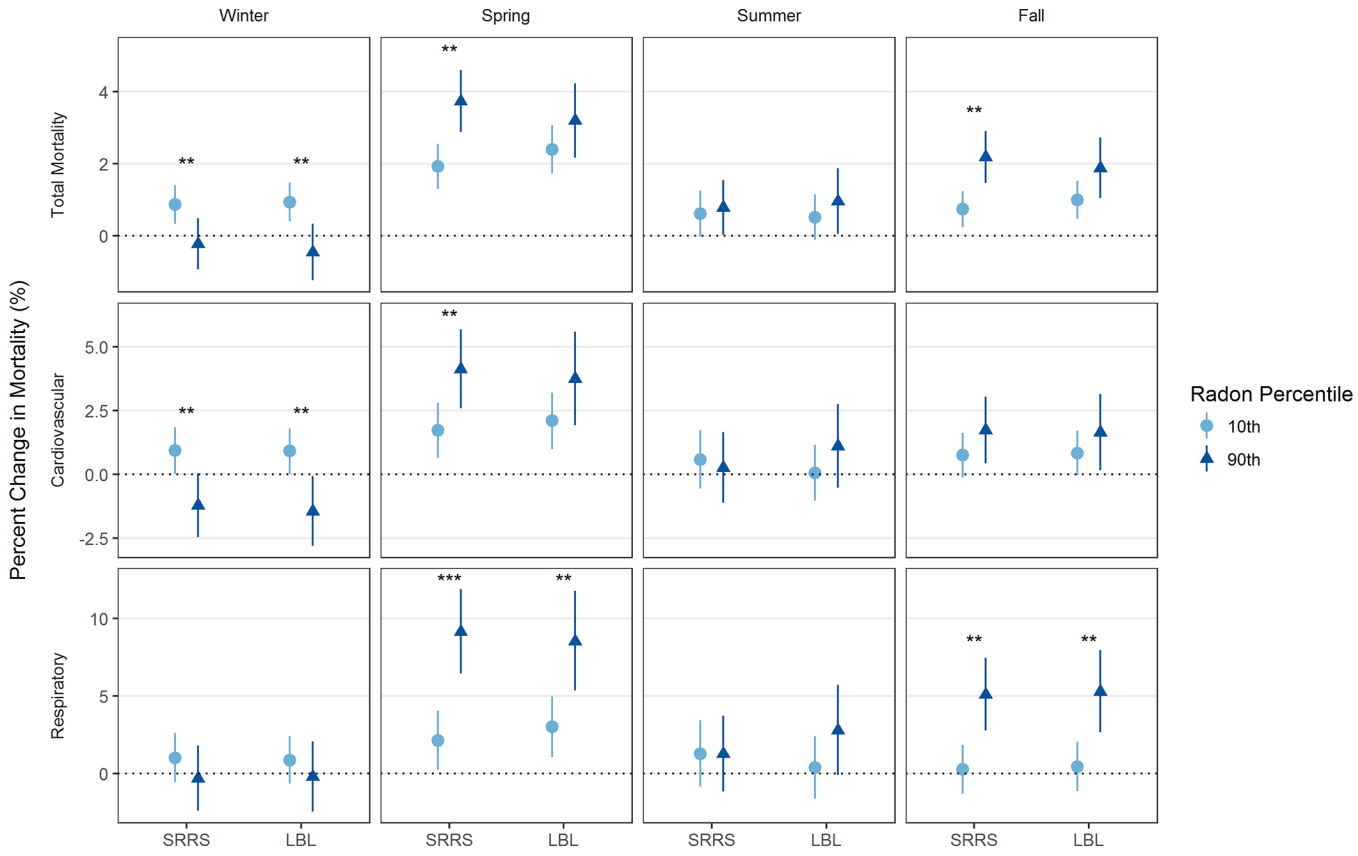

Figure 2:

Estimated percent change in mortality associated with a 10 μg/m^3 increase in $PM_{2.5}$ at the 10^{th} and 90^{th} percentile 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<0.1; ** p<0.05; *** p<0.001

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Table 1:

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

Variable	Overall	Winter	Spring	Summer	Fall
Daily Mortality (deaths/day)					
Total	27 (31)	30 (34)	28 (31)	25 (29)	26 (30)
Cardiovascular Disease	9 (11)	10 (13)	9 (11)	8 (10)	8 (11)
Respiratory Disease	3 (3)	3 (4)	3 (3)	2 (3)	2 (3)
Environmental Parameters					
Temperature (˚C)	14.7 (9.7)	4.7 (7.9)	14.0 (7.5)	24.1 (4.1)	15.6 (7.3)
Relative Humidity (%)	65.6 (16.6)	67.4 (16.6)	62.1 (17.3)	65.8 (15.9)	67.2 (16)
2-day Average $PM_{2.5}$ ($\mu g/m^3$)	12.7 (7.1)	13.1 (7.4)	11.3 (5.7)	14.4 (7.7)	12.3 (7.3)
Rn (Bq/m^3), SRRS[1]	111.4 (125.9)	—	—	—	—
Rn (Bq/m^3), LBL[1]	51.8 (42)				

[1]. In this paper we use the international units for radon concentration, Bq/m^3. The U.S. EPA still uses the conventional units of pCi/L.

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Table 2:

Estimated percent increase 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).

	Total	Cardiovascular	Respiratory
Winter	0.29 (−0.08, 0.67)	−0.19 (−0.85, 0.47)	0.32 (−0.79, 1.43)
Spring	2.86 (2.40, 3.33)	2.97 (2.16, 3.79)	5.74 (4.30, 7.19)
Summer	0.70 (0.30, 1.11)	0.41 (−0.31, 1.15)	1.27 (−0.04, 2.60)
Fall	1.49 (1.11, 1.87)	1.26 (0.57, 1.95)	2.76 (1.53, 3.99)