Greater Odds for Angina in Uranium Miners than Non-uranium Miners in New Mexico

Vanessa J.M. al Rashida, MD, MPH^{1,2}, Xin Wang, MS¹, Orrin B. Myers, PhD¹, Tawny W. Boyce, MS, MPH¹, Elizabeth Kocher, MPH¹, Megan Moreno, BS³, Roger Karr³, Nour Assad, MD¹, Linda S. Cook, PhD¹, and Akshay Sood, MD, MPH^{1,3}

¹Department of Internal Medicine, University of New Mexico School of Medicine

²Division of Cardiovascular Medicine, University of Arkansas for Medical Sciences

³Black Lung Program, Miners' Colfax Medical Center

Abstract

Objective: To test the hypothesis that uranium miners in New Mexico (NM) have a greater prevalence of cardiovascular disease than miners who extracted non-uranium ore.

Methods: NM-based current and former uranium miners were compared to non-uranium miners by using cross-sectional standardized questionnaire data from the Mining Dust in the United States (MiDUS) study from 1989 to 2016.

Results: Of the 7,215 eligible miners, most were men (96.3%). Uranium miners (n=3,151, 43.7%) were older and diabetic, but less likely to currently smoke or use snuff (p = 0.001 for all). After adjustment for covariates, uranium miners were more likely to report angina (O.R. 1.51, 95% C.I. 1.23, 1.85) than non-uranium miners.

Conclusions: Our data suggest that along with screening for pulmonary diseases, uranium industry workers should be screened for cardiovascular diseases.

Keywords

Cardiovascular diseases; uranium; minerals; miners

INTRODUCTION

Cardiovascular disease is the leading cause of death in both men and women in the United States (U.S.), amounting to 610,000 deaths in 2015 (1, 2). It is the leading cause of death among blacks, Hispanics, and non-Hispanic whites, but is second to cancer among American Indians or Alaska natives as well as Asians or Pacific Islanders (1). The estimated cost of heart disease in the U.S. is \$200 billion annually which includes the cost of health care services, medications, and lost productivity (1). Obtaining a history of patients' medical

Corresponding Author: Vanessa J. M. al Rashida, MD, MPH, Division of Cardiovascular Medicine, University of Arkansas for Medical Sciences, 4301 W. Markham St. #532, Little Rock, AR 72205, Office Telephone: 501-296-1401, Fax: 501-686-6439, vanessa.al.rashida@gmail.com.

Conflicts of Interest: None Declared

problems and lifestyle habits can help decipher what preventive measures are needed to reduce risk factors for cardiovascular diseases. Risk factors such as tobacco use, diabetes mellitus, dyslipidemia, and obesity are the most universally-known and well-studied causes of cardiovascular diseases (1). One important risk factor that has not been highlighted in the public arena is radiation exposure.

Radiation exposure has been studied extensively as a cause for pulmonary fibrosis, hematological disorders, and certain cancers (3–7). There is also a growing number of studies showing that high-dose ionizing radiation exposure in environmental and therapeutic settings increases the risk for cardiovascular diseases (8–10). Among Japanese atomic bomb survivors, acute whole-body irradiation was associated with increased risk for cardiovascular diseases with a linear dose response and a latency of approximately 10 years (11–15). Similarly, therapeutic chest irradiation, which involves high-dose ionizing radiation, among patients with lymphoma or different solid tumor cancers, also increases the risk for cardiovascular diseases (16–18). Occupational exposures to radiation, which are generally at lower doses but over longer durations than atomic bomb and therapeutic radiation exposure, have been inconsistently associated with cardiovascular diseases (19–22). Mining, processing, and transporting uranium ore, associated with occupational exposure to radiation, have been investigated as a risk factor for cardiovascular disease, but current literature is inconclusive, constituting a critical gap in this field (21, 23–28).

One of the richest uranium ore deposits in the U.S. is located in northwestern New Mexico (NM), an area that was extensively mined between 1949 and 1989, produced more than 225 million tons of ore during that period. Although much lower in amount, the U.S. continues to produce uranium amounting to 1,125 tons in 2016 (29). Uranium workers, due to the long latency period involved, continue to suffer from malignant and non-malignant respiratory health effects: the latter including chronic obstructive pulmonary disease (COPD), pneumoconiosis/silicosis, and pulmonary fibrosis (25, 30). American Indians are disproportionately affected with an elevated standardized mortality ratio of 2.6 found in Navajo uranium workers for nonmalignant respiratory diseases (31). Our objective was to examine the risk for cardiovascular diseases in uranium workers. We hypothesized that NM uranium workers have a higher prevalence of cardiovascular diseases relative to workers who extracted other minerals from the ground and were able to assess this in screening data from NM miners.

METHODS

Study design:

In this cross-sectional study, we used data obtained from the NM-based Mining Dust in the United States (MiDUS) study from 1989 to 2016. The MiDUS study recruits current or former workers employed in the NM mining industry who voluntarily undergo medical surveillance. These surveillance activities are performed using a mobile outreach clinic, organized by rotation in each of the 20 rural NM communities with high concentration of miners. This surveillance program is jointly run by Miners' Colfax Medical Center (MCMC) at Raton, NM and the University of New Mexico (UNM) School of Medicine at Albuquerque, NM and is supported by the New Mexico Black Lung Clinics Grant funded by

the Health Resources and Services Administration. Data collected at baseline evaluation was examined.

Inclusion Criteria:

The study included all those employed in the mining industry for at least one year who also participated in the above-mentioned clinical surveillance initiative.

Study Methods:

Upcoming mobile clinics are advertised in the target rural communities through print, media, and radio, as well as by working with community/church leaders and mine safety officers. Patients can also self-refer themselves for screening evaluations. Participants are not charged out-of-pocket expenses for their screening clinic visit, which takes approximately one hour to complete. At each mobile screening clinic, miners are assessed for respiratory, hearing, and musculoskeletal disorders associated with mining-related exposures. Assessment also includes common health conditions such as lung diseases and exposures such as tobacco use.

The mobile screening clinic is held in a specially outfitted trailer which is 53 feet long with a diesel generator to supply power. The clinic consists of five separate areas, including a patient reception area, a digital chest x-ray unit, sound-proof audiometry booth, spirometry room, and an examination room. The staffing model in the mobile screening clinic consists of a mid-level provider (*i.e.*, a physician assistant or nurse practitioner), a radiology/audiometry technician, and a medical assistant/nursing technician who is certified by the National Institute of Occupational Safety and Health (NIOSH) for performing spirometry. Race and ethnicity specific predicted values were used for non-Hispanic whites and Hispanics. Crapo American Indian reference standards was used for American Indians (32, 33).

Before the screening examination, patients complete a comprehensive occupational and clinical history intake form, based on the adult American Thoracic Society Diffuse Lung Disease 1978 (ATS DLD-78) Questionnaire (34). The questionnaire responses are reviewed and confirmed by the mid-level clinical provider. The screening visit includes a vital sign assessment, including a blood pressure assessment at rest and measurement of standing height and weight without shoes, pre-bronchodilator spirometry using ATS guidelines, audiometry, and a standard posterior-anterior chest radiograph. A complete history and physical examination is performed by a mid-level provider who develops a treatment and care plan for the patient depending on the primary diagnosis. The records are reviewed for quality by a UNM based preventive medicine and pulmonary medicine specialist.

Exposure:

Exposure status was classified as those who were ever employed with the uranium mining industry (termed uranium miners in this study) versus those who were never similarly employed, but instead worked with extracting and processing other minerals such as coal, metal, and nonmetals (termed non-uranium miners).

Outcomes:

Study outcomes included self-reported history of physician diagnosed angina, myocardial infarction, cerebrovascular events and hypertension, as well as measured systolic or diastolic hypertension. For self-reported angina, myocardial infarction, cerebrovascular events, and hypertension, the subjects were asked the following questions:

- Has a doctor ever told you that you have angina or chest pain from your heart?
- Has a doctor ever told you that you had a heart attack?
- Have you ever had a stroke (CVA)?
- Have you ever had high blood pressure/hypertension?

Measured hypertension was defined as either systolic blood pressure ≥ 140 mm of Hg or diastolic blood pressure ≥ 90 mmHg, measured by either a manual blood pressure cuff (sphygmomanometer) or automatic blood pressure cuff, in a resting sitting position. Severe hypertension or hypertensive urgency, a subset of measured hypertension, was defined as either systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 110 mmHg.

Covariates:

Selection of covariates was based upon known biological and/or mechanistic plausibility of each variable's role as a potential confounder in evaluating the risk for cardiovascular disease. Covariates in multivariable analysis model 1 included age, sex, race/ethnicity, body mass index (BMI), self-reported diabetes mellitus, current cigarette smoking status, current snuff use status, current alcohol use status, and total mining tenure. Current snuff user was defined as a subject who reported having ever used snuff or chewing tobacco for at least a week or more and had used it within the prior 6 months. Current alcohol user was defined as a subject who reported having consumed alcohol within the prior 24 hours. Total mining tenure was used as a continuous variable. The correlation between age and total mining tenure was modest at 0.33. The variance inflation factors for miners' age and total mining tenure was 1.24 and 1.19 respectively, which was small. It is therefore reasonable to include both variables in the multivariable analysis. Additionally, statistical model 2 included prebronchodilator forced expiratory volume in one second (FEV₁) as a covariate. Reliable information on lipid disorders was not available and therefore not used as a covariate. The multivariable analysis of cardiovascular outcomes also included self-reported hypertension or measured hypertension as an additional covariate.

Statistical analysis and IRB approval:

Chi-square and Student's t-test were utilized for univariate analysis of categorical and continuous outcomes respectively. For the chi-square test, a 2 by 2 test for each variable was created with the two categories of (uranium vs. non-uranium) miners. Logistic regression (PROC LOGISTIC function) was used for multivariable analysis. Formal two-way tests of interaction were separately performed between uranium mining exposure and underground mining/ mining tenure/smoking variables on the outcome 'angina'. Data were analyzed using Statistical Analysis Software (SAS) 9.4 version (Cary, NC) with two-tailed p-values <0.05 considered significant.

This study was approved by the University's Human Research Protection Office Institutional Review Board (HRPO 14–058) that also approved a waiver of consent from participants.

RESULTS

Table 1 demonstrates the distribution of select characteristics, many known to be associated with risk for cardiovascular disease, among all eligible uranium ($n=3,151$ or 43.7%) and non-uranium miners ($n=4,064$ or 56.3%). The two groups of miners had a similar gender distribution, which both were predominantly male. Relative to non-uranium miners, uranium miners were older, less educated, and more likely to be American Indian; however, reported lower pack years of smoking. They were also less likely to be current miners and current smokers or snuff or alcohol users ($p = 0.001$ for all). Uranium miners had fewer years of mining tenure and were more likely to be employed in underground mining activities than non-uranium miners ($p<0.001$). Despite a lower mean BMI, uranium miners had a significantly higher prevalence of self-reported diabetes mellitus than non-uranium miners ($p<0.001$). Absolute and percent predicted FEV₁ values were also lower and self-reported prevalence of COPD was higher in uranium miners than in non-uranium miners ($p<0.001$).

Uranium miners were significantly more likely than non-uranium miners to self-report hypertension, even after adjustment for covariates (Models 1 and 2, Table 2). Uranium miners were significantly more likely to have measured hypertension in the unadjusted model but this association was reversed, when adjustment was made for covariates, indicating that this association was explained by confounding variables.

Uranium miners were also more likely to self-report angina, myocardial infarction, and cerebrovascular event. In the multivariable model adjusting for self-reported hypertension, only the association with angina remained consistently significant (Table 3A). In the multivariable model adjusting for measured hypertension, the association with angina and myocardial infarction remained significant (Table 3B).

In unadjusted interaction analyses, underground mining and longer mining tenure were disproportionately associated with higher odds of self-reported angina in non-uranium miners than in uranium miners (interaction $p = 0.004$ and <0.001 respectively). As compared to never smoking, former smoking was disproportionately associated with self-reported angina among non-uranium miners than uranium miners (interaction $p = 0.002$). The adjusted interaction analyses confirmed differential angina association for non-uranium miners with smoking status ($p=0.04$) but not with mining location ($p = 0.89$) or mining tenure ($p = 0.50$).

DISCUSSION

Our cross-sectional study indicates that exposure to uranium mining is associated with greater odds for angina than exposure to non-uranium mining. This association is not fully explained by the older age and higher prevalence of diabetes mellitus in uranium miners, who also had lower BMI, lower nicotine use, and lower duration of mining tenure than non-uranium miners.

Kreuzer *et al.* utilized the German Wismut cohort, the largest cohort of uranium miners in the world, in assessing the risk for cardiovascular and cerebrovascular death in uranium miners (21). The results of their 2006 study showed that there was no significant increase in cardiovascular mortality among uranium miners (21). A Canadian group headed by Villeneuve *et al.* reviewed the Newfoundland fluorspar mining cohort in order to validate the previous study by Kruezer *et al.*, with results being consistent with a non-significant excess risk for cardiovascular mortality (23). Drubay *et al.*, studied French uranium miners in assessing the exposure risk of external gamma rays and radon on cardiovascular and cerebrovascular disease mortality by the use of the French National Vital Statistics Registry (24). These results again showed that there was no significant increase in cardiovascular death rates among uranium miners; there was however a significantly higher risk of cerebrovascular mortality. On the other hand, a study of non-white uranium miners, predominantly Navajo, in the Colorado Plateau Study group, found that the standardized mortality rate from cardiovascular causes was significantly lower than the mortality rates for non-whites (31). In a 1991 cross-sectional study, Samet examined a relatively young group of New Mexico underground uranium miners and noted that their observed death rate from circulatory causes, as identified on death certificate, was significantly lower than that expected for the general population, with a standardized mortality ratio of 0.6 (95% C.I. of 0.4–0.8) (35). These studies, like our own, did not directly measure occupational uranium exposure or even the exposure to particulate matter that they were studying but estimated cumulative radiation exposure. Another weakness of these studies is the unreliability of death certificates in helping to define the cardiovascular cause of death outside the hospital (36). Data indicate that clinical diagnoses certified in death certificate, and later found to disagree with autopsy findings were most frequent for cerebrovascular and cardiovascular disease (37). Our approach of documenting self-reported questionnaire-based physician diagnosis of cardiovascular diseases and measured hypertension among living miners may be more accurate than data abstracted from death certificates. Most studies compared uranium miners to the general population, an approach that is limited by the healthy worker effect, whereby workers may exhibit lower overall morbidity and mortality rates than the general population because the severely ill and chronically disabled are ordinarily excluded from taxing jobs or suffer attrition from the work force (38). By comparing uranium miners to miners involved in other extractive industries, our study minimizes the healthy worker effect. Depending on the mean miner age in individuals studies, cardiovascular morbidity may be a more sensitive measure than mortality, even if there will be an eventual cardiovascular cause of death. Given that excess mortality from cancers has clearly been demonstrated for uranium miners, excess cardiovascular morbidity may not lead to significant excess cardiovascular mortality (35).

A limited cross-sectional analysis of disease morbidity among 2,835 New Mexico miners screened during 2004–2014 in the MiDUS study has been previously published by Shumate *et al.* (39). As compared to the Shumate study that compared across various sectors of miners, our current analysis includes a larger number of miners accrued over a longer timeframe in a binary categorical analysis, and therefore has greater power. Similar to our current analysis, Shumate showed a significantly higher prevalence of self-reported hypertension among uranium miners than other miners (39). Although the odds for having

angina and heart attack in the Shumate study was higher in uranium miners, these associations did not reach statistical significance after adjusting for covariates including self-reported hypertension (39). A potential weakness of previously published studies of miners, including that by Shumate, is inadequate adjustment for the confounding effect of low FEV₁ value. It has been previously reported that low FEV₁ ranks second to smoking and above blood pressure and cholesterol as a predictor of cardiovascular mortality (40). Our study however demonstrated that the pattern of significant outcomes did not differ much with and without adjustment for FEV₁ in Tables 2 and 3, except in the case of self-reported myocardial infarction where the association lost statistical significance after additional adjustment for FEV₁.

Studies linking non-occupational uranium exposure to cardiovascular disease provide supportive evidence for our findings without establishing causality (41). A recent study highlighted the effects of inhalational environmental uranium exposure on cardiovascular disease outcomes among Navajo community members who live in close proximity to abandoned uranium mines in NM (41). Primary human coronary artery endothelial cells treated for 4 hours with serum provided by Navajo study participants revealed that proximity to abandoned uranium mine strongly predicted endothelial transcriptional responses to serum cell adhesion molecules and chemokines (including CCL2, VCAM-1, and ICAM-1), suggesting inflammatory potential associated with residential proximity to abandoned uranium mines (41). The upregulation of these cell adhesion molecules and chemokines by endothelial cells has been shown to play a role in the multistep process leading to cardiovascular diseases (42). Although our study does not demonstrate causation, it is possible that uranium miners exhibit similar inflammatory endothelial responses and this possibility needs further research.

Most studies pertaining to the radiation effect on the cardiovascular system involve doses above 2 Gy. Radiation specific mechanisms at low doses of exposure are as yet unclear, although there is evidence pointing to vascular structures and tissues of the heart as possible initiating targets (22). Basic research has shown that exposure to particulate matter during mining causes endothelial inflammation and dysfunction in both myocardial tissues and peripheral blood vessels, thus a mechanism to explain the increased risk of hypertension and cardiovascular diseases in miners (41). An increased thickness of the intima in irradiated arteries and an increase in proteoglycan deposition in the media has been demonstrated (43). Radiation also induces functional changes in the endothelium by increasing production of inflammatory eicosanoids and von Willebrand factor and decreased production in thrombomodulin and adenosine diphosphatase (44).

The strengths of our study include its large sample size and the use of a control population that was occupationally exposed to similar agents except radiation, reducing the possibility of healthy worker effect (38). Our study included significant proportion of American Indian and Hispanic miners, thus increasing the generalizability of this study to minority populations. Additional strength includes community-based recruitment of study subjects without charge to them. As compared to hospital-based recruitment, our recruitment strategy allows for greater geographic and socioeconomic inclusion as well as avoidance of Berkson's bias.

The limitations of our study include absence of occupational radiation and silica exposure measurements; absence of direct measurement of uranium concentrations via urine sampling; possible confounding from environmental radiation exposure from uranium tailings in and near homes; and information bias based upon self-report of vascular outcomes. Some studies have utilized a job-exposure matrix to obtain estimates on exposure without direct measurement. However, that would be difficult in the present study due to the history of remote uranium mining and associated recall bias. Urine samples for uranium testing were not collected since the mobile screening clinic lacks this capability, and the study lacks the resources for the same (45). Several of our study outcomes rested largely on self-report of previously physician-diagnosed health outcomes. Our study assumes that all miners are equally likely to have received a physician diagnosis. However, some health hazards associated with uranium mining are well known, and uranium miners may receive significantly more medical scrutiny than do other miners, such as through the Radiation Exposure Screening and Education Program (RESEP). This might increase the likelihood that uranium miners receive a physician diagnosis of cardiovascular disease or hypertension. This is however unlikely since our screening activity was funded by the New Mexico Black Lung and not the RESEP program and therefore, a reverse bias against uranium miners might be possible. Further, due to the greater awareness of the risks of uranium mining, it is possible that uranium miners themselves sought healthcare with primary care providers to a greater extent, were more likely to recall diagnoses, or had greater familiarity with the medical terms used in the question. This is less likely since uranium miners in our study were significantly less educated than other miners (Table 1). Nevertheless, molecular and imaging studies looking at biomarkers of cardiovascular disease in occupational cohorts will be helpful. Uranium miners are disproportionately American Indian, a group known to have a high prevalence of chronic health conditions including cardiovascular diseases (46). It is however unlikely that race and ethnicity explains away our findings since this was included as a covariate in our multivariable statistical model. Our study did not have data on and therefore could not adjust for dyslipidemia, an important risk factor for cardiovascular disease. There are many ways in which an opt-in community clinic screening can lead to selection bias based on who chooses to report for screening evaluations. For instance, retired miners are more likely to report for screening than current miners. Given the drop off in uranium mining in New Mexico, uranium miners of the same age are more likely to be retired or underemployed and have more time to report than non-uranium miners. Sicker workers are often assumed to be more likely to report to such a clinic, further contributing to selection bias.

Low lung function is a risk factor for cardiovascular diseases (40). Although uranium miners had a lower FEV₁ than non-uranium miners, the inclusion of FEV₁ in the multivariable analysis model in Table 2 did not significantly change the results for angina. Miners are typically screened for pulmonary diseases such as COPD and pneumoconiosis, due to significant data on the association of these diseases with mining and recent reports of increasing prevalence of pneumoconiosis among miners (47). Due to limited data on cardiovascular risk in miners, monitoring for cardiovascular disease has not been enforced during surveillance. However our study provides evidence for further research on cardiovascular disease monitoring in uranium miners.

CONCLUSIONS

Our data conclude that New Mexico uranium miners are more likely to demonstrate angina than non-uranium miners, after adjustment for covariates. This is the first study that we are aware of to demonstrate an association between cardiovascular disease and occupational radiation exposure. In conclusion, our data suggest that while screening for pulmonary diseases in uranium miners is well established, further research on cardiovascular disease monitoring is needed.

Acknowledgments

Sources of Funding: Health Resource Service Administration (HRSA) and Patient Centered Outcomes Research Institute (PCORI)

REFERENCES

- Centers For Disease Control And Prevention. Heart Disease Facts 1999–2015, updated August 24, 2017, accessed at <https://www.cdc.gov/heartdisease/facts.htm> on October 10, 2017.
- Centers For Disease Control And Prevention NCHS. Underlying cause of death, 1999–2013 on CDCWonder online database, released 2015, accessed February 3, 2015, at <https://wonder.cdc.gov/ucd-icd10.html>. 2015.
- Citrin DE, Prasanna PGS, Walker AJ, et al. Radiation-Induced Fibrosis: Mechanisms and Opportunities to Mitigate. Report of an NCI Workshop, September 19, 2016. Radiation research. 2017;188:1–20. [PubMed: 28489488]
- Beach TA, Johnston CJ, Groves AM, Williams JP, Finkelstein JN. Radiation induced pulmonary fibrosis as a model of progressive fibrosis: Contributions of DNA damage, inflammatory response and cellular senescence genes. Experimental lung research. 2017;43:134–149. [PubMed: 28534660]
- Zablotska LB, Lane RS, Frost SE, Thompson PA. Leukemia, lymphoma and multiple myeloma mortality (1950–1999) and incidence (1969–1999) in the Eldorado uranium workers cohort. Environmental research. 2014;130:43–50. [PubMed: 24583244]
- Wong FL, Yamada M, Sasaki H, et al. Noncancer disease incidence in the atomic bomb survivors: 1958–1986. Radiation research. 1993;135:418–430. [PubMed: 8378535]
- Tracy BL, Krewski D, Chen J, Zielinski JM, Brand KP, Meyerhof D. Assessment and management of residential radon health risks: a report from the health Canada radon workshop. Journal of toxicology and environmental health Part A. 2006;69:735–758. [PubMed: 16608836]
- Baker JE, Moulder JE, Hopewell JW. Radiation as a risk factor for cardiovascular disease. Antioxidants & redox signaling. 2011;15:1945–1956. [PubMed: 21091078]
- Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: Is the epidemiologic evidence compatible with the radiobiologic data? International journal of radiation oncology, biology, physics. 2007;67:10–18.
- Kreuzer M, Auvinen A, Cardis E, et al. Low-dose ionising radiation and cardiovascular diseases--Strategies for molecular epidemiological studies in Europe. Mutation research Reviews in mutation research. 2015;764:90–100. [PubMed: 26041268]
- Shimizu Y, Kodama K, Nishi N, et al. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950–2003. BMJ. 2010;340:b5349. [PubMed: 20075151]
- Takahashi I, Ohishi W, Mettler FA Jr., et al. A report from the 2013 international workshop: radiation and cardiovascular disease, Hiroshima, Japan. Journal of radiological protection : official journal of the Society for Radiological Protection. 2013;33:869–880.
- Ozasa K, Takahashi I, Grant EJ, Kodama K. Cardiovascular disease among atomic bomb survivors. International journal of radiation biology. 2017;93:1145–1150. [PubMed: 28151038]

14. Schollnberger H, Ozasa K, Neff F, Kaiser JC. Cardiovascular disease mortality of A-bomb survivors and the healthy survivor selection effect. *Radiation protection dosimetry*. 2015;166:320–323. [PubMed: 25948837]
15. Takahashi I, Shimizu Y, Grant EJ, Cologne J, Ozasa K, Kodama K. Heart Disease Mortality in the Life Span Study, 1950–2008. *Radiation research*. 2017;187:319–332. [PubMed: 28170314]
16. Senkus-Konefka E, Jassem J. Cardiovascular effects of breast cancer radiotherapy. *Cancer treatment reviews*. 2007;33:578–593. [PubMed: 17764850]
17. Little MP, Kleinerman RA, Stovall M, Smith SA, Mabuchi K. Analysis of dose response for circulatory disease after radiotherapy for benign disease. *International journal of radiation oncology, biology, physics*. 2012;84:1101–1109.
18. Cheng YJ, Nie XY, Ji CC, et al. Long-Term Cardiovascular Risk After Radiotherapy in Women With Breast Cancer. *Journal of the American Heart Association*. 2017;6.
19. Kashcheev VV, Chekin SY, Karpenko SV, et al. Radiation Risk of Cardiovascular Diseases in the Cohort of Russian Emergency Workers of the Chernobyl Accident. *Health physics*. 2017;113:23–29. [PubMed: 28542008]
20. Azizova TV, Muirhead CR, Moseeva MB, et al. Ischemic heart disease in nuclear workers first employed at the Mayak PA in 1948–1972. *Health physics*. 2012;103:3–14. [PubMed: 22647906]
21. Kreuzer M, Kreisheimer M, Kandel M, Schnelzer M, Tschense A, Grosche B. Mortality from cardiovascular diseases in the German uranium miners cohort study, 1946–1998. *Radiation and environmental biophysics*. 2006;45:159–166. [PubMed: 16897062]
22. Little MP, Azizova TV, Bazyka D, et al. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. *Environmental health perspectives*. 2012;120:1503–1511. [PubMed: 22728254]
23. Villeneuve PJ, Lane RS, Morrison HI. Coronary heart disease mortality and radon exposure in the Newfoundland fluorspar miners' cohort, 1950–2001. *Radiation and environmental biophysics*. 2007;46:291–296. [PubMed: 17453229]
24. Drubay D, Caer-Lorho S, Laroche P, Laurier D, Rage E. Mortality from Circulatory System Diseases among French Uranium Miners: A Nested Case-Control Study. *Radiation research*. 2015;183:550–562. [PubMed: 25807316]
25. Walsh L, Grosche B, Schnelzer M, Tschense A, Sogl M, Kreuzer M. A review of the results from the German Wismut uranium miners cohort. *Radiation protection dosimetry*. 2015;164:147–153. [PubMed: 25267854]
26. Nusinovici S, Vacquier B, Leuraud K, et al. Mortality from circulatory system diseases and low-level radon exposure in the French cohort study of uranium miners, 1946–1999. *Scandinavian journal of work, environment & health*. 2010;36:373–383.
27. Kreuzer M, Grosche B, Schnelzer M, Tschense A, Dufey F, Walsh L. Radon and risk of death from cancer and cardiovascular diseases in the German uranium miners cohort study: follow-up 1946–2003. *Radiation and environmental biophysics*. 2010;49:177–185. [PubMed: 19855993]
28. Eigenwillig GG. Comment on “Mortality from cardiovascular diseases in the German uranium miners cohort study, 1946–1998” by Kreuzer M, Kreisheimer M, Kandel M, Schnelzer M, Tschense A, Grosche B (2006) *Radiat Environ Biophys* 45:159–166. *Radiation and environmental biophysics*. 2007;46:423–425; author reply 427. [PubMed: 17704934]
29. World Nuclear Association. World uranium mining production, available at <http://www.world-nuclear.org/information-library/nuclear-fuel-cycle/mining-of-uranium/world-uranium-mining-production.aspx>, last accessed on December 11, 2017 2017.
30. Mohner M, Kersten N, Gellissen J. Chronic obstructive pulmonary disease and longitudinal changes in pulmonary function due to occupational exposure to respirable quartz. *Occupational and environmental medicine*. 2013;70:9–14. [PubMed: 23000825]
31. Roscoe RJ, Deddens JA, Salvan A, Schnorr TM. Mortality among Navajo uranium miners. *American journal of public health*. 1995;85:535–540. [PubMed: 7702118]
32. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *American journal of respiratory and critical care medicine*. 1999;159:179–187. [PubMed: 9872837]

33. Crapo RO, Lockey J, Aldrich V, Jensen RL, Elliott CG. Normal spirometric values in healthy American Indians. *Journal of occupational medicine : official publication of the Industrial Medical Association*. 1988;30:556–560. [PubMed: 3397781]
34. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). The American review of respiratory disease. 1978;118:1–120.
35. Samet JM, Pathak DR, Morgan MV, Key CR, Valdivia AA, Lubin JH. Lung cancer mortality and exposure to radon progeny in a cohort of New Mexico underground uranium miners. *Health physics*. 1991;61:745–752. [PubMed: 1659563]
36. Goldacre MJ, Roberts SE, Griffith M. Place, time and certified cause of death in people who die after hospital admission for myocardial infarction or stroke. *European journal of public health*. 2004;14:338–342. [PubMed: 15542866]
37. Cameron HM, McGoogan E. A prospective study of 1152 hospital autopsies: I. Inaccuracies in death certification. *J Pathol*. 1981;133:273–283. [PubMed: 7241267]
38. Kirkeleit J, Riise T, Borge T, Christiani DC. The healthy worker effect in cancer incidence studies. *American journal of epidemiology*. 2013;177:1218–1224. [PubMed: 23595008]
39. Shumate AM, Yeoman K, Victoroff T, et al. Morbidity and Health Risk Factors Among New Mexico Miners: A Comparison Across Mining Sectors. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine*. 2017;59:789–794.
40. Mannino DM, Watt G, Hole D, et al. The natural history of chronic obstructive pulmonary disease. *The European respiratory journal*. 2006;27:627–643. [PubMed: 16507865]
41. Harmon ME, Lewis J, Miller C, et al. Residential proximity to abandoned uranium mines and serum inflammatory potential in chronically exposed Navajo communities. *Journal of exposure science & environmental epidemiology*. 2017;27:365–371. [PubMed: 28120833]
42. Mestas J, Ley K. Monocyte-endothelial cell interactions in the development of atherosclerosis. *Trends in cardiovascular medicine*. 2008;18:228–232. [PubMed: 19185814]
43. Russell NS, Hoving S, Heeneman S, et al. Novel insights into pathological changes in muscular arteries of radiotherapy patients. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2009;92:477–483. [PubMed: 19541382]
44. Weshler Z, Raz A, Rosenmann E, et al. The effects of ionizing irradiation on production of thromboxane and prostacyclin by the isolated perfused rat kidney. *In Vivo*. 1988;2:289–293. [PubMed: 2979845]
45. Keith S, Faroon O, Roney N, et al. *Toxicological Profile for Uranium*. Atlanta (GA); 2013.
46. Nava LT, Zambrano JM, Arviso KP, Brochetti D, Becker KL. Nutrition-based interventions to address metabolic syndrome in the Navajo: a systematic review. *Journal of clinical nursing*. 2015;24:3024–3045. [PubMed: 26239838]
47. Blackley DJ, Halldin CN, Laney AS. Resurgence of a debilitating and entirely preventable respiratory disease among working coal miners. *American journal of respiratory and critical care medicine*. 2014;190:708–709. [PubMed: 25221884]

TABLE 1.

Comparison of Characteristics Between Uranium and Nonuranium Miners, $N = 7,215$, 1989–2016; MiDUS Cohort

Characteristic	All Miners $N = 7,215$ N (%) or Mean $\pm$ SD	Nonuranium Miners $N = 4,064$ N (%) or Mean $\pm$ SD	Uranium Miners $N = 3,151$ N (%) or Mean $\pm$ SD	P
Male sex	6,946 (96.3%)	3,897 (95.9%)	3,049 (96.8%)	0.05
Age, years	55.0 $\pm$ 14.3	51.9 $\pm$ 15.7	59.0 $\pm$ 11.1	<0.001
BMI, kg/m ²	28.8 $\pm$ 5.0	29.2 $\pm$ 5.2	28.3 $\pm$ 4.7	<0.001
High school education	3,090 (42.8%)	2,100 (51.7%)	990 (31.4%)	<0.001
Race/ethnicity				
(missing)	134 (1.9%)	87 (2.1%)	47 (1.3%)	
Non-Hispanic white	2,071 (28.7%)	1,586 (39.0%)	485 (15.4%)	
Hispanic	2,627 (36.4%)	1,742 (42.9%)	885 (28.1%)	<0.001
Black	39 (0.5%)	23 (0.6%)	16 (0.5%)	
American Indian	2,342 (32.5%)	624 (15.4%)	1,718 (54.5%)	
Other	2 (0.0)	2 (0.0)	0 (0)	
Smoking status				
(missing)	85 (1.2%)	25 (0.6%)	60 (1.9%)	
Never	3,424 (47.5%)	1,832 (45.1%)	1,592 (50.5%)	<0.001
Former	2,406 (33.3%)	1,383 (34.0%)	1,023 (32.5%)	
Current	1,300 (18.0%)	824 (20.3%)	476 (15.1%)	
Pack-years of smoking (for current and former smokers)	10.2 $\pm$ 19.5	11.2 $\pm$ 19.9	8.7 $\pm$ 18.8	<0.001
Snuff user				
(missing)	619 (8.6%)	47 (1.2%)	572 (18.2%)	
Never	4,713 (65.3%)	2,806 (69.0%)	1,907 (60.5%)	
Former	1,148 (15.9%)	676 (16.6%)	472 (15.0%)	<0.001
Current	735 (10.2%)	535 (13.2%)	200 (6.3%)	
Alcohol intake				
(missing)	630 (8.7%)	53 (1.3%)	577 (18.3%)	
Never	779 (10.8%)	392 (9.6%)	387 (12.3%)	<0.001
Former	4,922 (68.2%)	3,035 (74.7%)	1,887 (59.9%)	
Current	884 (12.3%)	584 (14.4%)	300 (9.3%)	
Current miner status	2,046 (28.4%)	1,895 (46.6%)	151 (4.8%)	<0.001
Mining location				
(missing)	1,731 (24.0%)	1,346 (38.0%)	185 (5.9%)	
Below ground mining	2,629 (36.4%)	724 (17.8%)	1,905 (60.3%)	
Above ground/open pit mining	1,812 (25.1%)	1,296 (31.9%)	516 (16.4%)	<0.001
Both below and above ground mining	1,043 (14.5%)	498 (12.3%)	545 (17.3%)	
Total mining tenure, years	15.0 $\pm$ 11.9	16.7 $\pm$ 12.6	13.5 $\pm$ 11.0	<0.001
Uranium mining tenure				
Unknown/no exposure	4,187 (58.0%)		123 (3.9%)	NA

Characteristic	All Miners <i>N</i> = 7,215 <i>N</i> (%) or Mean $\pm$ SD	Nonuranium Miners <i>N</i> = 4,064 <i>N</i> (%) or Mean $\pm$ SD	Uranium Miners <i>N</i> = 3,151 <i>N</i> (%) or Mean $\pm$ SD	<i>P</i>
1–4 years	926 (12.8%)		926 (29.4%)	NA
5–9 years	780 (10.8%)		780 (24.8%)	NA
10 years	1.322 (18.3%)		1.322 (42.0%)	
Total mining tenure category				
(missing)	1,540 (21.3%)	1,415 (34.8%)	125 (4.0%)	
1–4 years	1,173 (16.3%)	497 (12.2%)	676 (21.5%)	<0.001
5–9 years	1,057 (14.7%)	388 (9.5%)	669 (21.2%)	
10 years	3.445 (47.7%)	1.764 (43.4%)	1,681 (53.3%)	
FEV ₁ , L	3.2 $\pm$ 0.9	3.4 $\pm$ 0.9	3.1 $\pm$ 0.8	<0.001
FEV ₁ % predicted	97.0 $\pm$ 20.0	97.6 $\pm$ 19.7	96.3 $\pm$ 20.2	0.0037
Self-reported COPD/chronic bronchitis/emphysema	873 (12.1%)	472 (11.6%)	401 (12.7%)	<0.001
Self-reported COPD/chronic bronchitis/emphysema (missing)	629 (8.7%)	50 (1.2%)	579 (18.4%)	
Self-reported asthma	663 (9.2%)	405 (10.0%)	258 (8.2%)	0.95
Self-reported asthma (missing)	643 (8.9%)	57 (1.4%)	586 (18.6%)	
Self-reported diabetes mellitus	992 (13.7%)	507 (12.5%)	485 (15.4%)	<0.001
Self-reported diabetes mellitus (missing)	940 (13.0%)	287 (7.1%)	653 (20.7%)	

Missing data were noted among the 7,215 miners for the following continuous variables: age ($n = 20$ or 0.3%); BMI ($n = 87$ or 1.2%); pack-years of smoking ($n = 357$ or 4.9%); FEV₁ ($n = 448$ or 6.2%); and FEV₁ percent predicted ($n = 476$ or 6.6%). Missing data for total mining tenure (continuous variable) are provided in the row for the categorical variable total mining tenure.

Table 2:

Association between Uranium Mining Exposure and Hypertension, N= 7,215; 1989–2016; MiDUS cohort.

Cardiovascular Outcomes	Uranium Miners N=3151 N (%)	Non-Uranium Miners N =4064 N (%)	Unadjusted model O.R. (95% C.I.)	Multivariable model 1 ^{Note 1} O.R. (95% C.I.)	Multivariable model 2 ^{Note 1} O.R. (95% C.I.)
Self-reported Hypertension	1099 (44.4%)	1254 (33.6%)	1.58 (1.42, 1.75)	1.43 (1.24, 1.66)	1.42 (1.22, 1.65)
Measured Hypertension	1339 (43.3%)	1329 (33.5%)	1.51 (1.37, 1.67)	0.85 (0.74, 0.97)	0.88 (0.77, 1.02)
Hypertensive urgency	17 (0.5%)	21 (0.5%)	1.04 (0.55, 1.97)	0.53 (0.20, 1.38)	0.51 (0.19, 1.37)

Note 1: Multivariable analysis model 1 was adjusted for age, sex, race/ethnicity, diabetes mellitus, BMI, current smoking status, current snuff use status, current alcohol use status, and duration of total mining tenure. Model 2 additionally adjusted for absolute FEV₁ as a covariate. The missing data for total mining tenure is included in order to keep sample size among analyses consistent.

Table 3A:

Association between Uranium Mining Exposure and Vascular Diseases, N= 7,215; 1989–2016; MiDUS cohort. Covariates include self-reported hypertension.

Cardiovascular Outcomes	Uranium Miners N=3151 N (%)	Non-Uranium Miners N =4064 N (%)	Unadjusted model O.R. (95% C.I.)	Multivariable model 1 ^{Note 1} O.R. (95% C.I.)	Multivariable model 2 ^{Note 1} O.R. (95% C.I.)
Self-reported Angina	655 (21.3%)	390 (10.2%)	2.40 (2.10, 2.75)	1.61 (1.32, 1.97)	1.51 (1.23, 1.85)
Self-reported Myocardial Infarction	378 (13.5%)	274 (7.2%)	2.02 (1.72, 2.38)	1.35 (1.05, 1.73)	1.25 (0.98, 1.61)
Self-reported Cerebrovascular Event	141 (5.9%)	113 (3.8%)	1.58 (1.23, 2.04)	1.10 (0.79, 1.53)	1.06 (0.76, 1.49)

Note 1: Multivariable analysis model 1 was adjusted for age, sex, race/ethnicity, diabetes mellitus, BMI, self-reported hypertension, current smoking status, current snuff use status, current alcohol use status, and duration of total mining tenure. Model 2 additionally adjusted for absolute FEV₁ as a covariate. The missing data for total mining tenure is included in order to keep sample size among analyses consistent.

Table 3B:

Association between Uranium Mining Exposure and Vascular Diseases, N= 7,215; 1989–2016; MiDUS cohort. Covariates include measured hypertension.

Cardiovascular Outcomes	Uranium Miners N=3151 N (%)	Non-Uranium Miners N =4064 N (%)	Unadjusted model O.R. (95% C.I.)	Multivariable model 1 ^{Note 1} O.R. (95% C.I.)	Multivariable model 2 ^{Note 1} O.R. (95% C.I.)
Self-reported Angina	655 (21.3%)	390 (10.2%)	2.40 (2.10, 2.75)	1.68 (1.37, 2.06)	1.57 (1.28, 1.93)
Self-reported Myocardial Infarction	378 (13.5%)	274 (7.2%)	2.02 (1.72, 2.38)	1.42 (1.11, 1.82)	1.33 (1.04, 1.71)
Self-reported Cerebrovascular Event	141 (5.9%)	113 (3.8%)	1.58 (1.23, 2.04)	1.08 (0.78, 1.51)	1.05 (0.75, 1.48)

Note 1: Multivariable analysis model 1 was adjusted for age, sex, race/ethnicity, diabetes mellitus, BMI, measured hypertension, current smoking status, current snuff use status, current alcohol use status, and duration of total mining tenure. Model 2 additionally adjusted for absolute FEV₁ as a covariate. The missing data for total mining tenure is included in order to keep sample size among analyses consistent.