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## Non-malignant respiratory disease mortality in male Colorado Plateau uranium miners, 1960 – 2016

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### Abstract

**Background.**—To evaluate trends of non-malignant respiratory disease (NMRD) mortality among US underground uranium miners on the Colorado Plateau, and to estimate the exposure-response association between cumulative radon progeny exposure and NMRD subtype mortality.

**Methods.**—Standardized Mortality Ratios (SMRs) and excess relative rates per 100 Working Level Months (ERR/100WLM) were estimated in a cohort of 4,021 male underground uranium miners who were followed from 1960 through 2016.

**Results.**—We observed elevated SMRs for all NMRD subtypes. Silicosis had the largest SMR (n=52, SMR = 41.4; 95% CI: 30.9, 54.3), followed by other pneumoconiosis (n=49, SMR = 39.6; 95% CI: 29.6, 52.3) and idiopathic pulmonary fibrosis (IPF) (n=64, SMR=4.77; 95% CI 3.67, 6.09). SMRs for silicosis increased with duration of employment; SMRs for IPF increased with duration of employment and calendar period. There was a positive association between cumulative radon exposure and silicosis with evidence of modification by smoking (ERR/100WLM<sub>10packyears</sub> = 0.78; 95% CI: 0.05, 24.6 and ERR/100WLM<sub><10packyears</sub> = 0.01; 95% CI: -0.03, 0.52), as well as a small positive association between radon and IPF (ERR/100WLM = 0.06, 95% CI: 0.00, 0.24); these associations were driven by workers with prior employment in hard rock mining.

**Conclusions.**—Uranium mining workers had excess NMRD mortality compared with the general population; this excess persisted throughout follow-up. Exposure-response analyses indicated a positive association between radon exposure and IPF and silicosis, but these analyses have limitations due to outcome misclassification and missing information on occupational co-exposures such as silica dust.

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Authors' contributions: KKR and MKSB conceived of the work. MKSB, DRD, and KKR worked on provision of the data. KKR and SB analyzed the data. All authors participated in the interpretation of the work. KKR developed the initial draft of the work and MKSB, DBR, and DBR contributed to subsequent drafting of the work. All authors participated in critical revisions of work and all authors approve of the version to be published.

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## INTRODUCTION

The Colorado Plateau uranium miners are a historically significant cohort which contributes information on the association between radon and various causes of death.<sup>1-4</sup> Data from this cohort have provided important information on lung cancer risk from exposure to radon progeny for decades.<sup>2-4</sup> Continued mortality follow-up of this cohort improves understanding the occupational hazards associated with uranium mining work over the life course of workers, and allows for the estimation of exposure-response relationships between radon progeny and mortality with extended latency and induction periods.<sup>5</sup> The Colorado Plateau cohort is also one of the few uranium miner cohorts with smoking information, which allows estimates of the joint effects of radon and smoking.

Colorado Plateau uranium miners experienced higher mean radon exposures and dose rates than other enumerated cohorts of underground miners.<sup>6</sup> Additionally, workers were exposed to heat, noise, vibration, dust, and to a lesser extent, diesel fuel exhaust.<sup>6</sup> In the mid- to late-1960s, the introduction of mechanical ventilation decreased exposures to radon and particulate matter,<sup>6</sup> although most original mines were closed by this time. During the last follow-up of this cohort through 2005, excess mortality from non-malignant respiratory diseases (NMRD) including COPD, silicosis, idiopathic pulmonary fibrosis (IPF), tuberculosis, pneumoconiosis, and other and unspecified pneumoconiosis were observed.<sup>4</sup> Silicosis and IPF showed evidence of association with radon progeny exposure.<sup>4</sup> Several clinical observations of uranium miners indicate a high burden of obstructive and non-malignant respiratory disease, including pulmonary fibrosis.<sup>7-9</sup> In surveillance of the United States population, the rates of silicosis, IPF and pneumoconiosis are substantially higher in the areas of Arizona, New Mexico, Utah, and Colorado where there was intense uranium mining activity starting in the 1950s.<sup>10</sup> The etiology of IPF is largely unknown; there are numerous environmental and occupational risk factors.<sup>11,12</sup> Additionally, the incidence and mortality rates of IPF are rising globally.<sup>11,13,14</sup> Studies of uranium miners offer the opportunity to explore suspected occupational risk factors for IPF such as radon or silica dust exposure.

There is limited evidence that radon could cause NMRDs; the most evidence is on fibrotic lung disease.<sup>6,9,15,16</sup> Mechanistically, it is hypothesized that radon can cause inflammation of the respiratory system due to damage from the alpha particles emitted during the radioactive decay of radon.<sup>15,16</sup> Radon dosimetry indicates that these alpha particles can damage the alveoli, penetrate the interstitium, and can pass through the lungs into the bloodstream and reach other organs.<sup>6</sup> Animals exposed to high levels of radon (1000+ WLM) develop non-malignant respiratory disease.<sup>6,17</sup> Studies of radiotherapy patients indicate that radiation dose to the lung is linked to fibrosis.<sup>18,19</sup> A large case series reported interstitial fibrosis among uranium miners where the suspected cause was radon, as this fibrosis was radiographically distinct from silicosis.<sup>9</sup> The 1988 Committee on Health Risks of Exposure to Radon (BEIR IV) report noted the difficulty of separating radon exposure from other occupational agents such as silica,<sup>6,17</sup> but noted that animals exposed to high levels of radon develop interstitial and obstructive lung diseases.<sup>17</sup>

Several scientific groups have called for the need to understand the health effects of radon exposure other than lung cancer. We aimed to describe NMRD mortality relative to national and regional rates among workers in the Colorado Plateau cohort of US uranium miners, extending follow-up 11 years. We report excess relative rates (ERR) for radon exposure-NMRD mortality associations, and examine potential modifying effects of smoking. While we focus on fibrotic lung disease, we also examine other NMRDs such as COPD and silicosis for dose-response associations and as negative control outcomes to evaluate unmeasured confounding by silica. Our study adds to the understanding of occupational hazards experienced by this cohort over an extended period and provides some of the first excess relative rate estimates for the association between radon and causes of death other than lung cancer in this cohort.

## MATERIALS AND METHODS

### Study setting and vital status.

The Colorado Plateau cohort is based on records from 4,137 underground uranium miners who were employed for at least 1 month and participated in at least 1 medical screening between 1/1/1950 and 12/13/1960. Person time began either at the start of mortality rates (1/1/1960) or the date of first medical screening, whichever was later. Person time ended at date of death, date lost to follow-up, or the end of follow-up, 12/31/2016. Mortality ascertainment is described in detail in a previous study.<sup>4</sup> Briefly, mortality follow-up was conducted by linking name, Social Security number, and date of birth to the US National Death Index. The US Social Security Administration Death Master File and Internal Revenue Service records were also used to confirm or obtain vital status when needed.

### Exposure and covariates.

Cumulative radon progeny exposure is measured in Working Level Months (WLM). WLM calculations are described elsewhere,<sup>2-4,6</sup> briefly, WLM in this cohort is based on interpolation of dates when miners reached 1 of 9 categories of cumulative radon exposure.<sup>2-4</sup> Since the last published update of the Colorado Plateau cohort, WLM estimates have been recalculated to include more accurate estimates of annual cumulative exposure and exposure rates by reviewing original records to verify employment and exposure data. Additionally, cumulative radon exposure from previous non-uranium hard rock mining was estimated. Updated estimates were calculated by linking each miner back to original employment records by mine location and year, combined with available radon progeny measurement data.

Cigarette smoking is quantified in pack-years. Smoking information has also been improved since the last update of this cohort. Previously, miners' smoking status and pack-years was based on surveys last conducted in the 1970s or, for white miners, in 1985. In this update, smoking status, pack-years, and the last smoking date among ever-smokers were imputed from the date of the last survey to the end of follow-up. Smoking imputations were based on age and 5-year birth cohort and the cessation probabilities for U.S. men using U.S. National Health Interview Survey data.<sup>20</sup> Silica dust exposure was not quantified in the Colorado Plateau cohort.

## Outcomes.

We selected NMRD subtypes of a priori interest: asthma, COPD, idiopathic pulmonary fibrosis, pneumonia, silicosis, tuberculosis, other pneumoconiosis, and other respiratory diseases. Underlying causes of death are coded by the ICD revision in effect at time of death. Appendix table I reports the ICD codes for revisions 7 through 10 for each subtype. For temporal and ERR analyses, we focus on subtypes with more than 50 deaths.

## Statistical analyses.

Overall Standardized Mortality Ratios (SMRs) were calculated using SAS statistical software (SAS 9.4; SAS Institute Cary, NC). 95% confidence intervals were calculated using the Byar approximation of the Poisson distribution.<sup>21</sup> SMRs were adjusted for 5-year calendar period, 5-year age groups, and racialization. Expected numbers of deaths were calculated by multiplying the person-time at risk by regional population rates. The regional standard population rates for white miners are the age- and calendar period-specific underlying mortality rates for white non-Hispanic males in Colorado, Utah, New Mexico, and Arizona. The regional standard population rates for American Indian miners are the age- and calendar period-specific underlying mortality rates for non-white non-Hispanic males in New Mexico and Arizona. We also calculated SMRs by duration of employment, calendar period, and period of hire.

We performed regression analyses of associations between cumulative radon progeny exposure and mortality using Cox regression<sup>22</sup> with attained age as the time scale. Risk sets were further matched on year of birth (+/- 5 years of index case), and duration of employment in decades. The relationships between cumulative radon progeny exposure and NMRD deaths were modeled as linear excess relative rates and 95% profile likelihood-based confidence intervals using the general model form  $rate = h_0(1 + \beta_1 d)$  where  $\beta_1$  is an additive term representing the excess relative rate per WLM cumulative radon exposure  $d$ <sup>23</sup> and  $h_0$  represents the baseline/unexposed rate by the matched variables of age and birth date. Smoking was assessed as a potential modifier by performing analyses stratified by smoking pack-years ( or <10 pack-years).

## Sensitivity analyses.

Several sensitivity analyses were conducted: (1) In addition to using a 10 year lag in the main analyses, we explore the induction and latency periods<sup>5</sup> for different NMRD types. The latent period is the time between disease onset and detection (in this case NMRD death), and the induction period is the time between exposure and disease onset. Latency and induction were estimated through an empirical evaluation of model fit based on likelihood ratio tests. (2) We fit additional models of the associations between radon and silicosis and IPF, restricted to person time and events accrued at <1000 WLM and modeled as a restricted cubic spline with three evenly spaced knots across the lower 95% of exposures.in the period prior to ICD-10, (3) We conducted a sensitivity analysis that restricted idiopathic pulmonary fibrosis to deaths coded in the 10<sup>th</sup> revision in order to assess potential bias due to outcome misclassification in prior revisions. We also analyzed silicosis, other pneumoconioses, and IPF together as a group to assess the impact of outcome misclassification. (4) We

assessed the potential impact of unmeasured silica as a potential confounder in several ways. We restricted analyses to workers who had hard rock mining experience prior to uranium mining employment to assess the impact of prior hard rock mining experience on overall results. We also indirectly assessed potential confounding of the association between cumulative radon progeny exposure and silicosis by unmeasured silica exposure, using COPD as a negative control outcome. And, we indirectly assessed potential confounding of the association between cumulative radon progeny exposure and IPF by unmeasured silica exposure, using silicosis as a negative control outcome. (5) We assessed the impact of adjusting for duration of employment, since duration of exposure could be correlated with unmeasured silica exposures. We also assessed the impact of adjustment for racialization because of different working conditions and different health care systems between whites and American Indians.<sup>24</sup> (6) Finally, we conducted a sensitivity analysis restricting ERR estimates to person time and events among workers exposed to <1000 cumulative working level months to assess potential impacts of radon progeny exposure misclassification, which is higher for miners who worked in the early years of mining operations.

## RESULTS

4,021 male underground uranium miners met cohort inclusion criteria and were alive at the start of follow up (116 otherwise-eligible miners died before 1960). These miners contributed 128,578 person-years during the 56 years of follow-up (table I). Through 2016, 88% of workers died. Cause of death was available for 99% of deceased workers. Median duration of employment was 5 years. Median cumulative radon exposure was 431 WLM, with a mean of 806 WLM. 601 total NMRD deaths occurred, including 254 COPD deaths, 111 pneumonia deaths, and 64 IPF deaths (table II).

All NMRD causes of death were higher than expected, and some observed excesses were very large. SMRs for select NMRD causes of death are reported in table II. Deaths from silicosis were 40 times higher than expected (SMR = 41.4; 95% CI: 30.9, 54.3), other pneumoconiosis deaths were 40 times higher than expected (SMR = 39.6; 95% CI: 29.3, 52.3), and deaths due to IPF were 5 times higher than expected (SMR = 4.77; 95% CI: 3.67, 6.09). Mortality rates from asthma, COPD, pneumonia, and other respiratory diseases were also 1.5 to 3 times higher than expected (table II).

We examined temporal trends in SMRs by duration of employment, time since hire, calendar period, racialization, and smoking pack-years (table III). COPD, silicosis and IPF SMRs increased by longer duration of employment, with a silicosis SMR of 58.8 with 10 year duration of employment (table III). Pneumonia SMRs increased slightly by period of hire, whereas those for IPF decreased by period of hire (table III). There was a notable decrease in silicosis and IPF deaths for workers hired 1955+. Notably, SMRs increased by advancing calendar period for IPF, with an SMR of 9.28 between 2010 and 2016. In some instances, SMR results varied between American Indian and white miners (table III). We observed an elevated SMR for COPD among white miners and below the null for American Indian miners. When SMRs were stratified by smoking status as measured by pack-years, SMRs for COPD were substantially higher among smokers with 10 pack-years (SMR<sub><10packyears</sub> = 0.61; 95% CI: 0.42, 0.86; SMR<sub>10packyears</sub> = 2.64; 95% CI: 2.31, 3.02).

We also estimated the association between radon and NMRD mortality using linear ERR models (table IV) and for silicosis and IPF, a spline model (Figure 1). Assuming a 10-year exposure lag, the ERR/100WLM were slightly elevated for IPF (ERR/100WLM = 0.06; 95% CI: 0.00, 0.24) and silicosis (ERR/100WLM = 0.19; 95% CI: 0.01, 1.35). The group of other respiratory diseases was also associated with radon (ERR/100WLM = 0.05; 95% CI: 0.01, 0.15). Radon was not associated with other NMRD types, and notably, there was no association between radon and COPD. In analyses restricted to workers with prior hard rock mining experience, estimates of ERR/100 WLM silicosis, IPF, and combined silicosis, IPF, and pneumoconiosis were of larger magnitude than in the full cohort. The results of the fitted lag analysis were similar to the a priori analysis, with the exception of silicosis, which increased with a 3-year lag (ERR/100WLM = 0.79; 95%CI: 0.12, 14.13). Additionally, there was evidence of modification of the radon-silicosis association by smoking (table V), with 10 pack years having a higher ERR of silicosis than <10 (ERR/100 WLM<sub>10packyears</sub> = 0.78; 95%CI: 0.05, 24.57; (ERR/100 WLM<sub><10packyears</sub> = 0.01; 95%CI: -0.03, 0.52). For COPD, the ERR/100WLM was similar by smoking status. For all causes of death examined, cause-specific numbers among <10 pack years were small. Estimates made by restricting IPF person-time and events that occurred during the 10<sup>th</sup> ICD revision were not different from the unrestricted estimates.

In sensitivity analyses where models were not adjusted for duration of employment or were adjusted for racialization, there were minor changes (appendix table II). Some estimates increased when duration of employment was not included in the model. There were no changes to estimates when racialization was included in the model. Models were most sensitive to the restriction of person time and events accrued at <1000 WLM, with notable increases in ERRs for silicosis, IPF, and all NMRDs combined.

## DISCUSSION

We evaluated trends in NMRD mortality among the US Colorado Plateau uranium miners and estimated associations between radon and NMRD types, with 11 years of additional mortality follow-up and improved radon exposure and smoking estimates. We observed elevated SMRs for all NMRD types, some SMR trends in temporal factors, and positive associations between radon and silicosis and IPF. There was evidence of smoking modifying the association between radon and silicosis, in which the positive association was restricted to smokers. Exposure-response associations were limited by unmeasured confounding by silica and outcome misclassification.

### Standardized mortality analyses.

Large and persistent excess SMRs for NMRD types indicate that the uranium mining experience results in excess NMRD deaths compared to the regional population. We observed elevated SMRs for silicosis that increased by calendar period and duration of employment and decreased by period of hire. IPF SMRs also increased with advancing calendar period.

We observed differences in SMRs by racialization, which has been observed in prior analyses.<sup>4</sup> We found elevated SMRs for COPD among whites, but American Indian workers

had an SMR below the null for COPD. This is likely driven by the large differences in smoking rates between whites and American Indian workers.<sup>4</sup> Smoking is a strong risk factor for COPD,<sup>25</sup> and SMRs for  $\geq 10$  pack-years smoking were much higher than  $<10$  pack-years smoking for COPD. Higher silicosis and other pneumoconioses SMRs among white miners may be due to more dust exposure from other mining activities before or after uranium mining employment. These differences likely reflect several other factors including differences in the workplace safety and social experiences,<sup>24</sup> differences in healthcare access and diagnostic patterns, and disparities in the burden of pollution from uranium mining activities, which disproportionately impact American Indians.

The NMRD SMRs among this cohort are higher than in other uranium miner studies. In the largest pooled study of uranium miners, the Pooled Uranium Miners Analysis (PUMA), investigators analyzed SMRs for silicosis and COPD using data from 7 cohorts, including Colorado Plateau.<sup>26</sup> The PUMA SMR for COPD was 0.98 (95% CI 0.93, 1.02), and 13.56 (95% CI 12.64, 14.52) for silicosis.<sup>26</sup> Unlike PUMA, we observed a large excess COPD mortality, although this excess was driven entirely by smokers. We also observed an excess mortality rate of silicosis that was three times higher than PUMA. This is likely because the Colorado Plateau cohort is composed of workers from an early calendar period of hire when ventilation was poor, with high average cumulative radon exposure, and likely high dust exposures.<sup>26,27</sup>

The SMR analysis of the Colorado Plateau cohort indicates that uranium miners in the US continue to die of NMRDs at a higher rate than the comparable general population. The uranium industry employed tens of thousands of workers,<sup>28</sup> including 3,000 to 5,000 American Indian miners,<sup>29</sup> so the Colorado Plateau cohort represents only a small proportion of the US uranium worker population. Based on the SMRs by calendar year, it is expected that this occupational group will continue to exhibit high NMRD mortality. The Radiation Exposure Compensation Act (RECA), which provides benefits to uranium miners who developed certain diseases from uranium mining work between 1942 and 1971, is scheduled to expire in 2024.<sup>28</sup> This analysis indicates there will be uranium miners who will continue to develop RECA-eligible NMRDs after RECA ends.

### **Associations between radon and NMRD types.**

We observed no exposure-response associations between radon and pneumonia or other pneumoconioses despite a large SMR for other pneumoconioses. We also found no evidence of an association between radon and COPD death in this cohort.

Silicosis death was associated with radon exposure, and this association was modified by smoking, with a stronger association among heavier  $\geq 10$  pack-years smoking and no association among  $<10$ . Analyses restricted to workers with prior hard rock mining experience had a stronger association between radon and silicosis, suggesting that the associations observed in the full cohort are driven by workers exposed to silica via prior hard rock mining experience.

There was also a small positive association between radon and IPF that did not appear to be modified by smoking. As with silicosis, IPF analyses restricted to workers with prior hard



rock mining experience had a stronger association. A prior analysis of this cohort found positive associations between radon and silicosis and pulmonary fibrosis.<sup>4</sup> The authors suspected that this was a result of outcome misclassification of death certificates, or due to unmeasured exposure to dust which may have been correlated with duration of employment, or from.<sup>4</sup>

As in prior analyses of this cohort, unmeasured silica dust exposure is a limitation. In this analysis we assessed for confounding by silica exposure using negative control outcome logic. COPD and silicosis are strong candidates for negative control outcomes since there is little evidence that they caused by radon progeny, but could be caused by the unmeasured confounder of interest (silica dust exposure). We observed no association between radon and COPD, which suggests that radon may not be associated with silica and would not confound other radon-NMRD associations. But we did observe a strong association between radon and silicosis, which suggests that radon could be associated with silica, and could confound other radon-NMRD associations.

A key assumption for a valid negative control outcome is that the exposure of interest is not a cause of the negative control outcome. Although our analysis supports a large German uranium miner study that also found no association between radon and COPD,<sup>30</sup> a cohort study with an ecological metric of residential radon exposure reported an association between county-level radon and COPD mortality.<sup>15</sup> Given the null association between radon and COPD in the Colorado Plateau cohort it is unlikely that violation of this assumption is a major limitation of the current negative control outcome evaluation.

Results were also sensitive to restriction to person time and events <1000 WLM suggesting issues with exposure misclassification among higher exposures, which mostly occurred in early periods. As shown in figure 1, the RRs are lower in the highest exposure category, and the exclusion of the high exposure group leads to elevated estimates. Additionally, results were sensitive to categorization of exposure. Relative rates differed between quintiles and continuous estimates because the referent category of the quintiles included deaths among miners with radon exposures (figure 1).

Another source of uncertainty is that NMRD mortality based on death certificates is subject to outcome misclassification. Because of the known risks of silicosis, miners may be more likely to be diagnosed with silicosis than other radiographically similar NMRDs. Among the 52 silicosis deaths listed as underlying deaths in the cohort, 11 had a multiple cause of death listed as idiopathic pulmonary fibrosis, other pneumoconioses, or both. ERR analyses of silicosis, pneumoconioses, and IPF combined were lower than silicosis alone. Therefore, outcome misclassification and confounding are still substantial concerns in this analysis.

This is the first analysis to report NMRD risk per unit exposure in the Colorado Plateau uranium miner cohort. Other than in the German cohort, there have been few in-depth studies of NMRD subtypes among uranium miners. This analysis updates mortality follow-up 11 years since the last update, for a total of 56-years of mortality follow-up. This extended follow-up allows for the investigation of diseases with long latency and induction periods. Other strengths of this study include the improved cumulative radon exposure

estimates, which reduces bias from exposure misclassification, improved smoking pack-year estimates, and minimal loss to follow-up. This study is also strengthened by the smoking data, which was based on repeated questionnaires.

This study is limited by small numbers of deaths for several NMRD subtypes and limited information on occupational co-exposures. Silica dust and diesel fuel exhaust exposures may have been higher prior to the introduction of ventilation in the mid-1960s.<sup>4</sup> The exposure-response analyses are substantially limited by the absence of silica exposure estimates. Silica is known to cause silicosis and other NMRDs, including COPD independently of silicosis.<sup>31</sup> In estimating ERR/100WLM, we adjusted for duration of employment and temporal factors, which may be a proxy measure of silica exposure. We conducted a sensitivity analysis to assess the impact of adjustment for duration of employment but only saw slight changes in some estimates. (Appendix table II). We also used negative control outcome methods and restriction to evaluate the role of silica as a confounder of the radon-silicosis association.

Finally, it is important to note healthy worker survivor bias (HWSB) affects estimates with internal comparisons. We adjusted for duration of employment, but it is unlikely that this adjustment fully corrects for HWSB.<sup>32</sup> A prior study of lung cancer using data from this cohort indicated that HWSB caused substantial underestimation of radon-lung cancer associations.<sup>33</sup>

Despite these limitations, research on NMRD risks among uranium miners and other radon-exposed worker populations should continue for both epidemiological studies and public health surveillance. Epidemiologic studies of uranium miners are the basis for occupational radon standards.<sup>34</sup> The results of the ERR analysis suggest that radon may play a role in the development of some types NMRDs, even in the absence of silica exposure, although confounding and outcome misclassification remain concerns. Currently, the International Commission on Radiological Protection (ICRP) only considers radon risks from lung cancer in their recommendations for radiological protection systems.<sup>35</sup> There is increasingly more evidence that cancers other than lung, cerebrovascular disease, and some NMRDs are associated with occupational radon exposure,<sup>26,36,37</sup> which could influence the assessment of risks of radon exposure for contemporary workers and the general population.

We observed excess NMRD mortality for several subtypes of interest, indicating that the occupational hazards of uranium mining result in elevated mortality rates compared to regional standard population rates. In ERR analyses, we observed small positive associations between radon and silicosis, and radon and IPF. However, there are several limitations: data for outcomes were sparse, measurements for important potential confounders such as silica were not fully accounted for, there are concerns with outcome misclassification, and associations were driven by workers with prior hard rock mining experience. While our analysis provides only suggestive evidence for an association between radon and select NMRDs, we demonstrated a large excess mortality compared to the standard population, and we observed that these elevated rates continue to persist among surviving cohort members. The legacy of uranium mining continues to impact former miners, and the disease burden among this aging population requires ongoing attention.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### Disclaimer:

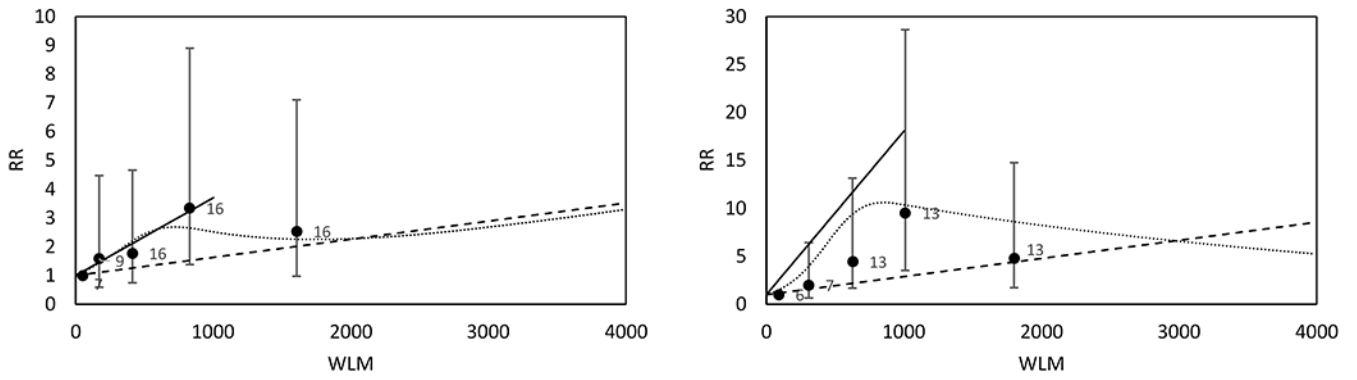
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**Figure 1.** Relative rate (RR) of death from interstitial pulmonary fibrosis (left) and silicosis (right) among male uranium miners in the US Colorado Plateau cohort 1960-2016. Linear model restricted to person time and events accrued at <1000 working level months (WLM) (solid line), restricted cubic spline with three evenly spaced knots across the lower 95% of exposures (dotted line), linear model (dashed line). Solid circles indicate relative rates by WLM, categorized by quintiles of deaths. Whiskers indicate 95% profile likelihood confidence intervals. Numbers indicate the cause-specific deaths in each quintile. For idiopathic pulmonary fibrosis, the midpoints for quintiles are approximately 50, 170, 410, 830, and 1610 WLM. For silicosis, the midpoints for quintiles are approximately 90, 310, 625, 1010, and 1800 WLM. All models Adjusted for age, year of birth (+/- 5 years of index case), and duration of employment in decades.

**Table I.**

Characteristics of the male Colorado Plateau uranium miner cohort 1950 - 2016

<b>Cohort characteristics</b>	
Male miners, n	4,137
Alive at start of follow up, n	4,021
White miners	3254
American Indian miners	767
Follow up period	1960 - 2016
Person years	128,578
Employment factors, median (interquartile range)	
Age at hire	29 (22, 39)
Year of first hire	1954 (1951, 1957)
Duration of employment	5 (2, 9)
Year of birth	1923 (1913, 1931)
Time since first employment	39 (26, 53)
Cumulative radon in WLM	431 (163, 1007)
Smoking pack-years, n (percent)	
<10 pack-years	1478 (37)
10 pack-years	2543 (63)
Vital status, n (percent or interquartile range)	
Alive in 2017	446 (11)
Deceased through 2016	3540 (88)
Lost to follow-up	35 (1)
Person years at risk	32 (18, 46)
Age last observed	72 (61, 80)
Age last observed among decedents	70 (59, 79)

**Table II.**

Number of observed underlying nonmalignant respiratory deaths, Standard Mortality Ratios (SMR) and 95% Confidence Intervals (95%CI) among white and American Indian uranium miners in the US Colorado Plateau region, 1960 - 2016. \*

Underlying cause of death (ICD-10)	Obs	SMR (95%CI)
Asthma	11	1.97 (0.98, 3.53)
COPD	254	1.85 (1.63, 2.09)
Interstitial Pulmonary Fibrosis	64	4.77 (3.67, 6.09)
Idiopathic Pulmonary Fibrosis **	42	6.22 (4.48, 8.41)
Pneumonia	110	1.44 (1.18, 1.73)
Tuberculosis	29	3.07 (2.05, 4.41)
Silicosis	52	41.4 (30.9, 54.3)
Other pneumoconioses	49	39.6 (29.3, 52.3)
Other respiratory diseases	121	2.84 (2.35, 3.39)

\* Adjusted for age, calendar period, and racialization. Standard rates are based on regional deaths and population.

\*\* Person time and events restricted to 1999 and later with the introduction of the code J84.1 in ICD-10



**Table III.**

Observed nonmalignant respiratory deaths, Standard Mortality Ratios (SMR) by duration of employment, period of hire, calendar period, and smoking pack-years. Uranium miners in the US Colorado Plateau region, 1960 - 2016.\*

	Pneumonia			COPD			Silicosis			Interstitial Pulmonary Fibrosis		
	obs	SMR	95% CI	obs	SMR	95% CI	obs	SMR	95% CI	obs	SMR	95% CI
<b>Duration of Employment</b>												
< 1 years	12	1.20	(0.62, 2.10)	28	1.60	(1.07, 2.32)	0	0.00	(NC, 28.4)	4	2.35	(0.63, 6.01)
1 - <10 years	62	1.49	(1.14, 1.91)	143	1.85	(1.56, 2.18)	27	38.4	(25.3, 55.9)	32	4.24	(2.90, 5.98)
10 years	36	1.44	(1.01, 2.00)	83	1.95	(1.55, 2.41)	25	58.8	(38.0, 86.8)	28	6.73	(4.47, 9.72)
<b>Period of hire</b>												
<1950	22	1.32	(0.82, 1.99)	46	1.8	(1.31, 2.39)	13	45.6	(24.2, 77.9)	16	7.13	(4.07, 11.6)
1950-1955	39	1.35	(0.96, 1.85)	102	2.12	(1.73, 2.57)	24	53.2	(34.1, 79.1)	24	4.93	(3.16, 7.33)
1955+	49	1.58	(1.17, 2.09)	106	1.66	(1.36, 2.01)	15	28.8	(16.1, 47.6)	24	3.81	(2.44, 5.67)
<b>Calendar Period</b>												
<1970	8	0.80	(0.35, 1.58)	20	1.93	(1.18, 2.98)	10	25.2	(12.1, 46.4)	2	1.98	(0.22, 7.13)
1970 - 79	13	1.02	(0.54, 1.75)	53	2.89	(2.17, 3.78)	5	18.3	(5.90, 42.7)	5	3.90	(1.26, 9.10)
1980 - 89	22	1.45	(0.91, 2.19)	52	1.92	(1.43, 2.52)	17	75.7	(44.1, 121)	5	3.04	(0.98, 7.09)
1990 - 99	29	1.47	(0.99, 2.12)	52	1.60	(1.20, 2.10)	8	49.8	(21.4, 98.1)	10	3.26	(1.56, 6.00)
2000 - 09	25	1.93	(1.25, 2.85)	51	1.67	(1.24, 2.19)	6	57.4	(21.0, 125)	18	4.71	(2.79, 7.44)
2010+	13	2.14	(1.14, 3.66)	26	1.39	(0.91, 2.03)	6	61.5	(22.4, 134)	24	9.28	(5.95, 13.8)
<b>Smoking pack-years</b>												
<10 pack-years	59	1.44	(1.09, 1.85)	33	0.61	(0.42, 0.86)	22	38.8	(24.3, 58.7)	32	4.44	(3.03, 6.26)
10 pack-years	51	1.43	(1.07, 1.89)	221	2.64	(2.31, 3.02)	30	43.5	(29.4, 62.1)	32	5.16	(3.53, 7.29)
<b>Racialization</b>												
white	68	1.37	(1.06, 1.73)	243	2.00	(1.75, 2.26)	44	47.1	(34.2, 63.3)	40	4.52	(3.23, 6.16)
American Indian	42	1.56	(1.13, 2.11)	11	0.70	(0.35, 1.25)	8	24.7	(10.7, 48.7)	24	5.25	(3.36, 7.81)

\* adjusted for age, calendar period and racialization. NC = not converged

**Table IV:**

Linear Excess Relative Rates per 100 Working Level Months (ERR/100WLM) and 95% profile likelihood Confidence Intervals (95%CI) of mortality from non-malignant respiratory disease among uranium miners in the Colorado Plateau region, 1960-2016.\*

Cause of death	Full cohort, 10-year lag			Prior mining experience		
	Cases (n)	ERR/100 WLM	95% CI	Cases (n)	ERR/100 WLM	95% CI
COPD	254	0.00	0.00 0.02	225	0.00	-0.01 0.03
Silicosis	52	0.19	0.01 1.35	39	0.45	0.04 10.9
Other pneumoconioses	49	0.01	-0.02 0.09	35	0.02	-0.03 0.21
Interstitial pulmonary fibrosis	64	0.06	0.00 0.24	34	0.16	0.02 1.06
Idiopathic pulmonary fibrosis <sup>^</sup>	42	0.06	-0.02 0.31	18	0.26	0.01 4.78
All NMRD	601	0.01	0.00 0.03	431	0.02	0.00 0.04
Other respiratory diseases	121	0.05	0.01 0.15	60	0.07	0.01 0.26
Pneumonia	110	-0.01	-0.03 0.02	62	0.01	-0.02 0.09
Silicosis, pneumoconioses, interstitial pulmonary fibrosis	165	0.05	0.00 0.13	108	0.12	0.03 0.34

\* Adjusted for age, year of birth (+/- 5 years of index case), and duration of employment in decades.

<sup>^</sup> Person time and events restricted to 1999 and later; the year ICD-10 revision went into effect.

Linear Excess Relative Rates per 100 Working Level Months (ERR/100WLM), under a 10-year lag assumption, and 95% profile likelihood Confidence Intervals (95%CI) of mortality from non-malignant respiratory disease by smoking pack years in the Colorado Plateau region, 1960-2016.<sup>^</sup>

**Table V:**

Cause of death	10 pack-years			<10 pack-years		
	Cases (n)	ERR/100 WLM	95%CI	Cases (n)	ERR/100 WLM	95%CI
COPD	221	0.00	0.00	33	-0.01	-0.03
Silicosis	30	0.78	0.05	22	0.01	-0.03
Other pneumoconiosis	33	0.01	-0.03	16	0.00	-0.02
IPF	32	0.08	0.00	32	0.02	-0.04
IPF (ICD-10 only) <sup>‡</sup>	17	0.06	-0.02	25	0.01	-0.04
All NMRD	402	0.01	0.00	199	0.00	0.00
Other respiratory diseases	59	0.04	-0.01	62	0.06	-0.01
Pneumonia	51	0.03	-0.02	59	-0.02	-0.03

<sup>^</sup> Adjusted for age, year of birth (+/- 5 years of index case), and duration of employment in decades.

<sup>‡</sup> Person time and events restricted to 1999 and later; the year ICD-10 revision went into effect.