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Associations between ambient particle radioactivity and lung function

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ABSTRACT

Previous studies have suggested increased risk of respiratory diseases and mortality following short-term exposures to ionizing radiation. However, the short-term respiratory effects of low-level environmental radiation associated with air pollution particles have not been considered. Although ambient particulate matter (PM) has been reproducibly linked to decreased lung function and to increased respiratory related morbidity, the properties of PM promoting its toxicity are uncertain. As such, we evaluated whether lung function was associated with exposures to radioactive components of ambient PM, referred to as particle radioactivity (PR). For this, we performed a repeated-measures analysis of 839 men to examine associations between PR exposure and lung function using mixed-effects regression models, adjusting for potential confounders. We examined whether PR-lung function associations changed after adjusting for $PM_{2.5}$ (particulate matter ≤ 2.5 μm) or black carbon, and vice versa. PR was measured by the USEPA's radiation monitoring network. We found that higher PR exposure was associated with a lower forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1). An IQR increase in 28-day PR exposure was associated with a 2.4% lower FVC [95% confidence interval (CI): 1.4, 3.4% $p < 0.001$] and a 2.4% lower FEV_1 (95% CI: 1.3, 3.5%, $p < 0.001$). The PR-lung function associations were partially attenuated with adjustment for $PM_{2.5}$ and black carbon. This is the first study to demonstrate associations between PR and lung function, which were independent of and similar in magnitude to those of $PM_{2.5}$ and black carbon. If confirmed, future research should account for PR exposure in estimating respiratory health effects of ambient particles. Because of widespread exposure to low levels of ionizing radiation, our findings may have important implications for research, and environmental health policies worldwide.

1. Introduction

Previous studies have suggested increased risk of mortality, cancer- and non-cancer respiratory disease following short-term exposures to ionizing radiation from the atomic bomb (Furukawa et al., 2013; Kamiya et al., 2015; Pham et al., 2013; Preston et al., 2003), from radiotherapy to treat thoracic malignancies, or longer term occupational radiation exposures (Vrijkeid et al., 2007; Vacquier et al., 2008; Belyaeva et al., 2008). A number of epidemiological studies have provided evidence of an association between radon, a naturally occurring radioactive gas, and lung cancer risk and mortality (Krewski et al., 2005; WHO, 2009; Turner et al., 2011; Kim et al., 2016). However, there is little research on the association between radon and non-malignant respiratory disease (Turner et al., 2012; NRC, 1988). Results from animal studies have shown associations of pulmonary fibrosis and emphysema with exposure to either radon progeny alone or in combination with uranium ore dust (NRC, 1988; Archer et al., 1998). The short-term respiratory effects of low-level radiation associated with air pollution particles have not previously been considered.

Particulate matter (PM) air pollution has been linked to short- and long-term respiratory conditions that include exacerbation and development of asthma, chronic obstructive pulmonary disease (COPD), pulmonary infections, bronchitis and cystic fibrosis (Dominici et al., 2006; Kelly and Fussell, 2011; Peng et al., 2008; Liu et al., 2017). Studies have reported associations between short-term air pollution exposure and decreased lung function, specifically lower forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) (Lepuele et al., 2014; Rice et al., 2013; Int Panis et al., 2017). However,

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there is little knowledge of the properties of PM that promote its toxicity.

While the radiometric composition of PM has been measured (Dueñas et al., 1999; Hernández et al., 2004), the association between particle radioactivity (PR) and lung function has not been investigated. Therefore, we investigate the effects of PR on respiratory health. We hypothesize that exposure to PR will decrease FVC and FEV_1, independent of other air pollution exposures.

Radiation is produced through the decay of unstable atoms called radionuclides (UNSCEAR, 2008). Radionuclides may decay by one of several processes: emission of alpha particles or beta particles, or by isomeric transitions such as gamma or X-ray emissions. Radon is a ubiquitous radioactive gas, formed by the decay of uranium radionuclides naturally present in rocks in the earth's crust. After formation, radon emanates from the soil and continues to decay into radon progeny. When radionuclide decay products are inhaled, they continue to decay and irradiate lung tissues (ICRP, 2007; US NAS, 2006; IARC, 2001; Kendall and Smith, 2002). Please see the Online Data Supplement for further details on the radioactive decay, radiation exposure, and dose.

The radiometric composition of airborne particulates has been quantified previously (Dueñas et al., 1999; Hernández et al., 2004). This includes analyzing particulate samples for gross alpha and gross beta activities, and gamma rays. Hernández et al. (2004) analyzed the radiometric compositions of airborne particulate samples over a four year period. For this, gross alpha and beta activities were measured, showing correlation with each other ($R = 0.72$). In the United States, environmental radioactivity is measured by the US Environmental Protection Agency's RadNet monitoring network (USEPA, 2017). In this study, we use gross beta activity as a surrogate for PR.

Nyhan et al. (2018) examined the associations between PR exposure and blood pressure. However, the impact of PR exposure from particulate matter on lung function has not been studied previously. In addressing a critical gap in the literature, we examine the associations of short- to medium-term average exposures (defined as from 7- to 28-days) to PR and lung function. Radionuclides attached to inhaled particulates may continue to emit radiation in the human respiratory tract, where they may promote inflammation and oxidative stress, and in turn affect respiratory function. We examined this in a longitudinal study in a cohort of men, with repeated clinical measurements taken approximately every four years. This study testing for independent PR-lung function associations complements previous research demonstrating decreased lung function with increased particle mass < 2.5 μm ($PM_{2.5}$) and black carbon (BC).

2. Methods

2.1. Study population

Our study included 839 participants who were enrolled in the Normative Aging Study (NAS) cohort, a longitudinal investigation established in Boston in 1963 by the U.S. Veterans Administration (VA) and limited to healthy men (Bell et al., 1972). At the time of initial enrollment, participants were free of heart disease, hypertension, diabetes, cancer, recurrent asthma, or bronchitis. Subjects completed one to seven clinical examinations with intervals of 3–5 years (a total of 2228 observations) during the period 1998 to 2013. Medical visits included on-site physical examinations and detailed questionnaires after smoking abstinence and an overnight fast. This study was approved by the Harvard School of Public Health and the VA Institutional Review Boards (IRBs). Subjects provided written informed consent to participate in this study. At each visit, information about medication use (corticosteroids, sympathomimetics, anticholinergics), pulmonary disorders, and smoking history were collected using the American Thoracic Society (ATS) questionnaire (Ferris, 1978).

Spirometric tests were performed following strict protocol in accordance with ATS guidelines, as previously reported (Sparrow et al., 1987). Spirometry was assessed in the standing position with a noseclip using a 10-L water-filled survey-recoding spirometer and an Eagle II minicomputer (Warren E. Collins, Braintree, MA, USA). Values were adjusted for body temperature and pressure. A minimum of three acceptable spirograms were obtained, of which at least two were reproducible within 5% for both FVC and FEV_1. Technicians underwent training before taking measurements for the study.

Methacholine challenge tests were conducted using procedures adapted from Chatham et al. (1982). Participants with ischemic heart disease or baseline $FEV_1 < 60\%$ of the predicted value were excluded, and some elected not to participate. Methacholine inhalations were administered at incremental doses corresponding to 0, 0.330, 1.98, 8.58, 16.8, and 49.8 μmol. Participants whose FEV_1 declined by 20% in response to any of the doses at or before 8.58 μmol were classified as having airway hyperresponsiveness. Participants whose FEV_1 did not decline by 20% in response to any of the administered doses, and participants who demonstrated a 20% decline in FEV_1 at higher methacholine dosages (16.8 or 49.8 μmol) only were categorized as having no airway hyperresponsiveness.

2.2. Particle radioactivity and gross beta activity

Similar to Nyhan et al. (2018) and Li et al. (2018), gross beta activity was used as a surrogate for PR in this study. Gross beta activity is a measurement of all particle bound ambient beta activity, regardless of the specific radionuclide source (USEPA, 2017). A note on radioactive decay and the release of radiation is included in the Supplementary materials. Gross beta activity data were acquired from the US EPA's RadNet monitoring network (USEPA, 2017). The RadNet stationary sampling stations provide airborne particulate samples on synthetic fiber filters. Gross beta activity on the filters are measured following a 5–15 day period to permit decay of short-lived radon progenies (e.g., ^{214}Pb, ^{214}Bi) that may be attached to the particles. Despite the decay of most of the short-lived radionuclides, there is still residual radioactivity especially from the last one to two days of the sampled particles, which can be related to the relatively long-lived radon progenies (e.g., ^{210}Pb and ^{210}Bi). We use these data as an indicator of radiation activity of particles collected on the filter. The validity of this assumption has been demonstrated previously (Hernández et al., 2004) where a significant linear correlation ($R = 0.72$) between gross beta and gross alpha activity was observed. To quantify the beta activity on filters, a background subtraction procedure is applied. As samples are collected over several days (typically from 5 to 7 days for each sampling period), we assigned all days within each sampling period with the same beta activity levels. Subsequently, we calculated moving averages based on these measures. Due to this multi-day sampling protocol, we calculated PR exposures for durations longer than 7 days.

Gross beta activity measurements were attained from monitoring sites in Boston MA, Worcester MA, Providence RI and Albany NY. The locations correspond to the geographical distribution of the residential locations of the NAS participants (please see Fig. S2 in the Supplementary materials). A regional mean gross beta activity was calculated based on the data collected and used as the PR exposure for the study. The data collected from each site did not cover the entire study period and different sites covered different periods. We therefore, used measurements from the Albany NY site, which covered the entire study period from 1998 to 2013, to predict levels in each of the other three sites. We did this using a multiple linear regression analysis. We then took an average of these three sites to represent the daily regional beta concentrations. The regression analyses used to model the missing PR exposures for the study population residing in the eastern MA area are described in Nyhan et al. (2018) and have been adopted by Li et al. (2018) also. We examined the effects of 7-, 14-, 21-, and 28-day moving average PR exposures.

2.3. Air pollution

Similar to a previous air pollution studies investigating the association between air pollution and respiratory-related outcomes (Lepuele et al., 2014), we explored short- and medium-term exposure windows. For short-term exposures, we focused on moving average air pollution concentrations computed from seven to 28 days prior to medical visits. From the year 1998 onwards, we measured ambient particle concentrations at the Harvard US EPA Supersite located in downtown Boston, MA and approximately 1 km from the medical center where the study participants were examined. The site (42°20′ north latitude, 71°06′ west longitude) is located on the roof of the Countway Library (a six-floor building) of the Harvard Medical School. This site is located within one block of a four-lane street with truck traffic and with two major highways nearby. Semi-continuous and integrated filter-based measurements of $PM_{2.5}$ (particles with an aerodynamic diameter of $\leq 2.5\,\mu m$) and BC concentrations were conducted. Hourly $PM_{2.5}$ mass concentrations were measured using a Tapered Element Oscillation Microbalance (Model 1400A, Rupprecht and Pastachnick, East Greenbush, NY). Ambient hourly concentrations of BC were measured using an Aethalometer (Magee Scientific Company, model AE-16, Berkeley, CA) on the basis of optical transmittance at a single wavelength ($\gamma = 880\,nm$). The precision of this method was examined using two collocated Aethalometers. BC concentrations were determined based on the attenuation of light transmitted through a sampled quartz-fiber filter tape. The attenuation coefficient used was a fixed value of $16.6\,m^2/g$ provided by the manufacturer. We calculated 7-, 14-, 21-, and 28-day moving average exposure using these hourly data. A detailed description of the supersite has been previously published (Kang et al., 2010).

2.4. Statistical methods

In separate models, we examined whether 7-, 14-, 21- and 28-day moving average PR and air pollution exposures ($PM_{2.5}$ and BC) were associated with lung function outcomes (FVC and FEV_1). Our primary models included a single exposure variable (PR, $PM_{2.5}$ and BC), while a second set of models included two exposure variables (PR and $PM_{2.5}$; PR and BC). We analyzed associations using linear mixed effects models with a random intercept for each subject. We evaluated FVC and FEV_1 as dependent variables. The models took the form:

$$Y_{it} = \beta_0 + u_i + \beta_E E_{it} + \beta_1 X_{1it} + ...+\beta_k X_{kit} + \varepsilon_{it},$$

where Y_{it} is the log-transformed lung function measurement in subject i at visit t, β_0 was the intercept, β_E was the effect of the exposure variable on lung function measurement, E_{it} is the mean exposure concentration for the subject i in the day-of and days prior to the visit t, the covariates for subject i at visit t are denoted by X_{1it} to X_{kit}, and ε_{it} was the within-participant error. Here u_i represents a subject-specific intercept, reflecting unexplained heterogeneity in subjects' overall level of outcome and accounting for longitudinal correlation among measurements taken on the same subject. We assume that u_i values are generated from a normal distribution with common variance, yielding the compound symmetry variance structure. The model accommodates unbalanced data (i.e., varying numbers of repeated measurements on each subject) under the assumption that any missing data is missing at random. We reported the effect estimates as the percent difference in FVC and FEV_1 outcome per interquartile range increase (IQR) in exposure, adjusting for the other covariates in the model. Exposure IQRs were calculated separately for each exposure window studied (from seven to 28-days prior to the medical visit). The IQR reflects the distribution (25th–75th percentiles) in the observed data, while also enabling a comparison of the effects of different exposure types measured with different units such as radioactivity and mass concentration units.

Based on previous NAS studies, we have selected the following adjustment covariates and added a quadratic term whenever it was significant: age (linear and quadratic), ln(height) (linear and quadratic) and standardized weight (linear), race, education level, smoking status, cumulative smoking in pack-years, season of the medical examination (using sine and cosine of time), day of the week, visit number, temperature and relative humidity (matched on exposure windows), physician-diagnosed chronic lung conditions (asthma, emphysema, chronic bronchitis), methacholine responsiveness, and medication use. We visually assessed the linearity of the association of PR and air pollution exposures on both FVC and FEV_1 by fitting penalized splines, using generalized additive mixed models. Because participants with chronic lung conditions are expected to be sicker than average, we explored potential modification of PR and air pollution effects by asthma, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease [COPD; defined as GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage II ($FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ predicted) or higher] by incorporating these variables into our primary analysis.

Several sensitivity analyses were performed. In these tests, we included each of the air pollutants ($PM_{2.5}$ and BC) in regression models with PR. In doing so, we examined whether the PR-lung function effect was changed by each of the air pollutant parameters. We also estimated the extent to which the air pollution-lung function effect estimates were modified by PR exposure. Furthermore, we examined potential interactions between PR and each of the air pollutants ($PM_{2.5}$ and BC).

We furthermore conducted a number of sensitivity tests whereby we completely excluded participants with cardiovascular diseases (coronary heart diseases, stroke), diabetes, and hypertension. Following this, we excluded participants with physician-diagnosed asthma, emphysema, and chronic bronchitis. These sensitivity tests were included for the PR-lung function and the particulate air pollution-lung function models. Following this, to account for the fact that healthier individuals are more likely to participate in follow-up visits, we applied inverse probability weighting to calculate the probability of having a follow-up visit given their age, education level, BMI, smoking status, medical conditions, FEV_1, and air pollution concentration at previous visits (Hernan et al., 2006). All analyses were performed using R software (http://cran-r-project.org). The R libraries and packages used are listed in the Supplementary materials.

3. Results

3.1. Descriptive results

Table 1 shows the longitudinal characteristics of the population. By study design, participants were all male, with a mean age of 75 years. At baseline, < 10% were current smokers, but the majority (67%) were former smokers. Participants had a mean BMI of $28\,kg/m^2$. Furthermore, 29.2% of participants had coronary heart disease, while 72.6% were hypertensive and 13.3% had diabetes during the study. The Spearman correlation between FVC and FEV_1 was 0.90.

Characteristics of the ambient PR and air pollution exposures during the study period and their correlations are presented in Tables 2, 3 and Table E2. The IQR exposures used to scale the effect estimates are also described. The mean 28-day PR exposure was found to be $2.68 \times 10^{-4}\,Bq/m^3$, with an IQR of $0.5 \times 10^{-4}\,Bq/m^3$. Mean 28-day $PM_{2.5}$ exposure was $9.66\,\mu g/m^3$ with an IQR of $3.78\,\mu g/m^3$. Mean 28-day BC exposure was $0.71\,\mu g/m^3$ with an IQR of $0.25\,\mu g/m^3$. The mean ambient temperature was 12.8 °C during all study visits.

3.2. Exposures and lung function

Higher PR exposures were significantly ($p < 0.05$) associated with lower FVC and FEV_1, after adjusting for confounders (see Fig. 1 and Table 4). The magnitude of the estimated associations increased as the exposure window increased. An IQR difference in 14-day PR exposure was significantly ($p < 0.05$) associated with differences of −1.24% (95% CI: −2.11, −0.36%) and −1.10% (−2.07, −0.14%) in FVC and

Table 1
Descriptive statistics for the NAS cohort, including lung function-related outcomes and demographic characteristics reported on the first medical examination (baseline) (n = 839 subjects) and over all clinical examinations (N = 2228). Visit characteristics are also reported.

	All visits
Study variable (unit)	*Mean* (*SD*)
FVC (L)	3.4 (0.7)
FEV_1 (L)	2.5 (0.6)
Age (years)	75.1 (7.0)
Height (m)	173.6 (7.0)
Weight (kg)	84.4 (14.3)
BMI (kg/m^2)	27.95 (4.07)
Cumulative smoking (pack-years[a])	19.85 (24.25)
Years of education (individual)	14.61 (2.91)

	All visits
Categorical variables	*N* (%)
Race	
White	818 (97.5)
Black	14 (1.7)
Missing	7 (1.0)
Smoking status	
Never	236 (28.1)
Former	564 (67.2)
Current	39 (4.6)
Asthma	49 (5.8)
Chronic bronchitis	54 (6.4%)
Emphysema	30 (3.6%)
Methacholine responsiveness	87 (10.1)
Missing	138 (16.0)
Corticosteroids	54 (6.4)
Sympathomimetics (α, β)	67 (8.0)
Anticholinergic	15 (1.8)
Coronary heart disease	245 (29.2)
Stroke	53 (6.3)
Hypertension	609 (72.6)
Diabetes[b]	112 (13.3)

	All visits
Visit characteristics	*N* (%)
Season	
Spring (March–May)	505 (22.7)
Summer (June–August)	609 (27.3)
Fall (September–November)	733 (32.9)
Winter (December–February)	381 (17.1)

Values for the continuous variables are reported as mean ± SD, while values for the categorical variables are no. (%).

[a] Pack-year is defined as the number of packs of cigarettes smoked per day times the number of years the person has smoked.

[b] Diabetic status was diagnosed by a physician.

Table 3
Correlation matrix of 7-day moving average PR (gross beta activity) and particulate air pollution variables ($PM_{2.5}$ mass and BC), for clinical examination days (N = 2228). All p-values were < 0.05.

	R^2		
Exposure	PR	$PM_{2.5}$	BC
PR	1		
$PM_{2.5}$	0.22	1	
BC	0.14	0.47	1

FEV_1, respectively. An IQR increase in PR exposures in the previous 28-days was significantly ($p < 0.001$) associated with a −2.41% (95% CI: −3.39, −1.43%) change in FVC and a −2.41% (95% CI: −3.49, −1.33%) change in FEV_1.

We evaluated the impact of additionally controlling for $PM_{2.5}$ and BC levels on the PR-lung function relationship, results of which are shown in Figs. 1 and 2, along with Tables 4 and 5. When models included both PR and $PM_{2.5}$, associations between PR exposure with both FVC and FEV_1 were attenuated across all exposure windows, but remained significant ($p < 0.05$) for 21- and 28-day exposures for both FVC and FEV_1. When PR and BC were included together in a model, the association of PR with FVC and FEV_1 was also attenuated. Even though the PR effect estimates were reduced, they remained statistically significant for the 21- and 28-day exposure windows.

$PM_{2.5}$ exposure was significantly ($p < 0.05$ or $p < 0.001$) associated with FVC and FEV_1 for all exposure windows (see Fig. 2 and Table 5). An IQR increase in 28-day $PM_{2.5}$ exposure was associated with a difference of −2.62% (95% CI: −3.68, −1.56%) in FVC and −2.30% (95% CI: −3.47, −1.13%) in FEV_1. When PR was simultaneously included in the models, $PM_{2.5}$-lung function associations remained stable for 7-day $PM_{2.5}$ exposures; however, they were attenuated for the 14-, 21- and 28-day exposures. BC exposure had a significant ($p < 0.001$) association with both FVC and FEV_1. For example, an IQR increase in 28-day BC exposure was associated with a −3.51% (95% CI: −5.17, −1.85%) difference in FVC. When the models were adjusted for PR exposure also, this did not affect the results of 7-day BC exposures. However, for 14-, 21-, and 28-day exposures, the BC-lung function associations were attenuated but remained significant ($p < 0.05$).

We assessed the linearity of the association of PR and air pollution exposures on both FVC and FEV_1 by fitting penalized splines for all exposure durations studies. For all the effects of 7-, 14-, 21-, and 28-day PR exposures on FVC and FEV_1, the AIC for each was minimized with a curve of > 1 degree of freedom; however, the overall trends were also approximately linear with no evidence of a threshold (data not shown). In the models that included two exposure variables (PR and $PM_{2.5}$, and PR and BC), we tested interactions by also including a multiplicative interaction term between the two pollutants in the model, but this interaction term was never significant ($p < 0.05$).

Table 2
Distributions of ambient measured PR (gross beta activity) and particulate air pollution variables ($PM_{2.5}$ mass and BC), starting in the year 1998 and ending in year 2013.

Exposure (unit)		PR (Bq/m^3)		$PM_{2.5}$ ($\mu g/m^3$)		BC ($\mu g/m^3$)	
		Mean ± SD	IQR	Mean ± SD	IQR	Mean ± SD	IQR
		$\times 10^{-4}$	$\times 10^{-4}$			$\times 10^{-1}$	$\times 10^{-1}$
Exposure window (days)	7	2.69 ± 0.73	0.90	9.61 ± 3.98	4.67	7.16 ± 2.23	3.13
	14	2.67 ± 0.62	0.82	9.61 ± 3.35	4.16	7.15 ± 1.88	2.60
	21	2.68 ± 0.56	0.74	9.63 ± 3.12	3.90	7.13 ± 1.76	2.43
	28	2.68 ± 0.53	0.69	9.66 ± 3.01	3.78	7.14 ± 1.70	2.49

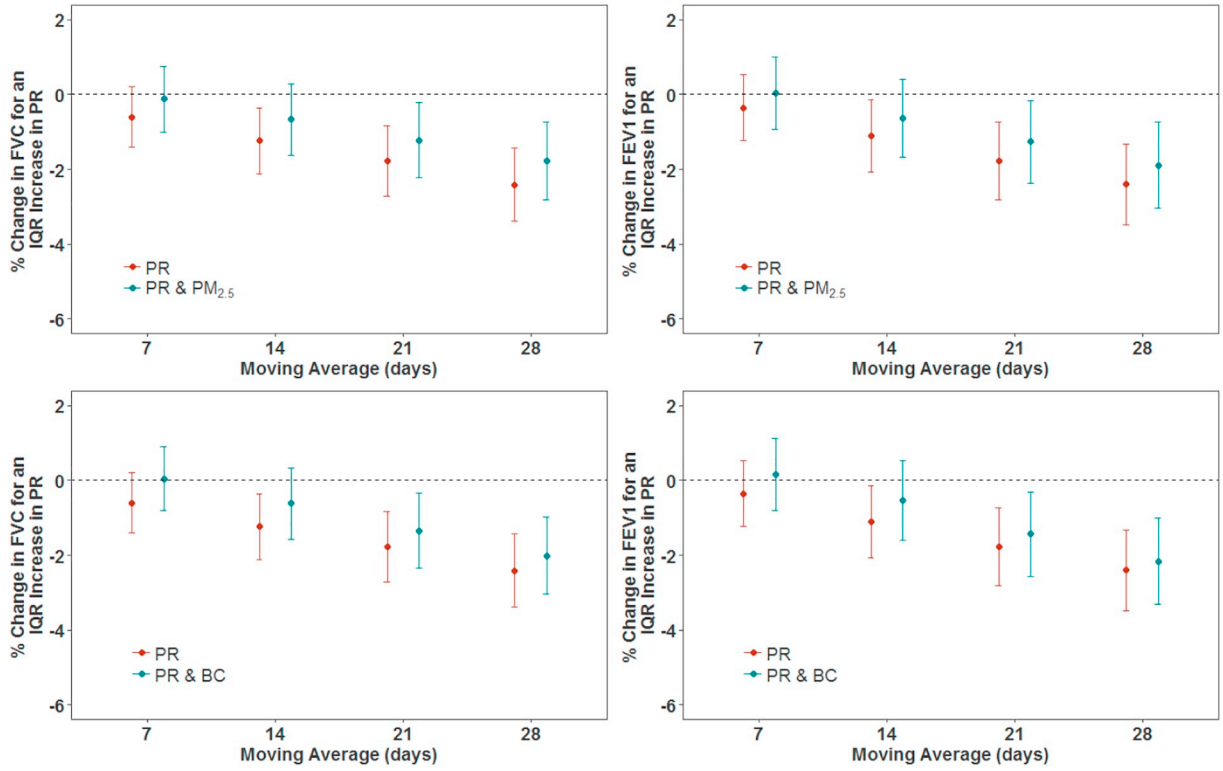


Fig. 1. Associations of PR exposure with FVC and FEV_1, and associations of PR with FVC and FEV_1 where the models have also included particulate air pollution ($PM_{2.5}$ and BC) exposures, in a cohort of men (n = 839 subjects). Results were adjusted for age, race, height, weight, education level, smoking status, cumulative smoking, sine and cosine terms of the day of the year, day of the week, visit number, temperature, relative humidity, asthma, chronic bronchitis, emphysema, methacholine responsiveness, corticosteroids, sympathomimetics, anticholinergics. The y-axis represents the percent difference (and 95% CIs) in FVC or FEV_1 per IQR increase in PR exposure. The IQRs for PR are shown in Table 2.

3.3. Sensitivity tests

By omitting participants with cardiovascular diseases including coronary heart disease (29.2% of participants) and stroke (6.3%), diabetes (13.3%), and hypertension (72.6%), the results did not change (see the Online Data Supplement, Tables S5 and S6). When participants with physician diagnosed asthma, emphysema and chronic bronchitis were excluded from the analysis (n = 1948 following the exclusions), model estimates were consistent with the main analysis, although p-values were larger (see the Supplementary materials, Tables S7 and S8). With further controlling for potential survival bias using inverse probability weighting, results varied slightly (see the Supplementary materies, Tables S9 and S10).

Table 4
Differences in lung function (FEV_1 and FVC) associated with an IQR increase in exposure to PR, as observed in the cohort of men, for 2228 clinical visits (n = 839 subjects). Outcomes are expressed as the percent difference in FEV_1 or FVC per IQR increase in PR. IQRs for PR are shown in Table 2 in the main manuscript.

		Difference in FVC per IQR increase in exposure to PR (95% CI)		
Exposures in model		PR	PR & $PM_{2.5}$	PR & BC
Exposure window (days)	7	−0.60 (−1.40, 0.20)	−0.12 (−1.00, 0.76)	0.05 (−0.81, 0.91)
	14	−1.24 (−2.11, −0.36)**	−0.67 (−1.61, 0.28)	−0.62 (−1.57, 0.33)
	21	−1.77 (−2.72, −0.83)***	−1.22 (−2.22, −0.21)**	−1.34 (−2.34, −0.35)**
	28	−2.41 (−3.39, −1.43)***	−1.77 (−2.81, −0.73)***	−2.02 (−3.04, −0.99)***
		Difference in FEV_1 per IQR increase in exposure to PR (95% CI)		
Exposures in model		PR	PR & $PM_{2.5}$	PR & BC
Exposure window (days)	7	−0.35 (−1.24, 0.53)	0.03 (−0.93, 1.00)	0.16 (−0.81, 1.13)
	14	−1.10 (−2.07, −0.14)**	−0.64 (−1.68, 0.41)	−0.52 (−1.59, 0.54)
	21	−1.77 (−2.81, −0.73)***	−1.26 (−2.36, −0.16)**	−1.44 (−2.56, −0.31)**
	28	−2.41 (−3.49, −1.33)***	−1.89 (−3.04, −0.74)***	−2.17 (−3.33, −1.01)***

All models were adjusted for age, race, height, weight, education level, smoking status, cumulative smoking, sine and cosine terms of the day of the year, day of the week, visit number, temperature, relative humidity, asthma, chronic bronchitis, emphysema, methacholine responsiveness, corticosteroids, sympathomimetics, anticholinergics.

** p-value < 0.05.

*** p-value < 0.001.

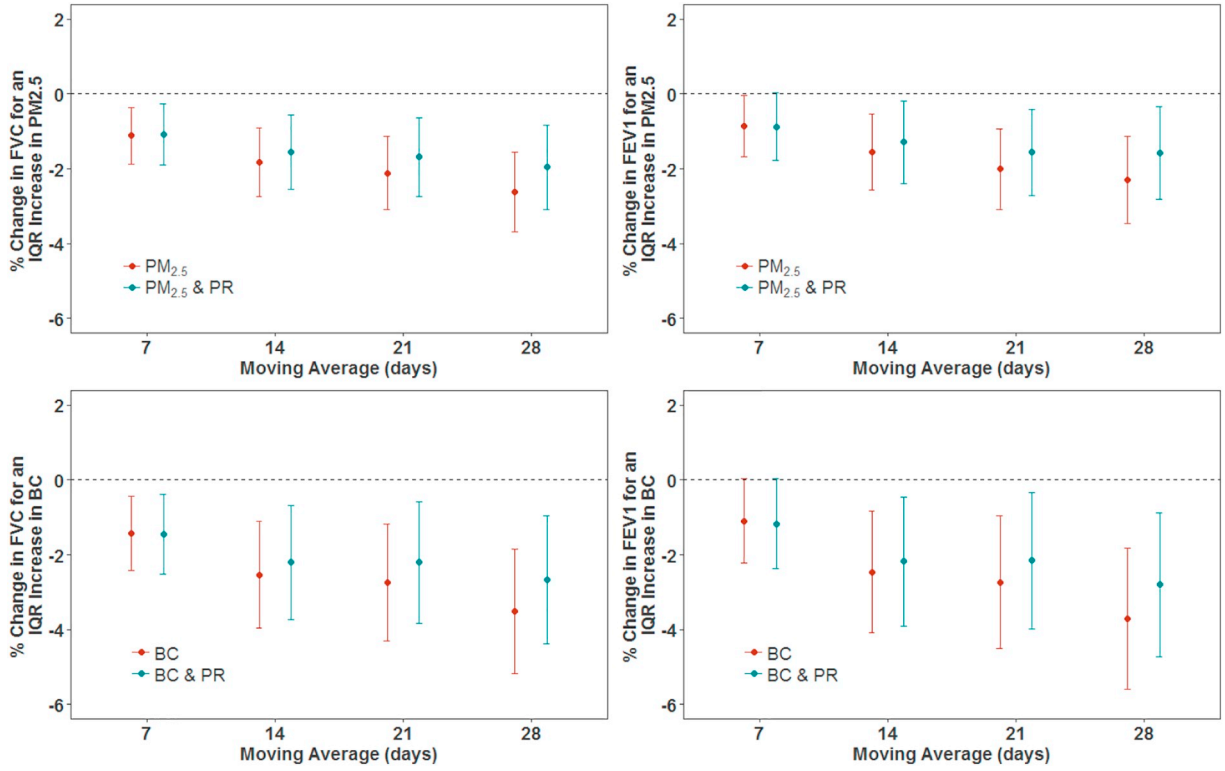


Fig. 2. Associations of particulate air pollution exposures ($PM_{2.5}$ and BC) with FVC and FEV_1, and associations of particulate air pollution exposure with FVC and FEV_1 where the models have also included PR exposures, in a cohort of men (n = 839 subjects). All models were adjusted for age, race, height, weight, education level, smoking status, cumulative smoking, sine and cosine terms of the day of the year, day of the week, visit number, temperature, relative humidity, asthma, chronic bronchitis, emphysema, methacholine responsiveness, corticosteroids, sympathomimetics, anticholinergics. The y-axis represents the percent difference (and 95% CIs) in FVC or FEV_1 per IQR increase in PR exposure. The IQRs for PR are shown in Table 2. The IQRs for $PM_{2.5}$ mass and BC are shown in Table 2.

Table 5
Difference in lung function (FEV_1 and FVC) associated with an IQR increase in exposure to particulate air pollution, as observed in the cohort of men, for 2228 clinical visits (n = 839 subjects). Outcomes are expressed as the difference in FEV_1 or FVC per IQR increase in particulate air pollution ($PM_{2.5}$ mass or BC). IQRs for $PM_{2.5}$ mass and BC are shown in Table 2.

		Difference in FVC per IQR increase in $PM_{2.5}$ (95% CI)		Difference in FEV_1 per IQR increase in $PM_{2.5}$ (95% CI)	
Exposures in model		$PM_{2.5}$	$PM_{2.5}$ & PR	$PM_{2.5}$	$PM_{2.5}$ & PR
Exposure window (days)	7	−1.12 (−1.86, −0.37)**	−1.07 (−1.89, −0.25)**	−0.86 (−1.68, 0.04)**	−0.87 (−1.77, 0.03)*
	14	−1.83 (−2.75, −0.90)***	−1.56 (−2.56, −0.55)**	−1.55 (−2.56, −0.53)***	−1.29 (−2.39, −0.18)**
	21	−2.11 (−3.10, −1.13)***	−1.68 (−2.73, −0.63)**	−2.01 (−3.09, −0.92)***	−1.56 (−2.71, −0.41)**
	28	−2.62 (−3.68, −1.56)***	−1.95 (−3.08, −0.83)***	−2.30 (−3.47, −1.13)***	−1.59 (−2.83, −0.34)**

		Difference in FVC per IQR increase in BC (95% CI)		Difference in FEV_1 per IQR increase in BC (95% CI)	
Exposures in model		BC	BC & PR	BC	BC & PR
Exposure window (days)	7	−1.43 (−2.43, −0.43)**	−1.45 (−2.51, −0.39)**	−1.10 (−2.23, −0.03)*	−1.17 (−2.37, 0.03)*
	14	−2.53 (−3.97, −1.10)***	−2.21 (−3.73, −0.68)**	−2.46 (−4.09, −0.84)**	−2.18 (−3.91, −0.46)**
	21	−2.75 (−4.32, −1.18)***	−2.21 (−3.82, −0.59)**	−2.73 (−4.50, −0.96)**	−2.15 (−3.97, −0.33)**
	28	−3.51 (−5.17, −1.85)***	−2.66 (−4.37, −0.96)**	−3.71 (−5.59, −1.83)***	−2.80 (−4.73, −0.87)**

All models were adjusted for age, race, height, weight, education level, smoking status, cumulative smoking, sine and cosine terms of the day of the year, day of the week, visit number, temperature, relative humidity, asthma, chronic bronchitis, emphysema, methacholine responsiveness, corticosteroids, sympathomimetics, anticholinergics.

* p-value < 0.1.
** p-value < 0.05.
*** p-value < 0.001.

4. Discussion

4.1. Significant findings

To our knowledge, this is the first study to investigate the effect of PR exposure on lung function in a cohort. We investigated the effect of PR exposure on FVC and FEV_1, using longitudinal data with repeated measurements for each subject. We examined the independent PR health effects while controlling for $PM_{2.5}$ and BC, and vice versa. This is the first study to apply PR exposure for a respiratory health effects study using data collected from a radiation monitoring network such as the USEPA's RadNet.

In quantifying the impact of PR exposure on FVC and FEV_1 in the cohort, we observed statistically significant negative associations. The size of PR-induced lung function effects were comparable to those produced by $PM_{2.5}$ and BC exposures in this study. When PR models also included $PM_{2.5}$ exposures, the PR-lung function associations were partially attenuated, but retained statistical significance for two exposure windows. Similar results were observed when PR-lung function models simultaneously included BC. This suggests that PR may have an independent effect on lung function. However, as beta activity is measured from and depends on TSP (up to 30 μm in diameter including ultrafine, fine, and coarse particles), the radioactivity that the beta activity represents may be associated with both fine and coarse particles. Despite this, even after accounting for regional particle concentrations, PR-lung function effects were observed.

The associations between increased particulate air pollution, namely $PM_{2.5}$ and BC exposures, and decreased FVC and FEV_1 were significant in the study. When models controlled for PR exposure, the adverse $PM_{2.5}$- and BC-lung function associations were attenuated for 14-, 21-, and 28-day exposures. This suggests that PR could potentially explain some of the previously reported associations between lung function and air pollution. The 7-day PM- and BC-lung function associations were not affected and therefore, may be independent of PR exposures. The associations with longer moving averages (14-, 21-, and 28-day exposures) were partially attenuated, suggesting that some of that particle toxicity may depend on radioactivity. The longer moving averages of beta activity (14-, 21-, and 28-day exposures) may be a more stable measure of radioactivity than the shorter 7-day moving averages, which depend more on sampling protocol. The PR measurements do not capture short-lived radionuclides, which may be important for acute lung function effects.

4.2. Comparison to the literature

As this is the first study to examine how PR exposure affects FVC and FEV_1, we are unable to directly compare our PR results to other studies. The associations between $PM_{2.5}$ and BC with lung function that we identified are comparable in magnitude, although slightly larger, than the effects of air pollution exposures determined in a previous NAS study (Lepuele et al., 2014). Although we defined our air pollution exposures using the same Harvard supersite and adjusted for similar covariates in our models to Lepuele et al. (2014), we used many more clinical measurements for a longer study period (from 1998 to 2013) than Lepuele et al. (2014) (from 1999 to 2009).

4.3. Biological mechanisms

Research regarding mechanisms mediating PR's negative effect on respiratory health is limited. However, the biological mechanisms for the health effects of high doses of ionizing radiation from radiotherapy have been reported in the literature. Pulmonary irradiation can produce reactive oxygen and nitrogen, which cause oxidative damage of DNA, lipids, and proteins. The resulting apoptosis of alveolar epithelial cells and vascular endothelial cells then induces inflammatory reactions and chemotaxis of monocytes, lymphocytes, and granulocytes in the lungs (Huang et al., 2016). Radiation-induced lung injury leads to radiation pneumonitis, an inflammatory response that involves alveolar cell destruction and inflammatory cell influx in the interstitial and alveolar space (Judge et al., 2015). When radiation-induced lung injury becomes chronic, it may lead to pulmonary fibrosis, which is an irreversible process characterized by fibroblast proliferation, collagen accumulation and destruction of normal lung structure (Huang et al., 2016; Christofidou-Solomidou et al., 2017). Our findings raise the question of whether ambient particle-bound ionizing radiation, at much lower levels than the dosage of pulmonary irradiation, may explain some of the toxic effects of particulate matter on the lung, which has also been found to cause intracellular oxidative stress and airway inflammation (Kelly and Fussell, 2011; Zhang et al., 2009; Rahman and MacNee, 2000; Stringer and Kobzik, 1998). Our results for PR suggest a symmetrical reduction in FVC and FEV_1, especially for exposure durations of 21- and 28-days. This symmetrical reduction may be indicative of restrictive lung conditions including interstitial lung disease and pulmonary fibrosis. In response to irradiation, other studies have suggested surfactant impairment, which affects interactions between alveolar membrane and respiration (Christofidou-Solomidou et al., 2017).

4.4. Limitations

There is potential for confounding by unaccounted factors in our study. However, we adjusted for a comprehensive list of individual and meteorological confounders, and ran sensitivity analyses, including additional adjustment for chronic disease, and inverse probability weighting, and our findings remained consistent. There may be confounding by specific PM constituents such as metals. Our study population was homogeneous, consisting entirely of men, 97% of whom were Caucasian. Therefore, our results cannot be generalized to other populations without further research.

A single monitoring site was used to estimate regional daily levels of particle pollution, as has been used in previous studies on the same NAS cohort (Lepuele et al., 2014). For PR, we assigned the average level measured by the USEPA's monitoring network, from multiple monitoring stations in the study area. We have included a correlation matrix of the PR measurements by study site in the Supplementary materials however (see Table S3). We assumed the measurement error of the air pollutants and PR levels to be primarily Berkson measurement error, which is random and causes little or no bias in exposures. Previous research supports this assumption for air pollution exposures determined at a central monitoring site (Zeger et al., 2000), and the same would likely be true for PR. The PR measurements are likely due to radon concentrations, which do not exhibit spatial variation.

There are additional limitations of the PR exposure estimate. As per the USEPA's protocol, integrated filter samples are collected over several days (from 5 to 7 days) (USEPA, 2017). As such, we examined the main effects of 7-, 14-, 21-, and 28-day averages of PR. As PM-bound gross beta activity is measured after the end of the multi-day sampling period, we were unable to assess any respiratory effects of short-lived radionuclides that had decayed prior to beta activity measurement. Also, we used PM-bound gross beta activity as a surrogate for PR, whereas particles also emit alpha and gamma radiation. Previous research has shown that gross alpha activity is correlated with beta activity (Hernández et al., 2004), while gamma rays may or may not be correlated with the beta activity.

5. Conclusion

In this study, we demonstrate that PR can impair lung function, with effect sizes similar to that of ambient particle pollution. The effects of radioactivity are attenuated after adjustment for particles. Our findings also suggest that a portion of the lung function effects of ambient particle exposure, averaged over 21 to 28 days, may be explained by the radioactivity level. We speculate that radionuclides associated with ambient particles, upon inhalation and deposition in the human respiratory tract, may subsequently lead to the activation of inflammatory pathways and oxidative stress, resulting in reduced lung function. Understanding these mechanisms of lung injury may inform future public health and air quality policy worldwide.

Declaration of interest

None.

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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.2019.04.066.

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