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Uranium Exposures in a Community near a Uranium Processing Facility: Relationship with Hypertension and Hematologic Markers

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Abstract

Background—Environmental uranium exposure originating as a byproduct of uranium processing can impact human health. The Fernald Feed Materials Production Center functioned as a uranium processing facility from 1951 to 1989, and potential health effects among residents living near this plant were investigated via the Fernald Medical Monitoring Program (FMMP).

Methods—Data from 8,216 adult FMMP participants were used to test the hypothesis that elevated uranium exposure was associated with indicators of hypertension or changes in hematologic parameters at entry into the program. A cumulative uranium exposure estimate, developed by FMMP investigators, was used to classify exposure. Systolic and diastolic blood pressure and physician diagnoses were used to assess hypertension; and red blood cells, platelets, and white blood cell differential counts were used to characterize hematology. The relationship between uranium exposure and hypertension or hematologic parameters was evaluated using generalized linear models and quantile regression for continuous outcomes, and logistic regression or ordinal logistic regression for categorical outcomes, after adjustment for potential confounding factors.

Results—Of 8,216 adult FMMP participants 4,187 (51%) had low cumulative uranium exposure, 1,273 (15%) had moderate exposure, and 2,756 (34%) were in the high (>0.50 Sievert) cumulative lifetime uranium exposure category. Participants with elevated uranium exposure had decreased white blood cell and lymphocyte counts and increased eosinophil counts. Female participants with higher uranium exposures had elevated systolic blood pressure compared to women with lower

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exposures. However, no exposure-related changes were observed in diastolic blood pressure or hypertension diagnoses among female or male participants.

Conclusions—Results from this investigation suggest that residents in the vicinity of the Fernald plant with elevated exposure to uranium primarily via inhalation exhibited decreases in white blood cell counts, and small, though statistically significant, gender-specific alterations in systolic blood pressure at entry into the FMMP.

Keywords

Hematology; hypertension; uranium

1. Introduction

Exposure to environmental uranium has been linked with several adverse health consequences, including cancer, nephrotoxicity, and respiratory diseases (ATSDR, 1999). Its presence in the environment as a byproduct of various anthropogenic activities has the potential to exert toxic effects on several important physiological processes including kidney function, bone development, and hematopoiesis (ATSDR, 1999). Uranium accumulation in the bone directly affects its structure and metabolism (Diaz Sylvester et al., 2002; Guglielmotti et al., 1984; Leggett and Pellmar, 2003; Pellmar et al., 1999; Ubios et al., 1991). Because red and white blood cells originate in bone marrow, uranium sequestered in bone has the potential to alter hematopoiesis. Red blood cell (or erythrocyte) production is regulated by the hormone erythropoietin, which is produced in the peritubular cells of the kidney (McCance and Huether, 2006). Uranium also is nephrotoxic, and can compromise kidney function by disturbing renal proximal tubule reabsorption (Malluche and Faugere, 1995). Thus, uranium may not only affect hematologic parameters directly via irradiation of bone marrow, but also indirectly by acting on the kidneys and potentially reducing erythropoietin production. In addition, estrogen influences blood pressure (Ashraf and Vongpatanasin, 2006; Reckelhoff, 2005) and uranium can exert estrogenic effects in laboratory animals (Raymond-Whish et al., 2007). Of the few animal and population-based studies that have examined this relationship, some have observed alterations in hematologic measures in association with uranium exposure (Dygert, 1949; Pinney et al., 2003; Vich and Kriklava, 1970). Dygert exposed rats to ammonium diuranate dusts containing 6.8 mg uranium/m³ for 6 hours/day for 30 days and observed decreases in red blood cell counts, lymphocytes, and white blood cell counts, and increases in neutrophils and eosinophils (Dygert, 1949). Another study of uranium miners with <5 up to 20 years of work experience had small but significant decreases in hemoglobin concentration and increases in red blood cell counts, although the ambient exposure concentration was not reported (Vich and Kriklava, 1970). A study examining individuals living near the Fernald uranium processing facility found that residents living within two miles of the plant had small increases in white blood cell counts and hemoglobin levels compared to those living beyond two miles (Pinney et al., 2003). Few studies have examined relationships between human uranium exposure and hypertension or kidney function. A recent investigation of a community in Finland with naturally elevated groundwater uranium concentrations (0.03 to 1,500 µg/L) reported elevated systolic and diastolic blood pressure among residents with high urinary uranium levels (Kurtio et al., 2006). We were unable to identify any other epidemiologic studies, occupational or otherwise, that evaluated the effects of uranium exposure on blood pressure.

While numerous studies have assessed the health risks associated with working in uranium mines, mills, or processing facilities (Boice et al., 2008; Darby et al., 1995; Hornung, 2001; UNSCEAR, 2006), few have examined the burden of this exposure on non-occupationally exposed residents in areas where environmental releases of uranium or other radionuclides have occurred. The Fernald Feed Materials Production Center (FMPC) in Ohio functioned as

a uranium processing facility from 1951 to 1989 producing uranium metal products as part of the United States' nuclear weapons production complex. Uranium was the primary hazardous substance released from the FMPC, although radon gas and a small amount of thorium (0.4% of uranium production) were also released (Meyer et al., 1996). From 1952 to 1980, approximately 3.62×10^8 kg of uranium was received and a lesser amount ($\sim 3.58 \times 10^8$ kg) was shipped to offsite locations. Of the materials received, about 54% was natural uranium, 20% enriched uranium, and 26% depleted uranium. Uranium metal was extracted by chemical digestion, producing uranium oxides and salts. Releases of these chemical forms of uranium to the atmosphere constituted the major source of offsite contamination, and inhalation was identified as the most important exposure pathway among nearby residents (Meyer et al., 1996). Airborne materials were derived from 126 stack release points in nine processing plants, as well as six non-production release points. These releases, combined with minor contributions from unmonitored sources (e.g., waste pits, silos, building air vents) and accidental releases, accounted for approximately 3.1×10^5 kg of total uranium released (Meyer et al., 1996; Voilleque et al., 1995).

The most significant offsite groundwater uranium contamination occurred in what is now known as the "South Plume" due to historical releases of liquid effluent to a storm sewer outfall ditch. Liquid effluents also were discharged to the Great Miami River and its tributaries east of the plant (Meyer et al., 1996). In addition, soil in the area was contaminated with uranium concentrations as high as 50 times natural background levels (Miller et al., 1994; Stevenson and Hardy, 1993).

The potential health impacts to non-occupationally exposed residents living near this plant were evaluated through the Fernald Medical Monitoring Program (FMMP), which was initiated in 1990 and ended in 2008 (Wones et al., 2009). Other than the study by Pinney et al (Pinney et al., 2003), which assessed health effects in FMMP participants living within two miles of the Fernald plant and a study that assessed mutagenic damage within FMMP participants (Wones et al., 1995), no other published studies of uranium exposure and health outcomes in this cohort were located. The purpose of this study was to utilize data collected through the FMMP to assess the potential hematologic and nephrotoxic effects of uranium exposure among residents living in the vicinity of this facility. We sought to test the hypothesis that elevated uranium exposure among FMMP participants was associated with an increase in hypertension or changes in hematologic parameters (red blood cells, platelets, and white blood cell differential counts) at the time of their first medical examination in the program.

2. Methods

The FMMP was an ongoing medical monitoring program for 18 years (Wones et al., 2009) consisting of residents who lived within five miles of the FMPC for at least two consecutive years between January 1, 1952 and December 18, 1984. The FMMP was voluntary program that followed 9,775 persons of which 8,770 (90%) were adults aged 18 years or older at the time of their first exam (<http://www.genmed.uc.edu/fmmp/index.cfm>; (Wones et al., 2009)). An estimated one-quarter of the residents eligible for the FMMP (those who lived within 5 miles [8 km] of the Fernald site) participated in the medical monitoring program. The Centers for Disease Control (CDC) estimated that the population of a 10 km exposure domain was 45,631 (Devine et al., 1998). Initial examinations began in December of 1990 and most were completed by December of 1993. These examinations included a detailed questionnaire that collected information on demographics, family and personal medical history, occupational and residential history, diet, and physical activity; a medical examination; and diagnostic and laboratory tests. The FMMP operated under University of Cincinnati Institutional Review Board (IRB) approval, and University of South Carolina (USC) investigators received USC IRB and FMMP approval to use data from the program for this study.

The study population included those who were considered adults at the time of their first exam, and had never worked at the Fernald plant; analyses were limited to data collected at the initial medical examination. Over 99% of the study participants were of European-American origin. For these analyses, FMMP participants were excluded if no cumulative uranium exposure estimate was available (n=1,576) or if they had missing demographic information (n=1). Participants were not assigned an exposure estimate if they had never lived within the five mile exposure domain or their address was insufficient for geocoding.

Systolic and diastolic blood pressure, or a physician's diagnosis (ICD-9: 401-405) were used to characterize hypertension. If the initial blood pressure reading was greater than 140/90 mmHg, some degree of exam anxiety was suspected, and a second blood pressure reading was obtained prior to completion of the exam. The second reading was considered the most representative of resting blood pressure and those values were used for the analysis, if available (23% of participants). Hematologic parameters (red and white blood cells, platelets, lymphocytes) were evaluated as continuous variables except for eosinophils, which were categorized into tertiles: ≤ 0.1 thousand cells/ μL , 0.1 - 0.6 thousand cells/ μL , or ≥ 0.6 thousand cells/ μL . Analyses were not performed for some white blood cell differentials (i.e., neutrophils, basophils, monocytes) because a large proportion of the samples did not have detectable numbers of these cells.

A cumulative uranium exposure estimate was used as the primary exposure measure. This estimate was developed by FMMP investigators and was derived from an exposure algorithm developed by the CDC as part of the Fernald Dose-Reconstruction Project (Killough et al., 1998). For the purposes of exposure assessment, the Fernald investigators considered the five-mile radius eligibility area for the FMMP as the exposure domain. The FMMP exposure domain was divided into 100 segments, each approximately one square mile. By applying the exposure estimation methods developed by the CDC to this cohort, they calculated, for each year of plant operation, the average concentration of airborne uranium for each segment in the FMMP exposure domain, based on the source term, particle size, dispersion and deposition, and distance and direction from the plant.

A participant's estimated exposure to uranium for each year was then calculated using the location, calendar year and duration of each place of residence. Addresses within the five-mile exposure domain and dates of residency were obtained from questionnaire data. The locations were then linked to one of the segments within the FMMP exposure domain. For each year (or part of a year), the participant's level of exposure to airborne uranium ($\mu\text{g}/\text{m}^3$) could therefore be determined. The yearly (or partial year) estimates of exposure were summed over all years to calculate cumulative exposure for each participant. This cumulative estimate reflected the cumulative amount of airborne uranium, resulting from FMPC emissions during the period of plant operations, to which a participant was exposed.

FMMP investigators categorized these exposure estimates into three levels, low (participants with minimal exposure, i.e., an estimated lifetime cumulative exposure < 0.25 Sievert [Sv]); moderate (0.25 to 0.50 Sv); or high (> 0.50 Sv). The annual average dose for the United States population is approximately 0.003 Sv. Both the discrete exposure estimate values and the categorical exposure assignments were provided to USC investigators as part of a data sharing agreement.

2.1 Statistical Analysis

The association between covariates and uranium exposure category (low, moderate, high) was evaluated using the chi-square test. When the overall chi-square test was significant, additional chi-square tests were performed to determine which exposure groups differed. The association between uranium exposure (low, moderate, high) and blood pressure and hematologic cell

counts (continuous outcomes), hypertension diagnosis (binary outcome), and eosinophil counts categorized into tertiles (ordinal outcome) was evaluated using generalized linear models, and quantile, logistic, or ordinal logistic regression. Eosinophil count was categorized into tertiles because its frequency distribution, which showed few high frequency values scattered among many low frequency data points, was incongruent with any classic discrete distribution (e.g., Poisson or negative binomial). Multiple linear regression models were used to adjust the inference on the mean for potential confounding variables. Since it was of interest to make inference on all percentiles of the outcome variables, and not just their means, quantile regression models were also estimated with SAS Proc Quantreg (Koenker and Hallock, 2001). For the dichotomous outcome of hypertension diagnosis, measures of association were obtained using logistic regression. Eosinophil count, categorized into tertiles, was analyzed using ordinal logistic regression. A multi-step statistical approach was used to test for an association between uranium exposure and each endpoint. Potential confounding variables (age; gender; body mass index [BMI=weight(kg)/height(m)²]; family history of high cholesterol, high blood pressure, diabetes, heart disease, and cancer; co-morbid cardiovascular disease diagnosis; and known exposure to anesthetics, animals, farming, lube oils, and vibrations) were obtained via the questionnaire or medical exam completed upon enrollment into the FMMP. Use of anti-hypertension medications and presence of acute illnesses were considered as potential confounding variables, but only small proportions of participants (2.6% and 1.2%, respectively) were included in these categories, and the proportions of these participants were evenly distributed among the uranium exposure groups. These variables were therefore excluded from further analyses. Variables were categorized to include at least 10% of the total sample size in each category level. If this was not possible, the variable was excluded from further analyses. Manual hierarchical backwards elimination was used to determine the optimal set of covariates for each outcome. Beginning with the full model, potential confounders were retained in the models if their removal caused the uranium exposure coefficients' estimates to change by more than 10%. Measures of association for both logistic and ordinal logistic regression analyses were calculated as odds ratios (OR) with 95% percent confidence intervals (CI). Geometric means (GM) and p-values were calculated for generalized linear models. All analyses were repeated in gender-specific strata to evaluate potential gender differences in the relationship between uranium exposure and the study outcomes. Analyses were performed using SAS version 9.2 (SAS Institute: Cary, NC).

3. Results

A total of 8,216 adult residents from the Fernald area were eligible for analysis (94% of all initial adult examinations). Of these, 4,187 Fernald area residents had low (51%), 1,273 residents had moderate (15%), and 2,756 had high (34%) cumulative uranium exposure (Table 1). Participants with elevated uranium exposure were older, had lower income and education, were more likely to be married, and more likely to have a higher BMI compared to participants in the low uranium exposure category (all $p < 0.05$; Table 1).

The patterns of quantile results were generally consistent with the other analyses for both hypertension and hematologic outcomes. There was a small but statistically significant decrease in systolic blood pressure among participants with moderate uranium exposures (GM: 128.2 mmHg, $p = 0.004$) and a suggestion of a modest increase among those with elevated uranium exposure (GM: 129.6 mmHg, $p = 0.06$) compared to those in the low exposure group (GM: 128.9 mmHg), after adjustment for family history of high cholesterol, cancer, heart disease, or high blood pressure; co-morbid cardiovascular disease diagnosis; sex; age at original exam; income; and BMI (Table 2). Uranium exposure was not associated with a change in diastolic blood pressure after adjustment for family history of cholesterol, heart disease, or high blood pressure; co-morbid cardiovascular disease diagnosis; sex; age at original exam; educational status; and BMI (Table 2). When analyses were stratified by gender, systolic blood

pressure was elevated among females in the highest exposure group (GM: 127.2 mmHg, $p=0.02$) compared to those with low uranium exposures (GM: 126.0 mmHg; Table 3), although no differences were observed among males.

Increases in systolic blood pressure associated with elevated uranium were observed among participants in the higher quantiles of systolic blood pressure (Figures 1a-c). In this case, the pattern was most apparent among men (quantiles: 0.80, 0.85, 0.90), but was also observed among women (quantiles: 0.50, 0.55, 0.65, 0.70, 0.80). Additional analyses were performed among women stratified by age ($<$ or ≥ 50 years old as a surrogate for menopausal status). A statistically significant increase in systolic blood pressure was observed among women <50 years old with elevated uranium exposure (parameter estimate for median outcome: difference of 2.0 mmHg from low to high exposure category, $p=0.002$), but not among women ≥ 50 years of age (1.30 mmHg, $p=0.28$). No other statistically significant associations between uranium exposure and diastolic blood pressure were observed using either generalized linear models or quantile regression (data not shown). There also was no association between uranium exposure and hypertension diagnoses after adjustment for potential confounding factors (Table 4).

A statistically significant decrease in white blood cell count was observed among participants in the high cumulative-uranium exposure group (GM: 6.28 thousand cells/ μ l, $p=0.02$; Table 2) compared to participants with low exposures (GM: 6.39 thousand cells/ μ l), after adjusting for the effects of age, income, education, marital status, BMI, and family cancer history. When stratified by gender, the exposure-related reduction in white blood cell count persisted among males but not females (Table 3). Results obtained using quantile regression exhibited a similar exposure-associated decrease in white blood cell counts among participants in the upper white blood cell quantiles (Figure 2a). As participants' initial white blood cell counts increased, the negative association between white blood cell count and uranium exposure tended to increase, and the association was more prominent among male participants compared to females (Figures 2b and c).

Decreases in adjusted mean lymphocyte counts were observed among participants with moderate (GM: 1.90 thousand cells/ μ l, $p=0.03$) and high uranium exposures (GM: 1.91 thousand cells/ μ l, $p=0.02$), compared to those in the low exposure group (GM: 1.94 thousand cells/ μ l; Table 2). Results from quantile regression analyses showed an exposure-related decrease in lymphocyte count among participants with higher (65th through 80th and 90th quantiles) lymphocyte levels (Figure 3a). When the analyses were stratified by gender, a significant decrease in lymphocytes was observed among females in both the moderate and high uranium exposure groups, although only the results for moderate exposure achieved statistical significance (GM: 1.90 thousand cells/ μ l, $p=0.04$; Table 3). As female lymphocyte counts increased, the association between uranium exposure and a lymphocyte reduction became stronger (Figure 3a-c). Exposure-related changes among men did not achieve statistical significance (Table 3 and Figure 3b).

Individuals with higher uranium exposures were more likely to have higher eosinophil counts (OR: 1.07; 95% CI: 1.01, 1.13; Table 4), after adjustment for age, marital status, educational status, and family history of cancer, diabetes, heart disease, and high blood pressure. Upon stratification by gender, this relationship was detected among females (OR: 1.09; 95% CI: 1.02, 1.18), but not among males (data not shown). No statistically significant relationship between uranium exposure and red blood cell or platelet count was observed using adjusted generalized linear models with or without stratification by gender (Tables 2 & 3). Quantile regression analyses for both red blood cell and platelet counts also showed no association with uranium, consistent with results from the generalized linear models (data not shown).

4. Discussion

Studies examining human non-occupational uranium exposure and hypertension or hematotoxicity are limited (ATSDR, 1999; Brugge et al., 2005). The FMMP has collected and maintained high-quality data on area residents, including extensive disease risk factor and medical history information (Wones et al., 2009). This study examined the hypothesis that elevated cumulative uranium exposures among adults residing near the Fernald uranium processing facility and participating in the FMMP were associated with hypertension and changes in hematologic outcomes.

The results suggested that systolic blood pressure may be elevated among participants with a high cumulative uranium exposure compared to those with low exposures, particularly among females. Results from quantile regression suggested that uranium-associated increases in systolic blood pressure were greatest within the subset of women whose blood pressure was above 113 mmHg at the time of their first exam. The results suggest that women whose blood pressure is already elevated may be more sensitive to the effects of uranium, or that uranium may act in combination with other factors to increase systolic blood pressure. Our results are somewhat consistent with those from an investigation of a community in Finland with elevated groundwater uranium concentrations (0.03 to 1,500 µg/L) that observed increases in systolic and diastolic blood pressure among both male and female residents with high urinary uranium (Kurtio et al., 2006), although the present study did not observe uranium associated changes in blood pressure among men. The observed increases in systolic blood pressure among women with high uranium exposures in this study were relatively modest. The greatest observed mean difference between females in the high and low uranium exposure groups was 1.2 mmHg, and the highest mean systolic blood pressure among exposed participants was approximately 130 mmHg (Table 2). Optimal blood pressure is defined as less than 120/80 mmHg; normal blood pressure is defined as less than 130/85 mmHg; high-normal or pre-hypertensive blood pressure is defined as 130-139/85-89 mmHg; and hypertension is defined as greater than 140/90 mmHg (WHO, 1999). Even minor increases in systolic blood pressure may merit some concern, because the risk of adverse health effects such as stroke increases continuously for blood pressures above 115/75 mmHg (Lawes et al., 2004). However, it is unclear whether these effects represent clinically important changes for several reasons. First, blood pressure measurements can vary due to measurement technique, equipment used, or natural circadian fluctuations (Musini and Wright, 2009), which could have influenced the results. However, a standardized procedure was used, and it is unlikely that these factors differed systematically among those with elevated uranium exposure. Second, the effect of uranium on systolic blood pressure was detected only among females and not males. Men, in general, present with higher blood pressures than pre-menopausal, but not post-menopausal, women (Reckelhoff, 2001). In the current study, the average (SD) systolic blood pressure for men was 132 mmHg (± 17), whereas the average systolic blood pressure for women <50 years of age was 120 (± 14) mmHg and the average for women ≥ 50 years of age was 136 (± 20) mmHg. Differences in mean systolic blood pressure across categories of age or BMI among male participants were about half that seen among women (data not shown), suggesting that there was perhaps less variation in blood pressure among men for uranium to exert an effect. These observations could represent a spurious association due to residual confounding, or they may represent early-stage effects that were not large enough to be observed among all participants or achieve clinical significance. Cautious interpretation of the results is warranted since the effect sizes were modest, they were only observed among females, and exposure was not associated with changes in diastolic blood pressure or with hypertension diagnoses. More follow-up is needed to confirm or refute these observations and examine possible mechanisms of action.

Results from this study also indicated that white blood cell and lymphocyte counts were lower among participants with higher cumulative uranium exposures. The observed changes in

lymphocyte counts, however, do not meet the definition of lymphocytopenia (i.e., a count less than 1,000 lymphocytes per microliter of blood in adults) (NIH 2009). Based on results from quantile regression, the inverse relationship between uranium exposure and white blood cells or lymphocytes was greater among subjects with elevated cell counts. Individuals with an elevated white blood cell count may suffer from infection, inflammation, trauma, and acute or chronic leukemia, among other conditions. Although the specific cause of higher white blood cell counts in this population was not known, this finding suggests that such individuals may be more susceptible to the effects of uranium exposure. A previous study examining individuals living near the same uranium processing facility found that residents living within two miles of the plant had small increases in white blood cell counts and hemoglobin levels compared to those living beyond two miles (Pinney et al., 2003). In general, lower socioeconomic levels are associated with higher white blood cell counts (Panagiotakos et al., 2005), and in the study by Pinney et al., the subset of FMMP participants living closer to the Fernald plant was of slightly lower income and education as compared to those living further from the plant. In the current study, those with higher exposures were more likely to have a lower educational status compared to those with lower exposures, although our analyses also were adjusted for the effects of these factors. Thus, socioeconomic status is not likely to have had a strong influence on this and prior analyses, but it may represent a susceptibility factor that merits closer examination in the future. The inconsistency between our results and those from the previous analysis may have been due to differences in the exposure estimates that were used. The current analysis applied results from the CDC's dose reconstruction, which incorporated numerous exposure-related factors including wind speed and direction, as well as the location and duration of residence (Killough et al., 1998). These exposure estimates are likely more rigorous than those used in the previous study, which were based solely on distance of the residence from the FMPC as a surrogate for exposure.

In contrast to the uranium-associated decreases in white blood cell or lymphocyte counts that were observed, a statistically significant increase in eosinophil counts was identified among participants with higher uranium exposures, although we note that the observed changes also were within the normal range for adults. Eosinophils, which comprise 1% to 4% of the normal adult leukocyte count, help facilitate inflammation and ingestion of antigen-antibody complexes. Eosinophils amplify in response to inflammatory processes including allergic disorders, nonspecific tissue injury, infections, and malignancy (Rothenberg and Hogan, 2006). Future studies of allergies in this or other uranium-exposed populations may be suggested from these findings. For example, evaluation of the effect of uranium on the secretion of inflammation mediators (e.g., eosinophilic cation protein), immunoglobins, or other immune cell types (e.g., B cells, T-cell subsets) may assist in further elucidating the potential effects of uranium on the immune system in humans. An inability to evaluate history of allergies or asthma limits the interpretation of these results. However, inhalation of uranium-containing dusts containing 6.8 mg uranium/m³ for 4 hours/day in rats over a 30 day period resulted in increased neutrophil and eosinophil counts and decreases in lymphocyte and white blood cells (Dygert, 1949), which is consistent with observations from the present study.

The exposure assessment used in the current study has limitations and strengths. An extensive dose reconstruction was conducted by the CDC to estimate individual doses of FMMP participants to uranium and other radionuclides originating from the site (Killough et al., 1998). These estimates incorporated residential location, duration of residence, wind speed and direction and other environmental factors potentially influencing exposure. Our analysis has focused on uranium as the primary hazardous agent that participants were exposed to due to releases from the Fernald site. Historical evidence suggests that exposure to other agents such as radon gas or thorium was likely minimal, although their potential contribution to the study outcomes represents an uncertainty. A cistern is a tank for storing water, often built to catch and store rainwater on the roof of a house. The exposure estimates used in this analysis did not

consider the internal uranium dose due to ingestion, especially if a person was drinking uranium contaminated water from a well or cistern. Although the CDC methods do include calculations of organ specific radiation doses incorporating ingestion of water from contaminated wells and foods, these calculations have not yet been implemented by us. CDC never developed a method for estimating internal uranium dose resulting from ingesting water from a contaminated cistern. For those who drank from a contaminated well, possibly up to 50% of the total effective radiation dose equivalent was attributable to drinking contaminated water (Killough et al., 1998), although for most participants this would have been much less. Of all those in the FMMP cohort, 49% used a well and 31% used a cistern for a primary drinking water source when living in least one residence in the exposure domain (although not necessarily a contaminated well or cistern). However, we do not expect exposure estimates among FMMP participants to be substantively altered by incorporation of cistern data because cistern-related exposures will increase in direct proportion to the airborne exposures since it is the airborne dust on the roof that would have entered the cistern. Without incorporation of exposure through the water pathway, the absolute uranium doses may have been underestimated, but participants would not be expected to change their exposure category since we used a relatively broad range of exposures to define each category. Additionally, the CDC experts clearly stated that inhalation was the most important exposure pathway among nearby residents (Meyer et al., 1996). Because this dose reconstruction was a thorough, yet indirect, exposure assessment approach, there is still some potential for exposure misclassification. This misclassification, however, is not likely to differ by study outcomes and would therefore be non-differential, and thus likely to reduce the strength of the reported associations. The exposure index has not been validated with biological measures, although the dose reconstruction did include validation and calibration of the environmental prediction model with historical air monitoring data. Results from the validation analysis indicated generally good agreement between predicted and observed concentrations (Killough et al., 1998). Finally, temporal relationships between uranium exposure and the study outcomes have not been delineated. The cumulative dose estimates used in this study incorporated each participant's duration of residence, thus providing an integrated measure of the intensity and duration of airborne uranium exposure, but eliminating the possibility for characterization of temporal aspects of dose-response.

Selection bias may have also influenced the results of this study. An estimated 25% of eligible residents participated in the FMMP. Compared to residents in Butler and Hamilton counties, the two counties containing the Fernald exposure domain, FMMP participants were fairly representative of the surrounding population, but were more likely to be male (FMMP: 56% vs. Butler: 49%, Hamilton: 48%), white (FMMP: 99% vs. Butler: 89%, Hamilton: 71%) and older (median age, FMMP: 43 years vs. Butler: 35 years, Hamilton: 38 years) (Census 2006-2008 American Community 3-Year Estimates, American FactFinder). At the end of FMMP enrollment in 1994, calculation of standardized mortality ratios for all causes, all cancers, and all cardiovascular disease (0.66, 0.64, 0.73, respectively) suggest potential for a healthy volunteer effect, as individuals choosing to participate in this medical monitoring program were possibly healthier or more health-conscious than their non-participating counterparts (Wones et al., 2009). If that were the case, the effects of uranium may have been underestimated in this population. There is also a possibility of residual confounding due to an inability to control for some covariates (e.g., smoking, season of participation). Nonetheless, several potentially important confounding factors were evaluated in this study, including the use of anti-hypertensive medications and presence of acute illness. The percentage of participants included in these groups was small (2.6% and 1.2% for anti-hypertensive medications and acute illnesses, respectively), and the distribution of participants in these categories did not differ across uranium exposure categories. When participants who were using anti-hypertensive medications or with acute illnesses were excluded from the analysis, the results were similar to those obtained among all participants.

In summary, the FMMP cohort provided a timely and cost effective assessment of hypertension and hematologic parameters in a relatively large sample of residents living near the Fernald uranium processing facility. Results from this investigation suggest that primarily female FMMP participants with elevated cumulative uranium exposures (estimated lifetime cumulative dose >0.50 Sv) had elevated systolic blood pressure. However, a cautious interpretation is advised since this effect was not observed among males and uranium exposure was not associated with diastolic blood pressure or a hypertension diagnosis. Elevated uranium exposure was also associated with decreased white blood cell and lymphocyte counts, and increased eosinophil counts. However, it is noteworthy that the observed changes in this study fell within normal ranges for adults. Ionizing radiation is a well known immunosuppressant, (Koenig et al., 2005) but few studies have examined the potential effects of uranium exposure in non-occupationally exposed human populations. Continued follow up of this population is needed to determine whether these primarily uranium-associated effects are spurious or if they represent early indicators with potential clinical relevance. The results may be used to help guide future analyses of clinical outcomes over the 18-year follow-up period.

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Abbreviations (alphabetical)

BMI	Body mass index
CDC	Centers for Disease Control
CI	Confidence interval
FMMP	Fernald Resident Medical Monitoring Program
FMPC	Fernald Feed Materials Production Center
GM	Geometric mean
IRB	Institutional review board
OR	Odds ratio
Sv	Sievert
USC	University of South Carolina

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a. All participants (N=8,216)

b. Males (N=4,623)

c. Females (N=3,593)

Figure 1.

Effect^a of cumulative uranium exposure on quantiles of systolic blood pressure among FMMP participants.

^a Plot of parameter estimates (and 95% confidence intervals - error bars) obtained via quantile regression for the following models: Figure a. Un-stratified results. Adjusted for: family history of high cholesterol, cancer, heart disease, and high blood pressure; co-morbid cardiovascular disease diagnosis; gender; age at original exam; income; body mass index. Figure b. Stratified results, males. Figure c. Stratified results, females. Models for Figure b and c were adjusted for the same covariates as a. except for gender.

FMMP: Fernald Medical Monitoring Program

a. All participants (N=8,216)

b. Males (N=4,623)

c. Females (N=3,593)

Figure 2.

Effect^a of cumulative uranium exposure on quantiles of white blood cells among FMMP participants.

^a Plot of parameter estimates (and 95% confidence intervals - error bars) obtained via quantile regression for the following models: Figure a. Un-stratified results. Adjusted for: known exposure to anesthetics; family history of diabetes; sex; age at original exam; marital status; educational status; body mass index. Figure b. Stratified results, males. Figure c. Stratified results, females. Models for Figure b and c were adjusted for the same covariates as a. except for gender.

FMMP: Fernald Medical Monitoring Program

Figure 3. Effect^a of cumulative uranium exposure on quantiles of lymphocyte count among FMMP participants.

^a Plot of parameter estimates (and 95% confidence intervals - error bars) obtained via quantile regression for the following models: Figure a. Un-stratified results. Adjusted for: known exposure to farming; family history of cancer, high blood pressure; sex; age at original exam; marital status; educational status; body mass index. Figure b. Stratified results, males. Figure c. Stratified results, females. Models for Figure b and c were adjusted for the same covariates as a. except for gender.

FMMP: Fernald Medical Monitoring Program

Table 1

Descriptive characteristics for the Fernald dataset by uranium exposure group.

Characteristics	Low Exposure	Moderate Exposure	High Exposure	Total	Overall chi-square p-value
Total	4,187 (51%)	1,273 (15%)	2,756 (34%)	8,216	
Sex					0.17
Male	1,869 (45)	533 (42)	1,191 (43)	4,623 (56)	
Female	2,318 (55)	740 (58)	1,565 (57)	3,593 (44)	
Age at original exam^{a,b}					<0.0001
<35 years	1,565 (37)	493 (39)	306 (11)	2,364 (29)	
35 to 50 years	1,535 (37)	351 (28)	1,125 (41)	3,011 (37)	
>50 years	1,087 (26)	429 (34)	1,325 (48)	2,841 (35)	
Income^{a,b}					<0.0001
<\$20,000	926 (23)	342 (28)	769 (30)	2,037 (26)	
\$20,000 - \$34,999	1,080 (27)	360 (30)	763 (29)	2,203 (28)	
\$35,000 - \$49,999	934 (24)	269 (22)	569 (22)	1,772 (23)	
>\$50,000	1,014 (26)	245 (20)	507 (19)	1,766 (23)	
Education^{a,b}					<0.0001
Some high school or less	511 (12)	193 (15)	573 (21)	1,277 (16)	
High school graduate	1,499 (36)	473 (38)	1,106 (41)	3,078 (38)	
Some college/vocational	1,270 (31)	346 (27)	594 (22)	2,210 (27)	
College or more	876 (21)	251 (20)	443 (16)	1,570 (19)	
Marital status^{a,b}					<0.0001
Single	765 (18)	207 (16)	142 (5)	1,114 (13)	
Separated/divorced/widowed	460 (11)	187 (15)	478 (18)	1,125 (14)	
Married	2,926 (71)	868 (69)	2,100 (77)	5,894 (73)	
BMI^{b,c}					<0.0001
<25 (normal)	1,695 (41)	518 (41)	864 (31)	3,077 (38)	

Characteristics	Low Exposure	Moderate Exposure	High Exposure	Total	Overall chi-square p-value
25 to 30 (overweight)	1,471 (35)	431 (34)	1,020 (37)	2,922 (36)	
>30 (obese)	1,021 (24)	324 (26)	872 (32)	2,217 (27)	
Family Disease History					
High cholesterol^{a,b}					<0.0001
Yes	1,196 (29)	352 (28)	734 (27)	2,282 (28)	
No	1,081 (26)	276 (22)	562 (20)	1,919 (23)	
Not sure/unknown	1,910 (46)	645 (51)	1,460 (53)	4,015 (49)	
High blood pressure^{a,b}					<0.0001
Yes	1,796 (43)	541 (43)	1,134 (41)	3,471 (42)	
No	1,153 (28)	304 (24)	671 (24)	2,128 (26)	
Not sure/unknown	1,238 (30)	428 (34)	951 (35)	2,617 (32)	
Family Disease History					
Diabetes^b					0.001
Yes	1,313 (31)	403 (32)	892 (32)	2,608 (32)	
No	1,762 (42)	510 (40)	1,023 (37)	3,295 (40)	
Not sure/unknown	1,112 (27)	360 (28)	841 (31)	2,313 (28)	
Heart disease^b					0.0003
Yes	1,853 (44)	588 (46)	1,194 (43)	3,653 (44)	
No	1,198 (29)	307 (24)	706 (26)	2,211 (27)	
Not sure/unknown	1,136 (27)	378 (30)	856 (31)	2,370 (29)	
Cancer^b					0.03
Yes	1,977 (47)	568 (45)	1,205 (44)	3,750 (46)	
No	1,162 (28)	361 (28)	780 (28)	2,303 (28)	
Not sure/unknown	1,048 (25)	344 (27)	771 (28)	2,163 (26)	
Co-Morbid Diagnoses					
Cardiovascular disease^b					<0.0001

Characteristics	Low Exposure	Moderate Exposure	High Exposure	Total	Overall chi-square p-value
	N (%)	N (%)	N (%)		
Yes	893 (21)	293 (23)	910 (33)	2,092 (26)	0.82
No	3,294 (79)	980 (77)	1,846 (67)	6,120 (75)	
Known Exposures					
Anesthetics					
Yes	3,646 (87)	1,100 (86)	2,398 (87)	7,144 (87)	0.79
No	541 (13)	173 (14)	358 (13)	1,072 (13)	
Animals					
Yes	2,589 (62)	774 (61)	1,693 (61)	5,056 (62)	<0.0001
No	1,598 (38)	499 (39)	1,063 (39)	3,160 (39)	
Farming ^{a,b}					
Yes	3,687 (88)	1,073 (84)	2,154 (78)	6,914 (84)	0.47
No	500 (12)	200 (16)	602 (22)	1,302 (16)	
Lube Oils					
Yes	3,142 (75)	939 (74)	2,037 (74)	6,118 (75)	0.88
No	1,045 (25)	334 (26)	719 (26)	2,098 (26)	
Vibration					
Yes	3,764 (90)	1,141 (90)	2,484 (90)	7,389 (90)	0.88
No	423 (10)	132 (10)	272 (10)	827 (10)	

^aSignificant difference of moderate versus low exposure group; chi-square $p < 0.05$.

^bSignificant difference of high versus low exposure group; chi-square $p < 0.05$.

^cBody mass index.

Percentages totaling less than 100% are due to unknown or missing data.

Table 2

Crude and adjusted effects of uranium exposure on blood pressure and hematologic parameters among FMMP^a participants.

Outcome	Unadjusted Model			Adjusted Model		
	GM ^c	p-value	Continuous p-value	GM	p-value	Continuous p-value
Uranium level^b						
Systolic blood pressure^d, mmHg						
Low	125.9	-	<0.0001	128.9	-	0.01 (0.001)
Moderate	125.8	<0.0001		128.2	0.004	
High	131.0	<0.0001		129.6	0.06	
Diastolic blood pressure^e, mmHg						
Low	79.4	-	<0.0001	81.0		0.35 (0.01)
Moderate	79.0	0.25		80.5	0.16	
High	81.2	<0.0001		81.0	0.89	
Red blood cells^f, million cells/μl						
Low	4.75	-	0.05	4.78	-	0.57 (<0.0001)
Moderate	4.72	0.04		4.77	0.31	
High	4.73	0.07		4.78	0.98	
Platelet count^g, thousand cells/μl						
Low	262.5	-	0.25	262.7	-	0.15 (0.35)
Moderate	259.3	0.11		258.9	0.05	
High	262.4	0.93		261.7	0.54	
White blood cells^h, thousand cells/μl						
Low	6.25	-	0.87	6.39	-	0.06 (0.87)
Moderate	6.22	0.66		6.33	0.28	
High	6.25	0.91		6.28	0.02	
Lymphocytesⁱ, thousand cells/μl						

Outcome	Unadjusted Model		Adjusted Model	
Uranium level ^b	GM ^c	p-value	Continuous p-value	GM p-value Continuous p-value
Low	1.92	-	0.05	1.94 - 0.02 (0.85)
Moderate	1.89	0.18		1.90 0.03
High	1.89	0.02		1.91 0.02

^aFernald Medical Monitoring Program.

^bUranium level refers to the estimated lifetime cumulative exposure. Low: <0.25 Sievert; moderate: 0.25-0.50 Sievert; high: >0.50 Sievert.

^cGeometric mean.

^dAdjusted for: family history of high cholesterol, cancer, heart disease, and high blood pressure; co-morbid cardiovascular disease diagnosis; sex; age at original exam; income; body mass index.

^eAdjusted for: family history of cholesterol, heart disease, high blood pressure; co-morbid cardiovascular disease diagnosis; sex; age at original exam; educational status; body mass index.

^fAdjusted for: known exposure to anesthetics; family history of diabetes; sex; age at original exam; marital status; educational status; body mass index.

^gAdjusted for: known exposure to farming; family history of cancer, high blood pressure; sex; age at original exam; marital status; educational status; body mass index.

^hAdjusted for: family history of cancer; age at original exam; income; education; marital status; body mass index.

ⁱAdjusted for: known exposure to farming & vibration; family history of cancer; age; sex; income; education; body mass index.

(p-value of gender*uranium interaction term)

Low uranium exposure N=4,187; moderate uranium exposure N=1,273; high uranium exposure N=2,756.

Table 3

Relationship of uranium exposure on blood pressure and hematologic parameters among FMMP^a participants, stratified by gender.

Outcome	Males (N=3,593)			Females (N=4,623)		
	GM ^c	p-value	Continuous p-value	GM	p-value	Continuous p-value
Uranium level^b						
Systolic blood pressure^d, mmHg						
Low	132.2	-	0.17	126.0	-	0.02
Moderate	130.9	0.10		125.5	0.02	
High	132.2	0.96		127.2	0.02	
Diastolic blood pressure^e, mmHg						
Low	83.4	-	0.01	78.8	-	0.89
Moderate	82.0	0.003		79.0	0.70	
High	83.1	0.37		78.9	0.71	
Red blood cells^f, million cells/μl						
Low	5.06	-	0.15	4.52	-	0.20
Moderate	5.05	0.51		4.50	0.08	
High	5.03	0.05		4.53	0.39	
Platelet count^g, thousand cells/μl						
Low	248.3	-	0.92	279.2	-	0.10
Moderate	247.2	0.70		273.3	0.03	
High	247.7	0.80		278.0	0.60	
White blood cells^h, thousand cells/μl						
Low	6.35	-	0.09	6.44	-	0.75
Moderate	6.29	0.45		6.40	0.68	
High	6.21	0.03		6.39	0.46	
Lymphocytesⁱ, thousand cells/μl						
Low	1.93	-	0.28	1.95	-	0.07

Outcome	Males (N=3,593)		Females (N=4,623)	
	GM ^c	Continuous p-value	GM	Continuous p-value
Uranium level ^b				
Moderate	1.91	0.35	1.90	0.04
High	1.90	0.13	1.92	0.09

^aFernald Medical Monitoring Program.

^bUranium level refers to the estimated lifetime cumulative exposure. Low: <0.25 Sievert; moderate: 0.25-0.50 Sievert; high: >0.50 Sievert.

^cGeometric mean.

^dAdjusted for: family history of high cholesterol, cancer, heart disease, and high blood pressure; co-morbid cardiovascular disease diagnosis; sex; age at original exam; income; body mass index.

^eAdjusted for: family history of cholesterol, heart disease, high blood pressure; co-morbid cardiovascular disease diagnosis; sex; age at original exam; educational status; body mass index.

^fAdjusted for: known exposure to anesthetics; family history of diabetes; sex; age at original exam; marital status; educational status; body mass index.

^gAdjusted for: known exposure to farming; family history of cancer, high blood pressure; sex; age at original exam; marital status; educational status; body mass index.

^hAdjusted for: family history of cancer; age at original exam; income; education; marital status; body mass index.

ⁱAdjusted for: known exposure to farming & vibration; family history of cancer; age; sex; income; education; body mass index.

Males: low uranium exposure N=1,869; moderate uranium exposure N=533; high uranium exposure N=1,191.

Females: low uranium exposure N=2,318; moderate uranium exposure N=740; high uranium exposure N=1,565.

Table 4

Unadjusted and adjusted effects of uranium exposure on hypertension diagnoses and eosinophil counts among FMMP^a participants.

Outcome	Unadjusted Model		Adjusted Model	
	OR ^c	95% CI ^d	OR	95% CI
HTN^e Diagnosis^f				
Low	1.00	-	1.00	-
Moderate	1.07	0.89, 1.30	0.90	0.73, 1.12
High	1.85	1.62, 2.10	1.04	0.90, 1.21
Eosinophils^g, thousand cells/μl				
Ordinal outcome	1.12	1.06, 1.17	1.07	1.01, 1.13

^aFernald Medical Monitoring Program.

^bUranium level refers to the estimated lifetime cumulative exposure. Low: <0.25 Sievert; moderate: 0.25-0.50 Sievert; high: >0.50 Sievert.

^cOdd ratio.

^dConfidence interval.

^eHypertension

^fAdjusted for: family history of high cholesterol & high blood pressure high blood pressure; age at original exam; educational status; body mass index.

^gAdjusted for: family history of cancer, heart disease, high blood pressure, & diabetes; age; marital status; educational status.