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County-level radon exposure and all-cause mortality risk among Medicare beneficiaries

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ABSTRACT

Background: Radon is an inert gas formed from the decay of naturally-occurring materials in the earth's crust. It infiltrates into homes from soil, water, and construction materials. Its decay products are radionuclides, which attach to ambient particles. Residential radon is one of the leading risk factors for lung cancer. The scarce evidence for associations with other mortality causes originates mostly from occupational studies.

Methods: In a cohort study with 14 years of follow-up (2000 – 2013), we evaluated the association between chronic radon exposure and all-cause mortality, and explored whether there are subpopulations who are more vulnerable to radon effects. We included 87,296,195 person-years of follow-up from all Medicare beneficiaries in the Mid-Atlantic and Northeastern U.S. states. We examined the association between the logarithm of county-averaged radon (ln(Rn)) and mortality and assessed effect modification by chronic conditions.

Results: An interquartile range increase in the ln(Rn) was associated with a 2·62% increase (95% CI 2·52%; 2·73%) in mortality, independent of $PM_{2.5}$ exposure. Larger mortality risks were observed among individuals with respiratory, cardiovascular and metabolic diseases, with the highest associations observed among those with diabetes (4·98% increase), heart failure (4·58% increase), and chronic obstructive pulmonary disease (4·49% increase).

Conclusion: We found an increased risk for all-cause mortality associated with increased radon exposure. The risk was enhanced among susceptible individuals with chronic conditions. We believe this is the first cohort study to identify populations at higher risk for non-malignant health consequences of radon exposure. Due to the limitations in exposure assessment and availability of individual confounders, these findings should be interpreted with caution.

1. Introduction

Radon is an inert gas formed from the decay of naturally-occurring materials in the earth's crust. It infiltrates into homes from soil, water and construction materials, and can accumulate to high levels in enclosed spaces with poor ventilation (Noh et al., 2016). Radon gas decays into radioactive progeny, which quickly react with water vapor and trace atmospheric gases to form fast diffusing ultrafine clusters. These clusters then attach to airborne particles and can be inhaled (Porstendorfer, 1994). Radon progeny continue to decay after inhalation and deposition, which exposes the lung and other tissues to high energy α-particles that otherwise, could not penetrate the epidermis. Therefore, it is a significant source of human exposure to alpha radiation (United Nations Scientific Committee UNSCEAR on the Effects of Atomic Radiation (UNSCEAR), 2012). Radon through its progeny is the primary source of naturally-occurring radiation exposure in the U.S. population (National Council on Radiation Protection and Measurements (NCRP), 1984; Lopez-Abente et al., 2018).

Radon decay products are known carcinogenic agents, and exposure to radon is a well-established risk factor for lung cancer (Noh et al., 2016; Duan et al., 2015). The continuing radioactive decay in the lungs is believed to induce the carcinogenesis process (Duan et al., 2015). A recent study found a 34% increased risk for lung cancer death among study participants who were exposed to radon levels above the U.S.

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Environmental Protection Agency guidelines threshold of 4 pCi/L (148 Bq/m^3) (Turner et al., 2011).

Radon exposure has been found to be related to outcomes other than lung cancer (Lopez-Abente et al., 2018; Nusinovici et al., 2010; Douple and Samet, 2000), but the evidence is scarce and inconsistent. Turner et al. found a positive association between radon exposure and COPD (Turner et al., 2011), but found no evidence for an association between radon exposure and non-respiratory mortality (Turner et al., 2012a). Similarly, evidence from a collaborative analysis of 11 cohorts among miners concluded that mortality from cancers other than lung cancer is unlikely to be caused by radon (Darby et al., 1995). Studies that have found positive associations between radon and non-respiratory mortality are subject to significant limitations, including potential bias from the study design and confounding. For example, a case-cohort study among Czech uranium miners has found a positive association between radon exposure and leukemia. However, a potential exposure measurement error, especially for high exposures acquired in the early study period, is a major limitation of this study (Rericha et al., 2006). Other ecological studies have found associations between radon and leukemia, both among miners and in the general population. However, these results may be subjected to biases which are common in ecological study designs (World Health Organization (WHO), 2009). Another example is a study of French uranium miners that found a significant increase in cerebrovascular mortality associated with cumulative radon exposure, but could not fully adjust for confounding by cardiovascular risk factors (Nusinovici et al., 2010).

Our study addresses this knowledge gap by investigating the association between radon exposure and all-cause mortality using individual mortality and hospital admissions data of all Medicare beneficiaries in the Mid-Atlantic and Northeastern U.S. states for the period 2000 to 2013. In addition, we explore whether certain subpopulations are more susceptible to radon exposures.

2. Methods

2.1. Study population

We included all Medicare beneficiaries 65 years and older who were included in the Fee-For-Service program and who resided in the following Mid-Atlantic and Northeastern states including: Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Delaware, Pennsylvania, Maryland, Washington, D.C., Virginia, and West Virginia, for the years 2000 to 2013. Medicare is an open cohort; each enrollee either entered the cohort in 2000 or after 2000 when they turned 65. Subjects who were alive on January 1 of the year following their enrollment in Medicare entered the open cohort. For each enrollee, a record was created for each year of follow-up, and each subject was followed annually until the year of their death or the end of our study period (December 31, 2013). The outcome of this analysis was all-cause mortality. This study was approved by the Harvard T.H. Chan School of Public Health Human Subjects Committee.

2.2. Exposure data

We obtained county mean radon levels, modeled by the Lawrence Berkeley National Laboratory (LBL). The data was available for 409 of the 411 counties in the study area. In brief, long-term average indoor living area radon concentrations were estimated using the EPA/State Residential Radon Surveys (SRRS) short-term measurements (Phillips et al., 1992), long-term indoor radon measurements, and additional regional characteristics including geologic and housing characteristics (Price, 1997; Price and Nero, 1996). Long-term indoor radon concentrations have been demonstrated to depend largely on geologic and soil information as well as house construction (Price and Nero, 1996). As these factors do not change rapidly with time, therefore, we expect long-term radon to remain relatively consistent. As a result, we treated these historic residential radon levels as indicators of chronic exposure (Turner et al., 2011; Turner et al., 2012b), and we assigned to each study participant the mean radon value from the county containing that participant's ZIP code.

As a sensitivity analysis, we used a second measure of radon concentrations obtained from the SRRS, in which approximately 60,000 measurements were collected during 1987–1992 to estimate county-level mean indoor radon levels (Phillips et al., 1992). The majority of state-level surveys were conducted by the U.S. EPA using short-term charcoal canister samplers in the winter, which were exposed for approximately seven days in the lowest livable level of each residence (White et al., 1992). These measures were available for 399 counties (97%).

2.3. Other covariates

2.3.1. Individual data

Medicare data on the participant's age at entry, sex, race, date of death, ZIP code of residence, dual eligibility for the Medicare and Medicaid service, and primary and secondary admission causes. Participants were defined as having a condition if they had at least one emergency admission for the following outcomes, classified by the International Classification of Disease ninth revision codes (ICD-9) as follows: chronic obstructive pulmonary disease (COPD; ICD-9 490–496, except 493), diabetes (ICD-9 250), congestive heart failure (CHF; ICD-9 428), ischemic stroke (ICD-9 433-435), and myocardial infarction (MI; ICD-9 410).

2.3.2. Neighborhood socioeconomic data

We obtained the following ZIP code level socioeconomic status (SES) variables from the 2000 U.S. Census and the American Community Survey (ACS) 5-year estimates for 2009–2013: median household income, population density, and percent of residents with no high school education. We also obtained age-adjusted yearly prevalence estimates of smoking from the Centers for Disease Control and Prevention (CDC) Behavioral Risk Factor Surveillance System (BRFSS) (Behavioral Risk Factor Surveillance System (BRFSS), 2013).

2.3.3. Fine particulate matter ($PM_{2.5}$) exposure

We obtained highly spatially-resolved $PM_{2.5}$ data (1×1 km resolution) from a hybrid Aerosol Optical Depth (AOD) based model, which incorporates daily satellite remote sensing data and classic LUR methodologies. For more in-depth description, please refer to Kloog et al. (2014). The exposure values of all grid cells located within each ZIP code and a 500 m buffer around the ZIP code borders were averaged annually and assigned to participants based on the ZIP codes corresponding to their residential address.

2.4. Statistical analysis

We used mixed Poisson survival analysis (Whitehead, 1980) using the Anderson-Gill formulation with a random intercept for each ZIP code, time-fixed predictors (radon exposure, sex, race), and time-varying predictors (age, diabetes, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), myocardial infarction (MI), stroke, annual ZIP code level $PM_{2.5}$ concentration, population density, median household income, percent of residents without a high school diploma, and percent smokers). Because each subject has time-varying confounders, we fit a proportional hazard model using the equivalent Poisson regression. We generated an artificial Poisson observation for each subject in the risk set at each non-censored year with an outcome of zero for all person-years except those experiencing the event at that time. We allowed a piecewise constant hazard for each year by adding a penalized spline function of year (Whitehead, 1980).

As the mean Rn distribution was highly skewed, we defined the log of county-averaged radon, ln(Rn), as the main exposure of interest.

The model is:

$$Log\,(E(Y_{i,z})) = \beta_0 + \beta_1 X_c + \beta_2 U_{z,t} + \beta_3 W_i, + \beta_4 W_{i,t} + s\,(t)$$

where $Y_{i,z}$ is the outcome of person i, in ZIP code z; X_c is the ln(Rn) associated with county c; $U_{z,t}$ are spatial and temporal confounders that vary between ZIP codes and over time ($PM_{2.5}$, median household income, population density, percent population with no high school diploma, and percent smokers); W_i are the person's individual confounders that do not vary over time (race and sex); $W_{i,t}$ are the person's individual confounders that do vary over time (age, diabetes, CHF, MI, stroke, and COPD); and *s(t)* is a penalized spline for year of study.

To identify susceptible populations, we repeated our model to assess the association between ln(Rn) and all-cause mortality and added multiplicative interaction terms with each of the following morbidities separately: COPD, CHF, MI, ischemic stroke, and diabetes.

To further explore the potential non-linear effects of radon we also ran a version of the model using a regression spline with three degrees of freedom for the ln(Rn) term, instead of a linear term. In addition, to explore the potential joint synergistic effect of $PM_{2.5}$ and radon, we also ran a version of the main analysis adding a multiplicative interaction term between $PM_{2.5}$ and ln(Rn).

Finally, results are presented as percent change and 95% confidence interval per interquartile range increase (IQR) in the ln(Rn).

To make sure the associations found in our study are not driven by lung cancer mortality alone, we added a sensitivity analysis in which we repeated our model with the exclusion of persons who, at any time, had been admitted to the hospital with a primary or secondary diagnosis of lung cancer.

3. Theory

An association between radon exposure and non-respiratory and non-malignant mortality causes is biologically plausible. Non-malignant effects can result from a radiation-induced cell activation, which may directly damage the organ structure and impair their functionality (Little et al., 2008). Although radon exposure has been found to be related to non-respiratory malignant and nonmalignant outcomes (Lopez-Abente et al., 2018; Nusinovici et al., 2010; Douple and Samet, 2000), the evidence is scarce and inconsistent. While most studies found no clear associations with non-respiratory mortality (Auvinen et al., 2005; Kreuzer et al., 2010), some found increased risks (Lopez-Abente et al., 2018; Nusinovici et al., 2010; Douple and Samet, 2000). Furthermore, while several recent radon studies have focused on the general population, most of them have investigated the effects of occupational exposures which are considerably higher. Therefore, little is known about non-malignant health effects of residential radon exposure (Sheen et al., 2016).

4. Results

We included 87,296,195 person-years of follow-up for 13,045,126 persons 65 years and older. This population is 42.8% male, majority white, and has a mean age of 79 years at death or the end of follow up. From the participants, 2·8% were diagnosed with COPD, 0·3% MI, 3·5% CHF, 0·3% stroke, and 2·8% diabetes. 35·8% died at the end of follow-up (Table 1).

The county-averaged radon concentration ranged from 6·6 to 265·6 Bq/m^3, with a mean value of 50·0 Bq/m^3 (Fig. 1).

The 25th and 75th percentiles of ln(Rn) were 3·4 and 4·0, respectively, yielding an IQR of 0·6. This IQR corresponds to 24.6 Bq/m^3 and 0.7 pCi/L. The mean annual $PM_{2.5}$ concentration during the study period was 10·7 $\mu g/m^3$ and ranged from 4·0 to 28·5 $\mu g/m^3$ (IQR = 3·0 $\mu g/m^3$). A low correlation was observed between ln(Rn) and annual $PM_{2.5}$ ($r = 0{\cdot}03$, $p < 0{\cdot}001$). Of the predictors included in the models, the highest correlation was observed between ln(Rn) and population density ($r = -0{\cdot}09$, $p < 0{\cdot}001$).

Table 1
Population characteristics during 2000–2013.

Population characteristics	N = 13,045,126
Male gender, no. (%)	5,588,039 (42·8)
Race, no. (%)	
White	11,412,678 (87·5)
Black	1,223,583 (9·4)
Other	408,865 (3·1)
Age, mean (SD), years	77.93 (8·6)
Comorbidities, no. (%)	
COPD	371,553 (2·8)
MI	33,165 (0·3)
CHF	456,500 (3·5)
Ischemic stroke	38,046 (0·3)
Diabetes mellitus	366,756 (2·8)
Death, no. (%)	4,674,731 (35·8)

COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; CHF = congestive heart failure.

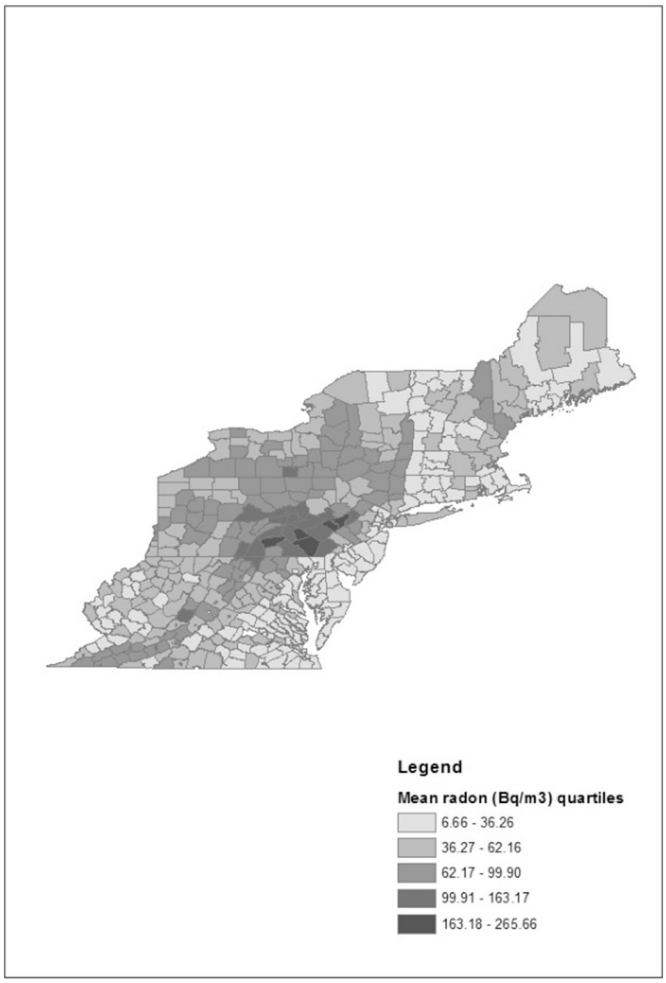

Fig. 1. County mean radon level by quartiles.

An IQR increase in the ln(Rn) was associated with 2·62% increase (95% CI: (2·52%; 2·73%)) in all-cause mortality. Without adjustment for $PM_{2.5}$, the effect size for the association with radon remained similar (2·61% increase; 95% CI (2·51%; 2·72%)). Similarly, the $PM_{2.5}$ effect did not change with the exclusion of ln(Rn) in the model. In a model with ln (Rn), an IQR increase of 3 $\mu g/m^3$ in $PM_{2.5}$ was associated with 5·83% increase in mortality (5·58%; 6·09%); in a model without the ln(Rn) term, an increase of 3·0 $\mu g/m^3$ was associated with 5·80% increase in mortality (5·54%; 6·05%).

Table 2
The association between radon and mortality among all study participants and individuals with respiratory, cardiovascular and metabolic diseases.

	Percent change (95% CI)	Interaction p value
All available data	2·62% (2·52%; 2·73%)	
COPD		
No	2·59% (1·80%; 3·39%)	
Yes	4·49% (3·69%; 5·30%)	< 0·001
CHF		
No	2·58% (1·88%; 3·28%)	
Yes	4·58% (3·88%; 5·29%)	< 0·001
MI		
No	2·63% (0·28% 53·03%)	
Yes	0·65% (−1·64%; 3·00%)	0·099
Stroke		
No	2·62% (0·42%; 4·84%)	
Yes	4·19% (1·96%; 6·47%)	0·168
DM		
No	2·59% (1·73%; 3·46%)	
Yes	4·98% (4·10%; 5·86%)	< 0·001

Table 2 shows the % change in all-cause mortality associated with IQR increase in ln(Rn) (0·6 units) among all study participants and individuals with chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), myocardial infarction (MI), ischemic stroke or diabetes mellitus (DM). The effects reported among individuals with the comorbidities above were obtained by adding multiplicative interaction terms with each morbidity separately.

Larger mortality risks were observed among persons with COPD (4·49% increase in mortality, interaction p value < 0·001), CHF (4·58% increase in mortality, interaction p value < 0·001), and diabetes (4·98% increase in mortality, interaction p-value < 0·001). MI and stroke did not modify the association with radon (Table 2).

When allowing for a nonlinear association between mortality and ln (Rn) within the Poisson log-linear model, we observed a weak protective effect at lower radon levels followed by an increased mortality risk with increasing ln(Rn) for exposure values between 3 and 4·5 (Fig. 2).

When assessing the interaction between ln(Rn) and $PM_{2.5}$ we found a significant negative interaction which indicates larger ln(Rn) effects in lower exposure to $PM_{2.5}$.

We conducted sensitivity analyses to make sure our findings are consistent. First, when we repeated our model with the exclusion of persons who were diagnosed with lung cancer, the association remained similar (2.87% increase, 95% CI 2.76%; 2.97%). Second, in a sensitivity analysis among the 399 counties for which we had available SRSS radon measurements, we still observed a positive and statistically significant association between radon exposure and mortality (1·44% increase; 95% CI (1·36%; 1·52%)). Like the main analysis, we observed a statistically significant interaction with stroke. However, we found no interaction with the other morbidities tested.

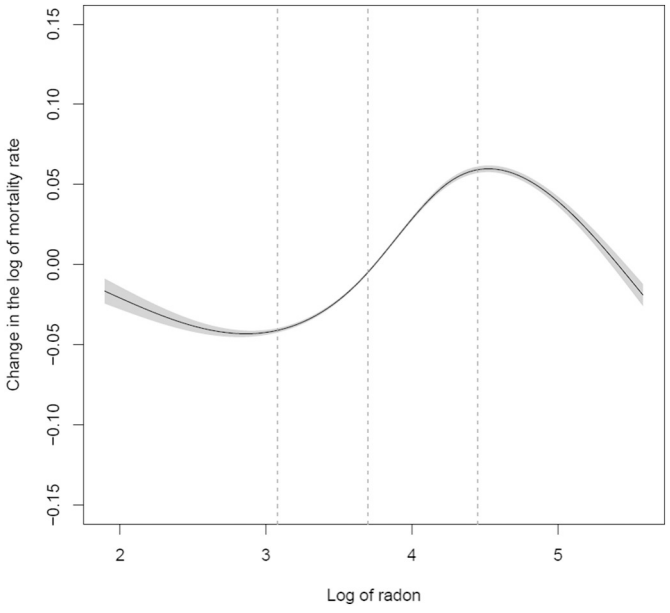

Fig. 2. The non-linear association between radon and mortality.
Fig. 2 shows the dose response curve for the association between penalized spline of ln(Rn) and all-cause mortality. The dashed lines represent the quartiles of the log of radon.

5. Discussion

We found an increased risk for all-cause mortality associated with residential radon exposure. The association was robust to the exclusion of persons who were diagnosed with lung cancer. People with respiratory, circulatory or metabolic diseases appeared to be more susceptible to radon exposure. The dose-response curve for all-cause mortality was nonlinear, and higher mortality risks with increasing radon levels were found only for exposures around the median of the ln (Rn) distribution.

We studied both the effect of ln(Rn) and $PM_{2.5}$ on mortality and found that the correlation between the exposures was low and that the association with each exposure was not confounded by the other. The primary factor in determining radon-related radiation dose is the activity size distribution of decay products, which determines the amount of inhaled activity deposited in the lungs and the final deposition location. The activity size distribution, in turn, is governed by the size and concentration of atmospheric aerosols, including $PM_{2.5}$ (Porstendorfer, 2001).

Unlike our initial hypothesis, we found a negative interaction between $PM_{2.5}$ and radon. In a previous analysis done by our group found a synergistic effect of radon and $PM_{2.5}$. In this analysis, city-specific estimates of average indoor radon (both SRRS and LBL measurements) were associated with increased $PM_{2.5}$-related total, cardiovascular and respiratory mortality risk, with stronger mortality effects of $PM_{2.5}$ in cities with high average indoor radon concentrations (Blomberg et al., 2018). Although both of these studies assessed the interaction between $PM_{2.5}$ and radon, they are very different in their design. First, this previous study focused on effect modification of radon on $PM_{2.5}$-associated daily mortality in 108 U.S. cities, and our study looks at chronic effects of radon on all-cause mortality. Second, the previous study analyzed city level counts of mortality cases, while our study population comprises individuals with annual follow up data. The negative interaction observed in our study may be related to residual confounding due to the nonlinear effect of radon. It is also possible that part of the radon effect is captured by the $PM_{2.5}$ effect which resulted in a negative interaction between the two exposures.

The association between radon and lung cancer mortality, both in occupational and environmental settings, is well established (Darby et al., 2005; Krewski et al., 2005). Associations between radon and other mortality causes are inconsistent across existing studies. Increased levels of indoor radon exposure were associated with a higher risk for non-Hodgkin's lymphoma (NHL) among female children and adolescents in Korea (Ha et al., 2017). In Colorado, however, mortality from NHL was not associated with cumulative radon exposure (Schubauer-Berigan et al., 2009). Contradicting results were also found when studying the association with leukemia (Tong et al., 2012; Laurier et al., 2001), stomach cancer (Auvinen et al., 2005) urinary cancer (Kurttio et al., 2006), and cardiovascular mortality (Nusinovici et al., 2010; Turner et al., 2012a). We found a significantly higher risk for all-cause mortality to be associated with increasing residential radon exposure, supporting the growing evidence of links between radon and non-malignant mortality.

Moreover, we identified patients with diabetes, COPD, and CHF as more susceptible to the radon effect. The effect of radon on human tissue involves the formation of DNA mutations, DNA lesions and may

damage neighboring tissue by inducing oxidative stress in adjacent non-irradiated cells. These processes, which were found to increase genetic susceptibility among lung cancer patients who were lacking specific genes (Ruano-Ravina et al., 2014), may also play a role in patients with non-malignant respiratory, circulatory, and metabolic disorders.

To our knowledge, this is the first large-scale study to identify these patients as more susceptible to the radon effect on mortality risk. There are studies, however, that found associations between radon exposure and morbidity or cause-specific mortality from these diseases, mostly from COPD. The Cancer Prevention Study-II, a longitudinal analysis of nearly 1.2 million Americans, found a significant increase in the risk of COPD mortality, associated with residential radon exposure (Turner et al., 2012b). Similarly, a study in Spain found higher radon exposure to be associated with an increased risk for COPD hospital admissions (Barbosa-Lorenzo et al., 2017).

When testing the nonlinear effect of radon, we found it increased total mortality risks only for levels around the median value of exposure. In lower levels, ln(Rn) had a protective effect. The same pattern was observed by Duan et al. (2015) who assessed the association between radon exposure and lung cancer. The authors attributed the protective effect to an adaptive response, which enhanced the DNA repair capacity among exposed individuals. They hypothesized that low radon exposure might stimulate apoptosis and immunity and, therefore, provide protection against oxidative tissue damage.

One major strength of this study is its inclusion of a large cohort followed over 14 years. In addition, we assessed the relationship between radon and $PM_{2.5}$ exposure in a non-occupational setting, providing more evidence on the health risks associated with these environmental exposures in the general population.

A major limitation of this study is the radon exposure assessment, which was estimated at a county level and was assumed fixed over time. This leaves a potential for spatial confounding, although we did adjust for some spatial characteristics including income, education, and population density. It also adds additional Berkson error as we assume the same exposure for all individuals living in the same county. We added a sensitivity analysis using a different source for exposure data, which supported our main findings. In addition, we were not able to explore the role of season in the radon-mortality relationship because the study utilizes annual follow-up of health.

Finally, we did not have information on important individual confounders (such as smoking, income, and BMI). Although we could not adjust for individual smoking or income, we did adjust for the smoking rate and SES at the neighborhood level. A previous study, performed among this study population, investigated how the lack of adjustment for smoking, BMI and income could have resulted in residual confounding. They obtained individual data from a representative subsample of Medicare enrollees and found that smoking and income were not associated with $PM_{2.5}$ or ozone and therefore were not likely to confound the association with mortality (Di et al., 2017). This supports the use of neighborhood smoking rate to remove confounding by smoking status. Regarding SES, we did control for individual race and eligibility to Medicaid – which can serve as a proxy for socioeconomic status. Additionally, we observed a very low correlation between the mean county level and the neighborhood SES characteristics, which supports the assumption that there is no residual confounding by SES.

6. Conclusion

In conclusion, we found an increased risk for all-cause mortality, associated with increased radon exposure, independent of exposure to $PM_{2.5}$. The risk was enhanced among susceptible individuals with respiratory, cardiovascular, and metabolic conditions. Due to the limitations in exposure assessment and availability of individual confounders, these findings should be interpreted with caution.

Declaration of Competing Interest

The authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.05.059.

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