DISSERTATION

INVESTIGATING THE RELATIONSHIP BETWEEN IONIZING RADIATION AND NEURODEGENERATIVE MORTALITY: ADDRESSING ISSUES OF BIAS, DATA POOLING, AND EFFECT MODIFICATION

Submitted by

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In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Spring 2025

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ABSTRACT

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Background

Much of the current understanding of the adverse health effects of ionizing radiation (IR) exposure comes from studies of Japanese atomic bomb survivors who experienced acute, high doses of IR. However, these findings may not be generalizable to populations exposed to chronic low doses of IR such as workers and the general population. The U.S. Million Person Study (MPS) was founded to investigate the effects of chronic low dose IR for improved guidance of radiation safety. To address this gap in knowledge, worker cohort studies have been and continue to be conducted to assess the potential risks associated with chronic low dose IR, including neurodegenerative diseases. These studies aim to improve the understanding of IR dose ranges and risks that underly current radiation safety policy. Recent findings underscore a potential increase in risk of neurodegenerative disease from chronic low dose IR which may be of great concern considering the significant burden of such diseases.

However, there are inconsistencies in prior research findings regarding the relationship between chronic low dose IR exposure and neurodegenerative disease. Several factors we focus on that can contribute to these inconsistencies are co-exposures to non-radiological substances, lack of power to investigate specific

neurodegenerative disease outcomes, and selection mechanisms like the healthy worker survivor effect (HWSE) and competing events. This dissertation research introduces novel techniques to evaluate and improve the internal and external validity of prior and future occupational studies of IR and neurodegenerative-related mortality. The specific objectives of the present study include assessing the role of co-exposures as effect modifiers and/or confounders, enhancing the understanding of the trade-offs of pooling data diverse cohorts together, and addressing selection mechanism concerns.

Methods

Our first objective focused on assessing the role of co-exposures in the relationship between IR and neurodegenerative-related mortality among workers at the Fernald Feed Materials Plant, referred to as Fernald, and to investigate neurodegenerative-related mortality risk across different job categories. Individual-level, brain IR dose estimates were used alongside co-exposure data from job exposure matrix application to evaluate potential confounding and effect modification. Co-exposures for this evaluation were selected *a-priori* based on literature review. Cox proportional hazards regression models were used to observe risk of neurodegenerative-related mortality at 10 milligray (mGy) IR brain dose across different groupings of co-exposure status, while logistic regression models were used to calculate odds of neurodegenerative-related mortality across 9 job categories.

In our second objective our goal was to evaluate the implications of data pooling in the context of the relationship between IR exposure and neurodegenerative-related mortality by combining data from the Fernald, Linde Ceramics Plant, hereafter called Linde, and Mallinckrodt Chemical Works (MCW) cohorts. The Linde cohort's data was

updated to prepare for merging with Fernald and MCW. Extensive data harmonization, such as collapsing continuous IR exposure measurement into a categorical form, was undertaken. Cox proportional hazards regression was again used in data analysis across three distinctive steps that analyzed different aggregation parts between the cohorts, co-exposures of uranium and silica dusts were evaluated. A meta-analysis was also conducted of these same three cohort's individual studies to qualitatively compare overall analogous estimates to the pooled analysis.

Lastly, our third objective employed the parametric g-formula to address selection mechanism concerns of HWSE and competing events. The parametric g-formula estimated the effect of hypothetical interventions on the risk of neurodegenerative-related mortality to evaluate the potential for HWSE by reducing IR exposure in hypothetical intervention scenarios. Expert interviews were conducted and supported with literature review to develop feasible hypothetical intervention endpoints of reducing IR exposure with possible real-world explanations including engineering and administrative controls. To investigate competing events, in one approach we modeled a likely competing event, cardiovascular disease (CVD) mortality, and compared cumulative incidence results to another approach without modeling for CVD mortality.

Results

Aim 1 findings highlighted that occupational exposure to machining fluids may act as an effect modifier of the relationship between IR and neurodegenerative-related mortality. Workers highly co-exposed to machining fluids showed significantly increased risk of neurodegenerative-related mortality at 10 mGy IR brain dose (HR 1.25, 95% CI 1.11, 1.40) compared to the overall baseline estimate (HR 1.01, 95% CI 0.96, 1.06).

Additionally, certain job categories such as store and supply services had elevated odds of neurodegenerative-related mortality compared to administrative workers (OR 2.30, 95% CI 0.97, 4.96).

Findings in Aim 2 revealed overall results consistent with Aim 1 of no increased risk of neurodegenerative-related mortality at low/moderate IR category (HR 0.95, 95% CI 0.73, 1.24) and high IR category (HR 1.05, 95% CI 0.80, 1.37). There was no evidence of confounding or effect modification by silica or uranium dusts. The meta-analytic estimate of these same cohort's individual studies had a similar summary estimate null finding compared to the pooled analysis finding for high categorical IR (HR 0.95, 95% CI 0.75, 1.20).

Results of Aim 3's application of the parametric g-formula indicated that the HWSE may not be a key factor in the relationship between IR and neurodegenerative-related mortality as cumulative incidence (CI) did not change considerably between the natural course (cumulative incidence, 16.99%), engineering control (17.43%), and administrative control (17.14%) interventions in the application modeling for competing events. When comparing approaches that modeled and did not model for competing events, we did find evidence that CVD mortality acts as a competing event for neurodegenerative-related mortality.

Conclusions

This dissertation found that occupational co-exposures, such as machining fluids, may modify the relationship between IR and neurodegenerative-related mortality. In a pooled analysis of worker cohorts we encountered significant data harmonization challenges that emphasized the importance of careful selection of data pooling

candidates and meta-analyses as an alternative to aggregating data for some research questions. Furthermore, the selection mechanism of HWSE may not be a key factor for IR and neurodegenerative-related mortality in Fernald, but CVD mortality appears to act as a competing event to neurodegenerative-related mortality.

These findings offer potential explanations and insights into the inconsistencies in prior research of IR and neurodegenerative-related mortality and highlight the need to consider co-exposures, data aggregation approaches, and selection mechanisms. This research contributes by showing the importance of evaluating the role of co-exposures as effect modifiers, providing insights into the goals of multi-cohort pooling efforts by discussing trade-offs of data pooling versus meta-analytic approaches, and exemplified a relatively innovative and novel method of addressing selection mechanism concerns in the field of occupational radiation epidemiology. Future research should focus on replicating these approaches in different circumstances that may alleviate the limitations of the present investigations to continue the overarching goal of best informing radiation safety policy for the general population and modern workforce.

ACKNOWLEDGEMENTS

This work was supported by the Mountain and Plains Education and Research Center (MAP ERC), a National Institute for Occupational Safety and Health education and research center for occupational and environmental health and safety under PHS Grant Number 5 T42 OH-9229-18. I must start by thanking the MAP ERC. Serving as an occupational ergonomics and safety trainee under the MAP ERC imparted lifelong insights from experiences among the many interdisciplinary projects, amazing people, valuable mentorship, and illuminating shared vision for a better future.

I would also like to extend a strong thanks to my collaborators at Oak Ridge Associated Universities who helped form some of the base ideas for this project and shared the privileged data that was used for this dissertation, without their openness to collaborative work this project would not have been possible. Much appreciation and recognition is extended to everyone involved in the U.S. Million Person Study team and the Department of Energy uranium processing workers whose data have made advances in understanding radiation health effects possible. Similarly, thank you to Dr. Thomas Johnson who opened the door to such a project to begin with.

My sincerest thanks are given to my advisor Dr. Andreas Neophytou and my co-advisor Dr. John Rosecrance, both of whom offered great advice and support through many of the challenges of pursuing a PhD, whether they were statistical headaches, technical writing ruts, or simply when difficult personal happenings made it hard to carry on with what was next. There was never a time that I doubted that I was in good hands. Additionally, thank you to my other committee members, Dr. Sheryl Magzamen and Dr.

Ander Wilson, and to the entire epidemiology section at Colorado State University (CSU). Over the course of 3 years I felt appropriately challenged to improve the most important professional career skills for my future.

I would like to give my dearest gratitude to the friends I made along the journey and the ones I have known for over a decade, these are friends that cheered on my academic pursuits and/or joined me in silly tabletop roleplaying games when healthy breaks were warranted. I thank my family that has always supported me in everything I do and every step of the way, making sure I keep my eyes on the dreams that brought me here to begin with and helping shape me into the person I am proud to be today. Lastly, but most importantly, I thank my partner who was the sunshine that could pull away any day's dark clouds. She made sure I ate on days that were 18 hours long, she celebrated my every victory no matter how big or small, and she supported me in so many more ways than words could aspire to describe.

DEDICATION

This dissertation work is dedicated to my late mother, Terri Ann Zbysinski (March 14th, 1965 – May 30th, 2023). She passed away pursuing a better tomorrow at the end of my first year of doctoral study. She persevered through each difficult day when life kept throwing struggle after struggle, yet remained a shining star, always finding plenty cause to laugh, to find joy, to smile, and to look forward to the future. When I call to mind these simple truths of her lived experience, how bravely she carried on throughout her entire life, her memory could inspire emotions that made even the worries and challenges of writing a dissertation diminish to near nothing. With unmeasurable appreciation for all her sacrifices I dedicate this work in tribute to her legacy.

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CHAPTER 1: INTRODUCTION

Background and Summary

Much of our understanding of adverse health effects associated with ionizing radiation (IR) exposure comes from the Life Span Study of Japanese atomic bomb survivors, a population exposed to an acute high dose of IR (*Life Span Study (LSS) – Radiation Effects Research Foundation (RERF)*, 2024). Results from such on-going research underly our current radiation regulations, even though it may not be generalizable to populations that are exposed to chronic low doses of IR. The U.S. Million Person Study (MPS) has the broad goal of filling this gap in knowledge (Boice et al., 2022). Recent studies have found evidence of increases in risk of neurodegenerative disease associated with low and moderate doses of chronic IR in worker cohorts (Dauer et al., 2024; Lopes et al., 2022; Srivastava et al., 2023). This is of particular concern due to potential cumulative impacts of chronic low dose exposure, as well as the growing prevalence of neurodegenerative disease among older adults (*ADI - Dementia Statistics*, 2024). However, the U.S. MPS and other international cohort studies have not studied the present co-exposures, evaluated implications of pooling many cohorts together to better investigate specific neurodegenerative outcomes, or assessed selection mechanism related biases that are common in cohort studies. Co-exposures, like welding fumes or vehicle exhaust, have been shown to be associated with increased risk of neurodegenerative diseases (Rana et al., 2019; Shkirkova et al., 2022). Findings of increased risk from IR may instead be obfuscated by these co-exposures in worker cohorts. The U.S. MPS intends to pool together diverse cohorts to

better detect potential risks at low doses comparable to today's exposures for diseases such as neurological conditions (Boice et al., 2022). Pooling data invites challenges of data harmonization which can result in loss of information, and dosimetry updates that require considerable resources. Healthy worker survivor effect may cause some workers to accumulate more exposure and time at risk than their counterparts and competing events may preclude neurodegenerative-related mortality. These concerns could very well be implicated in the study of IR exposed workers (Baillargeon & Wilkinson, 1999; Li & Sung, 1999), making study of IR's relationship with neurodegenerative diseases especially challenging.

Despite such limitations, occupational cohorts provide a unique opportunity to study IR and neurodegenerative-related mortality due to individual-level organ specific IR dose estimates, fitting criteria for chronic low dose IR, having death certificate mortality data relatively complete, and access to job exposure matrices which allows for the categorization of co-exposure status to address potential generalizability concerns. They can aid our understanding of low dose-related burdens that would be applicable beyond the occupational context, improving understanding of IR dose ranges and risk that is relevant to all populations. Altogether, this project's overarching and significant goal was to introduce novel techniques in the field and investigate, evaluate, and improve internal and external validity of prior and future studies of IR and neurodegenerative disease. Our specific goals were to investigate the role of co-exposures as effect modifiers and/or confounders, to enhance understanding of data aggregation techniques, and to address common selection mechanism concerns. We hypothesize that co-exposures will act as effect modifiers, that a pooled analysis will

result in considerable information loss, and that managing selection biases will reveal new significant findings.

Literature Review

Ionizing Radiation Exposure

Radiation as an exposure has long been a source of interest, fear, and study (Allison, 2009). Radiation can be divided into two forms, ionizing and non-ionizing radiation. Non-ionizing radiation has less energy than ionizing radiation and thus lacks the ability to remove electrons from atoms. On the other hand, ionizing radiation can be best explained through electromagnetic waves. At the higher end of the electromagnetic spectrum is ionizing radiation (IR) with high energy, enough to remove electrons from air, water, and living tissue. Furthermore, when IR passes through organic matter, it can disrupt electrons within our cells that may cause harm (CDC, 2024). IR can typically be described as having four major types, alpha, beta, neutrons, and electromagnetic waves such as gamma rays or x-rays. These different types of IR travel different distances and have varying ability to penetrate matter, having implications for different safety implementations depending on the type that is being addressed (NRC, 2020).

IR is found in our daily lives with a wide range of sources (US EPA, 2014b). The background IR that the general population is exposed to can be divided into primarily two different categories, background and medical. Background sources include radon and thoron, space, terrestrial, and more, while medical sources include nuclear medicine, computed tomography, interventional fluoroscopy, and conventional radiography/fluoroscopy (US EPA, 2015). When considering IR, specifically its source and how to measure IR, the most important factor is how much energy the source is

emitting as the size, weight, and volume of the source is of little consequence. Radioactivity is the amount of radioactive material present at a location or within something, dose rate is the amount of radiation coming from a source that is absorbed during a defined period of time, and dose is the amount of radiation that is absorbed by matter (CDC, 2024). Relevant to this project is the measurement of dose. Radiation doses are typically reported, in international units, in gray (Gy), for just dose, or sievert (Sv), that is equivalent or effective dose which takes into consideration the biological effects of different types of radiation. Often in radiation epidemiology the Gy is used for organ-specific or whole-body measurements, with dose weighting factors applied in consideration of different types of IR. Dose can be external, coming from without, or internal, coming from within. An example of internal would be the inhalation of radon gas (Materials, 1999). Altogether, background sources of IR give a U.S. individual an average whole-body annual radiation dose of about 5.4 mSv, however this number can vary based on radon levels in homes, travel frequency, elevation, and frequency of medical diagnostics (Kase et al., 2009, p. 160; Mettler et al., 2019, p. 184).

Additional dose can be accumulated from occupational sources, such as uranium processing. IR monitoring began early in the use of IR sources for nuclear weapons development and other nuclear research. The then Atomic Energy Commission, now Department of Energy (DOE), implemented safety regulations to reduce radiation exposure. But in the early and mid-1900's the highly praised benefits of nuclear technology were a strong focus, with earlier years of nuclear technology having workers exposed to substantially higher doses than those found amongst radiation exposed workers today (Walker & Wellock, 2010). A key principle of radiation safety created by

the National Council on Radiation Protection and Measurements was first mentioned in 1954. As Low As Reasonably Achievable, referred to as ALARA, had the intention of keeping doses as low as possible for the protection of individuals from potential harmful effects of IR. This standard is still in effect today and enforced by the DOE and the Nuclear Regulatory Commission (*10 CFR Part 20 -- Standards for Protection Against Radiation*, 2024; *10 CFR Part 835 -- Occupational Radiation Protection*, 2023, p. 835). ALARA primarily stands on the principles of minimizing time and maximizing distance from a source and shielding for radiation protection. The Occupational Safety and Health Administration additionally outlines the core components of modern day radiation protection programs, which include ALARA, radiological controls, emergency procedures, and most relevantly a dosimetry program (*Ionizing Radiation - Control and Prevention | OSHA.Gov | Occupational Safety and Health Administration*, n.d.). Radiation dosimetry is the science of measuring, calculating, and assessing IR dose absorbed, relevantly by the human body. In historical worker cohorts that are often the study of IR exposure and adverse health many measurements and methods are often used to recreate and estimate organ-specific IR dose estimates. Often, epidemiologic studies of IR exposure and health collaborate with radiation dosimetrists to assist in updating dose estimates for workers. Radiation dose estimates often use the International Commission on Radiological Protection's (ICRP) and the National Council on Radiation Protection and Measurement's (NCRP) reports and publications to guide best practices (Preston et al., 2020, p. 186). Historical personal film badges, area radon measurements, and surface sampling of radioactive materials are just a few examples of measurements used to recreate and ascertain radiation doses in historical facilities.

Such measurements are combined with radiation dosimetry techniques, such as using biokinetic models and details of worker tasks, to estimate organ-specific IR from both external and internal sources. Ellis and colleagues have keenly summarized the nuances of accurately measuring occupational IR dose amongst workers. They describe in an example of the Mallinckrodt Chemical Works (MCW) cohort, a historical DOE uranium processing facility, that workers had seven different exposure sources including external gamma radiation and internal radiation from inhalation and ingestion of pitchblende dust (which includes uranium, radium, and silica), occupational medical x-rays, previous IR exposure at prior facilities, and more (Ellis et al., 2018). It is the overarching goal in IR exposure assessment in occupational radiation epidemiology to best capture occupational-specific IR exposure.

The DOE's radiation Exposure Monitoring System helps give a snapshot of how dose has changed for DOE workers over the years as safety improvements have been made, with workers in 1973 having an average measured whole-body occupational dose of approximately 3 mSv. In 2012 DOE workers averaged a measured whole-body occupational dose of just 0.63 mSv (Rao & Hagemeyer, 2014). Chronic low-dose IR exposed workers stand in stark contrast to other populations, such as the Japanese atomic bomb survivors who received their dose in a much narrower timeframe. In the Life Span Study of Japanese atomic bomb survivors IR dose has a wide distribution. Those few within 1 km of the bomb hypocenters had an estimated weighted IR dose of 7 Gy for Hiroshima and 10 Gy for Nagasaki. While only approximately 42% of survivors experienced greater than 0.005 Gy colon dose, an organ dose often used for solid cancer incidence calculation, those receiving higher dose drove the dose-response

effect (Grant et al., 2017). Despite the distinct differences between occupational workers and the Japanese Atomic Bomb Survivors, particularly in the way they received IR exposure, much of our radiation safety standards are supported by research of the Life Span Study of Japanese atomic bomb survivors due to the retrospective nature and challenges of studying worker cohorts.

Large Multi-Cohort Pooling Efforts

The differences between the Japanese atomic bomb survivors and the modern working population occupationally exposed to IR is why data pooling efforts began and are ongoing. The U.S. MPS (Boice et al., 2022), the International Nuclear Workers Study [INWORKS, (Laurier et al., 2017)], and the International Pooled Analysis of Uranium Processing Workers [iPAUW, (Zablotska, 2019)] are some major multi-cohort studies that are behind data pooling efforts. INWORKS expanded upon the “15-Country Study” that used a common core protocol and collected information on nearly 600,000 workers, with most information contributed by the U.S., UK, and France. INWORKS aims to contribute understanding of risks of members of the public exposed to background IR and nuclear workers with prolonged exposure to low dose IR, it is organized by the International Agency for Research on Cancer [IARC, (Hamra et al., 2015)]. iPAUW is a much more recent development headed by Zablotska and colleagues to support international pooled analysis of uranium workers specifically. This would include workers that were involved in uranium milling, processing, and refining from five countries: Canada, France, Germany, the UK, and the U.S. Its data coordination efforts are centered at the University of California, San Francisco and is supported by the DOE, National Institute of Occupational Safety and Health, the

Canadian Nuclear Safety Committee, and radiation regulatory agencies in other included countries (Zablotska, 2019).

Specifically, and relevantly to this project, the U.S. MPS has the goal of investigating the effects of chronic low dose IR for improved guidance of radiation safety policies and enhanced understanding of health effects at low doses for U.S. workers. Additional goals include improving compensation schemes for workers, veterans, and the public, and to assist in producing evidence for or against the use of the linear no threshold dose-response model used in radiation safety (Boice et al., 2022). The large multi-cohort framework of the U.S. MPS is composed of many components which include: DOE workers, nuclear weapons test participants, nuclear power plant workers, industrial radiographers, medical radiation workers, nuclear submariners, other U.S. Navy personnel, and the radium dial painters. Statistical reasons drive the goal of a large, multi-cohort study to understand low dose effects, dose rate effects, rare diseases, and differences between men, women, and racial groups. Pooling of data is emphasized as being needed to achieve proper statistical power for these goals (Boice et al., 2022). Furthermore, the U.S. MPS has a special intent for highly accurate individual level exposure data that accounts for as many potential sources as possible, as in the case for the previously mentioned MCW cohort study (Ellis et al., 2018). This includes using organ-specific IR dosimetry estimates. Such dosimetry has been repeatedly stressed as important for DOE facility workers and other populations exposed to low dose IR (Boice et al., 2006, 2018; Leggett et al., 2005). Fortunately the Atomic Energy Commission had industrial hygiene programs for worker safety and

collected comprehensive records that could be used for research in the future (Ellis et al., 2022).

Unfortunately, not all facilities achieved such granular levels of exposure information that could be continually updated based on new biokinetic models and dosimetry techniques, such as the Linde Ceramics Plant cohort (Dupree et al., 1987). This disrupts the end goal of the U.S. MPS and other large-scale multi-cohort studies as data harmonization can sacrifice valuable information such as continuous measurements of IR or other important covariates. From another perspective, inclusion of these cohorts also contributes new information and more importantly bolsters statistical power in understanding the overall research question. New information can include data on co-exposures or other factors that may act as effect modifiers or confounders of the relationship under study. Many large multi-cohort data pooling efforts face significant harmonization challenges that result in dropping of some cohorts that could yield informative insights. Additionally, the resources and time to pool together many diverse cohort's data is intensive and many multi-cohort efforts are slow to progress as a result. An evaluation of the tradeoffs of information loss and gained has yet to be completed, particularly in extreme situations where continuous IR measurements may be sacrificed in favor of co-exposure data. It is possible that while meta-analyses and multi-cohort pooling are distinctive approaches, meta-analyses may provide similar answers to cohort pooling efforts with far less resource cost. While pooling efforts are ongoing and in progress to generate pooled estimates, meta-analyses have sought to answer similar questions yet the similarity in conclusions between both information aggregation approaches has not been assessed.

Ionizing Radiation and Health, Neurodegenerative Disease

As previously mentioned, much of our understanding of IR and health originates from the Japanese Life Span Study of atomic bomb survivors (National Research Council (US) Board on Radiation Effects Research, 1998). There has been extensive work in attempting to extrapolate estimates from this cohort down to lower dose levels that are more generalizable (Brenner et al., 2022; Little & Hamada, 2022). However, this work is challenged because even the definitions of low dose in such studies are different than what the general population is currently exposed to, indicating a gap in generalizability. This is intensified when considering the population differences between war-torn 1940s Japan and today's population (Wing et al., 1999). Additionally, there is much debate about the dose-response effect of IR and adverse health. It is assumed that there is a linear dose-response relationship, however, both biological mechanisms of cellular repair and other studies investigating responses at low doses further indicate an issue for this assumption and the many studies deriving from the Atomic Bomb Survivors Life-Span Study (Azizova et al., 2020; Cullom & Bateman, 2010; Mossman, 1998; Socol & Dobrzyński, 2015). Results from the U.S. MPS and other large-scale multi-cohort and low dose occupational studies have revealed a variety of potential health risks from prolonged exposure to low dose IR that is more generalizable to our working population, including cardiovascular disease (Baselet et al., 2016; Gillies et al., 2017), circulatory disease (Gillies et al., 2017; McGeoghegan et al., 2008), cataracts (Little et al., 2021), and several cancers (Boice et al., 2022; Dupree et al., 1987; Silver et al., 2013). One area of particular concern that is understudied but seeing increased

consistency across the literature is potential increases of risk for neurodegenerative-related disease, with a call in further study (Pasqual et al., 2021).

Perhaps the strongest study in the discipline to date regarding neurodegenerative concern is of Russian Mayak workers. Azizova and colleagues assessed risk of Parkinson's disease incidence among 22,377 Russian Mayak workers, finding significant excess risk per Gy unit increase in IR exposure (ERR 1.02, 95% CI 0.59, 1.63). Strengths of this study included exploration of the dose-response effect, neurological evaluation for neurodegeneration by a physician, and considerations for potential confounders (Azizova et al., 2020). In a pooled analysis of 12,403 uranium processing workers, standardized mortality ratios (SMRs) were significantly elevated for dementia and Alzheimer's disease [SMR 1.29, 95% CI 1.04, 1.54; (Golden et al., 2021)]. A review by Little and colleagues found some evidence of neurological detriment following low-moderate doses, 0.1-0.2 Gy, in context of radiation exposure in utero or early childhood (Little et al., 2021). Many of the U.S. MPS cohorts have estimated effects on mortality outcomes, such as neurodegenerative-related mortality, using death certificate data. The results of these and other studies, including standardized mortality ratios, relative risks, and excess relative risks have been succinctly summarized by 3 distinctive systematic reviews and meta-analyses. Lopes et al found increased risk for Parkinson's disease morbidity and mortality from prolonged IR exposure in 4 studies [overall ERR at 100 mGy 0.11, 95% CI 0.06, 0.16; (Lopes et al., 2022)] and Srivastava and colleagues also had results of increased risk of dementia outcomes in 8 studies for those exposed to over 100 mSv of IR [overall RR 1.11, 95% CI 1.04, 1.18 (Srivastava et al., 2023)]. Another recent systematic review and meta-analysis of specifically 6 U.S.

MPS cohorts found a significant increase in risk for Parkinson's disease [overall ERR at 100 mGy 0.17, 95% CI 0.05, 0.29; (Dauer et al., 2024)]. These efforts show trending evidence that IR can lead to an increase in risk of neurodegenerative-related disease. This is of particular importance given the ubiquity of IR exposure in both occupational and medical settings, the latter being emphasized as the use of medical diagnostics continues to rise (Smith-Bindman et al., 2008). However, not all evidence across occupational radiation epidemiology is consistent. Specific to the U.S. MPS the most recent study of the U.S. MPS cohort of Los Alamos, which has 26,328 workers, had nonsignificant findings for combined neurodegenerative-related cause of death at 100 mGy IR [ERR -0.01, 95% CI -0.19, 0.16; (Boice Jr., Cohen, et al., 2022)]. The MCW uranium processing cohort of 2,514 workers also found null results for combined neurodegenerative-related causes of death at 100 mGy IR [HR 0.87, 95% CI 0.57, 1.33; (C. M. Milder et al., 2023)]. Inconsistencies across the literature for IR and neurodegenerative-related mortality warrant further investigation, particularly in pooled analysis frameworks where the greatest statistical power can be achieved. These inconsistencies could also potentially be explained by greater ranges of exposure, different measures of association or comparisons used, or differences in unmeasured co-exposure scenarios.

In light of the increasing evidence between IR and neurodegenerative disease, there are concerning implications. It is estimated that ten million new dementia cases occur worldwide every year (*ADI - Dementia Statistics*, 2024). Neurodegenerative diseases are often incurable and debilitating which can lead to isolation of those who suffer them, these diseases lead to extensive burden upon families and caregivers, and

high healthcare costs (Rushford & Harvey, 2016; Van Bulck et al., 2019). It is believed that there are strong similarities between the biological mechanisms that motivate the progression of neurodegenerative diseases (Mayo et al., 2021; Pîrşcoveanu et al., 2017), although, the mechanism for IR is not understood. IR has been discussed as a risk factor for aging which could be explained causally through the oxidative stress pathway (Richardson, 2009). This is similar to how the accumulation of beta amyloid and neurofibrillary tangles also leads to the oxidative stress pathway (Begum et al., 2012; Hardy & Selkoe, 2002). Knowing that neuroinflammation is a hallmark of Alzheimer's disease, it would be reasonable to consider the oxidative stress pathway for IR as a biological mechanism. Research has suggested that IR may act through this pathway in the multifactorial view of neurodegeneration (Kempf et al., 2013). Furthermore, some evidence has indicated that cerebrovascular dysfunction, which IR may contribute to, might be a factor in Alzheimer's disease and related dementia development (Viticchi et al., 2012) which can lead to neurodegenerative alterations (Zlokovic, 2008). However, this is contradicted when there also exists some evidence that would point to a protective effect of IR on neurodegeneration (Ceyzériat et al., 2020; Coelho et al., 2022; Pasqual et al., 2021).

Occupational Co-Exposures to Ionizing Radiation

While occupational cohorts allow for the unique opportunity to study IR and neurodegenerative disease, there exists a gap in the consideration of co-exposures. As described by Lopes and colleagues, co-exposure to various non-radiological hazards in the occupational setting occurs often and may confound and/or modify the relationship between IR exposure and adverse health (Lopes et al., 2022). Within many of the

cohorts there likely exist co-exposures that are often uncharacterized given the lack of industrial hygiene measurements that would otherwise provide insightful data into co-exposures' role. Uranium workers were particularly exposed to co-exposures that were used in the processing of uranium, and many were employed at Department of Energy (DOE) facilities. A majority of these cohorts are included in the U.S. MPS. Namely, the Fernald Feed Materials, Linde Ceramics Plant, and in-part MCW cohorts of the U.S. MPS offer a unique opportunity to study the role of co-exposures due to available data. The call for future research to investigate modification by co-exposure to IR and appropriate control for potential confounding is necessitated for the study of IR and neurodegenerative disease (Golden et al., 2021). Confounding is likely possible because job-specific tasks would directly cause exposure to IR or co-exposures, and co-exposures may already be associated with neurodegenerative-related mortality. Furthermore, experiencing co-exposure likely varies greatly by job type and tasks performed (Dupree-Ellis et al., 2000; Zhivin et al., 2013), yet, there exists no literature with characterization of neurodegenerative mortality experience by job categories within cohort.

Other studies have investigated the impact of potential non-radiological co-exposures individually on cancer mortality outcomes (Ritz, 1999; Zhivin et al., 2013), but not as often for non-cancer outcomes, and their potential as effect modifiers or confounders remains unexplored in this context. Literature supports chemicals, air pollutants, and other co-exposures to IR to be associated with neurodegenerative disease, with varying degrees of evidence. Nitric acid and nitrogen dioxide (HNO3/NO2) has moderately strong support to be associated with increased risk of dementia (Chang

et al., 2014; Peters et al., 2019), as well as welding fumes (Stampfer, 2009) and vehicle exhaust (Costa et al., 2017; Milani et al., 2020; Shkirkova et al., 2022). Other co-exposures have weaker evidence of an association with neurodegenerative disease or brain cancer such as asbestos (Bianchi et al., 1986; Kanazawa et al., 1970), coal dust (Chang et al., 2014; Pu et al., 2023), silica dust (Rondeau, 2002; Rondeau et al., 2009), tributyl phosphate and kerosene [TBPK, (Helou & Jaecker, 2014; Ritz, 1999)], trichloroethylene [TCE, (DeBono et al., 2019; Dorsey et al., 2023)], uranium dust (Brugge & Buchner, 2011; Craft et al., 2004) and machining fluids (Calvert et al., 1998). Understanding the role of these co-exposures has significant implications for generalizability and the future of the sub-discipline of radiation epidemiology. While results of large multi-cohort data pooling efforts such as the U.S. MPS's ongoing work are far more generalizable to the target population than those of acute high dose events, co-exposures prove to be an unaddressed gap and potential issue.

Selection bias and generalizability

Lastly, it is well known, however understudied, that the effects of healthy worker bias are typically stronger than normal in radiation worker cohorts (Baillargeon & Wilkinson, 1999). Healthy worker bias can be thought of as two distinct concepts. Healthy hire effect is a form of selection bias arising in observational studies of occupational exposures. It is explained that the general population is mixed with both healthy and unhealthy individuals, however, workers are not children, retired elderly people, or ill individuals so those employed do not share the same underlying risks and disease susceptibility as the broader population. This bias represents a concern for generalizability and external comparison. Specifically, this bias is not uniform across

covariates and types of occupation, nor is it constant over time. It is particularly impactful to the use of standardized mortality ratios (SMRs) when using the general population as a reference. The generation of SMRs and the presence of the healthy worker hire effect has been noted in many studies in this field, likely understating even statistically significantly elevated SMRs (Dupree et al., 1987; Golden et al., 2021; Silver et al., 2013). Secondly, the workers who are healthier in any given cohort are more likely to accrue more exposure due to longer tenure than their counterparts who may leave the cohort earlier from health complications. This latter explanation contrasts to the healthy hire effect and is referred to as the healthy worker survivor effect [HWSE, (Buckley et al., 2015)]. When the exposure of interest, IR, is aggregated over time workers at higher risk for the outcome of interest tend to leave the job at higher rates than workers at low risk, therefor this HWSE may mask associations in previous analyses. (Keil et al., 2015; Keil & Richardson, 2017). This masking of association by healthy worker survivor effect, which there exists tools to address the effect, is one potential explanation for inconsistencies found in the literature between IR and neurodegenerative-related mortality across different worker cohort studies.

Given the significant increased risk of other mortality events such as cardiovascular disease, competing events should be considered in the study of neurodegenerative-related mortality and are another form of selection bias that should be managed. Competing events are events, such as cardiovascular-related death that has been found to be elevated in IR exposed worker cohorts, that preclude the primary outcome of interest. In a very recent study of the Fernald cohort by Milder et al., a competing risks analysis was performed for cardiovascular disease and ischemic heart

disease. Two extreme assumptions were tested, the maximum cardiovascular survival assumption and the minimum cardiovascular survival assumption. The former set all employees who died of competing causes to not be censored until end of follow-up, and the latter assumed all employees who died of competing causes would have died of cardiovascular or ischemic heart disease on the same day otherwise. The authors concluded that competing-risks modified estimates in Fernald and future cohort studies may aid in predicting radiation dose-response in other populations by showing the extreme boundaries that a dose-response may be anticipated (C. Milder et al., 2024). Competing event concerns have been highlighted as an issue in cohort studies especially those that require a very long period of follow-up for diseases such as neurodegenerative outcomes (Mansournia et al., 2022). Competing events are not a new phenomenon in survival analysis and there are viable methods to manage this selection mechanism issue (Coemans et al., 2022).

Specific Aims

Aim 1

Assess modification and confounding of IR and neurodegenerative-related mortality's relationship by co-exposures and characterize exposure and mortality experience by job category. We will use a job exposure matrix to set co-exposure status in the Fernald cohort of the U.S. MPS. Effect modification will be evaluated with a product term p-value and confounding through adjustment and assessment of estimate change.

Aim 2

Evaluate concerns of confounding and effect modification for the relationship between IR exposure and neurodegenerative-related mortality in a pooled analysis of multiple cohorts and assess overall conclusions in comparison with meta-analytic estimates. We will pool data of the Fernald, Linde, and Mallinckrodt cohorts and use Aim 1 methods with modifications based on data harmonization required. Then we will qualitatively compare overall analogous estimate results to a meta-analysis of those same studies and discuss driving differences, strengths, and limitations of the approaches to best inform future radiation epidemiological research.

Aim 3

Develop hypothetical interventions to mitigate exposure and estimate its effect on risk of neurodegenerative-related mortality while managing selection mechanism issues using innovative causal inference methodology. We will leverage the parametric g-formula, an extension of standardization in time-varying settings. Application of the g-formula will estimate risk of neurodegenerative-related mortality if exposure was mitigated earlier under intervention scenarios, while allowing us to address issues of HWSE and competing events.

Innovation and Contribution

The proposed project represents a departure from standard research approaches in occupational radiation epidemiology by addressing critical gaps in our understanding of IR's association with neurodegenerative disease. It is the first of its kind to evaluate effect modification and information loss in the occupational radiation epidemiology context. The approach in the second aim will further inform the potential of strategies in

addressing the overall research questions of the field. Methods employed in the third aim help address critical forms of selection mechanism concerns common in occupational studies that are rarely discussed in occupational radiation epidemiology. Such methods have the potential to transform the scientific knowledge around these forms of selection bias and adapt future methodology used. Results will illuminate generalizability issues, data pooling concerns, and selection bias impacts of prior and future studies. Significance extends beyond the occupational context, as findings will lead to improved generalizability of results to a variety of IR exposure scenarios, including household radon and medical diagnostics, the latter being of particular concern for the aging population's health. The comprehensive approach not only enhances the field's current methods and science but also has broader implications for public health, informing future studies and interventions targeting various low-dose IR exposures beyond the occupational context. Future research of occupational low dose IR will need to consider co-exposures and employed methods, impacting how the field will conduct new projects. Lastly, once analysis has been concluded for each aim, data will be completely de-identified and made available in line with transparency practices. It will be available through the Comprehensive Epidemiologic Data Resource (CEDR) as per usual protocol for U.S. MPS studies (*Comprehensive Epidemiologic Data Resource (CEDR)*).

CHAPTER 2: IONIZING RADIATION AND NEURODEGENERATIVE-RELATED MORTALITY IN A URANIUM PROCESSING COHORT: ASSESSING EFFECT MODIFICATION AND CONFOUNDING BY CO-EXPOSURES

Introduction

Ionizing radiation (IR) is found in our daily lives with a wide range of sources, such as environmental radon found in basements, long duration flights, or medical diagnostics (US EPA, 2015). IR's effects on health at acute high doses are well supported (National Research Council (US) Board on Radiation Effects Research, 1998), but low doses, generally defined as being under 100 millisieverts [mSv; (Vaiserman et al., 2018)], are less understood. The average individual in the U.S. may receive an estimated annual whole-body background dose of 6.2 mSv (US EPA, 2014). Those who work with sources of IR also typically experience chronic low doses on top of natural background doses. Low doses may lead to different effects on health compared to high doses (Boice et al., 2022). It is because of these concerns the U.S. Million Person Study (MPS) began, with the goal of investigating the possible health effects of chronic low dose IR exposure. It includes cohorts of individuals exposed to IR from uranium processing for the Department of Energy (DOE), nuclear test participants, nuclear power plant workers, and more (Boice et al., 2022). With a large number of individuals across many cohorts, some recent, albeit inconsistent, findings report increased risk of outcomes such as Parkinson's disease (Boice Jr., Cohen, et al., 2022; Boice Jr., Quinn, et al., 2022).

Increased risk of Parkinson's disease agrees with some broader literature, showing potential for increased risk of neurodegenerative-related disease from chronic

low dose IR (Pasqual et al., 2021). The burden of neurodegenerative disease is extensive with an estimated 6.2 million cases of Alzheimer's disease in the U.S in 2022 (*Neurodegenerative Diseases*, 2022). Furthermore, neurodegenerative disease leads to a heavy burden upon families, caregivers, and raises healthcare costs (Rushford & Harvey, 2016; Van Bulck et al., 2019). One of the strongest studies to date regarding neurodegenerative disease and IR is a cohort study of Russian Mayak Workers. Azizova and colleagues assessed risk of Parkinson's disease incidence, finding a significant excess risk per Gray (Gy) unit increase in IR. Understanding the dose-response relationship is critical in informing safety and public health regulations. The Russian Mayak study evaluated the dose-response shape among workers exposed to a broad range of dose, finding that linear-quadratic and linear-exponential models fit their data best (Azizova et al., 2020). Azizova et al.'s study and other's assessments of dose-response, as well as understanding of biological repair mechanisms following IR exposure, warrant further investigation of dose-response shape in many cohorts to evaluate conflicting evidence and if a trend persists (Cullom & Bateman, 2010; Mossman, 1998; Socol & Dobrzyński, 2015). However, such investigations are challenging given statistical power needs, the possibility that shape may differ based on outcome, and that the broader literature still strongly supports a linear model as best fitting (Little et al., 2009). The Azizova et al. study was weighted strongly by two systematic reviews and meta-analyses, supporting evidence that IR can lead to an increase in risk of neurodegenerative-related disease (Lopes et al., 2022; Srivastava et al., 2023).

Most helpful to understanding chronic low dose IR's effect on neurodegenerative disease is the exposure level that U.S. MPS study worder cohorts face. Occupational radiation cohorts for the study of IR and health have advantages with many having individual level and organ-specific IR dose estimates and fitting criteria for chronic low dose IR. However, some cohorts include workers co-exposed to a variety of non-radiological substances in their occupation, where it is likely that such co-exposures occurring concurrently with radiological exposure vary by job type and tasks performed (Dupree-Ellis et al., 2000; C. Milder et al., 2024; C. M. Milder et al., 2023; Zhivin et al., 2013). Co-exposures may act as confounders or effect modifiers of the relationship between IR and health (Lopes et al., 2022). There also exists no literature with characterization of neurodegenerative mortality experience by job categories within occupational cohorts. There is previous literature on neurodegenerative-related outcomes by general facility, which could be specific to uranium processing (Dupree et al., 1987). Yet, within sites the IR exposure, co-exposure, and mortality experiences of workers across job categories, that perform different tasks, has not been investigated. Analyses of occupational categories could help identify at risk groups for future interventions and subsequent safety policy guidance. Specialized operations of uranium processing are a case where elimination and engineering controls may not be feasible or may be costly. Work design interventions, such as rotation of workers (Castro & A.B. (Butch), 2003) would have great potential for those who may be co-exposed to not only IR but also harmful non-radiological substances.

The present study's main objectives are to explore the IR exposure and neurodegenerative-related mortality experience of workers by job category and to

evaluate potential confounding and effect modification by co-exposures on the relationship between IR and neurodegenerative-related mortality. These objectives will be accomplished by using the Fernald Feed Materials Plant, hereafter referred to as Fernald, cohort of the U.S. MPS (C. Milder et al., 2024). Fernald was a Department of Energy uranium processing facility with its primary focus being to produce high-purity uranium metal for nuclear weapons (*Comprehensive Epidemiologic Data Resource (CEDR)*, 2024; Silver et al., 2013). The Fernald cohort offers an opportunity to accomplish these goals compared to other cohorts due to the individual-level measured low IR exposure of the 6,403 workers and availability of co-exposure data (Anderson et al., 2012; Silver et al., 2013). The present study will address the limitation of co-exposures mentioned in prior studies by building upon previous research of the Fernald cohort, being the first to investigate the potential of effect modification.

Methods

Data Description

Data was acquired from with Oak Ridge Institute for Science and Education through the Department of Energy's Comprehensive Epidemiologic Data Resource (*Comprehensive Epidemiologic Data Resource (CEDR)*, 2024). This study was conducted under an IRB reliance agreement between Colorado State University and the Central Department of Energy Review Board, under HSRD ID DOE000954. Initially, ORISE gathered employment data, radiological exposure information, and vital status information through 1989 on Fernald employees in a study that only assessed 4,014 white males (Cragle et al., 1996). Then, Silver and colleagues expanded the mortality study this to 6,409 workers that included additional work history data and vital status

updates through 2004 (Silver et al., 2013). A data sharing agreement with the National Institute for Occupational Safety and Health linked the separate studies and provided IR organ-specific doses, pay category, and co-exposure data. The result was a dataset consisting of 6,403 Fernald employees who worked ≥30 days at Fernald from 1951 through 1985. Variables were subset from this dataset and used to create a clean analytic dose and person file by Milder et al. for the most recent mortality study of Fernald, which extended the follow-up through 2017 (C. Milder et al., 2024). This cohort data was shared, and merged with historical co-exposure information, to accomplish the present study's objectives.

IR dosimetry has been best described in previous literature for the Fernald cohort in greater detail (Anderson et al., 2012; C. Milder et al., 2024). Briefly, 10-year lagged annual cumulative organ-specific doses from external, internal and combined IR exposures were available and previously estimated using personal and area monitoring data. Anderson et al. initially calculated internal dose using urine samples with reported positive uranium concentrations and assuming chronic inhalation (Anderson et al., 2012), Milder et al. expanded this by reevaluating the uranium dosimetry model and creating yearly organ dose estimates from date of first uranium intake through the new follow-up date of 2017 (C. Milder et al., 2024). External exposure to IR was measured via film badge and thermoluminiscent dosimetry (Anderson et al., 2012). This work by Anderson et al. was expanded upon by Milder and colleagues, which estimated cumulative annual absorbed dose to 15 organs and added external dose received at other workplaces (C. Milder et al., 2024).

Vital status for all individuals was originally determined through 1989 by Cragle et al., but updated through December 31st, 2017, as described by Milder et al. Ascertainment was accomplished using the National Death Index, the Social Security Administration and Pension Benefits, Inc.. Death certificates used the International Classification of Diseases revision at time of death. Underlying causes of death were unavailable before 1979, thus a trained nosologist coded causes of death prior to that date from death certificates. For neurodegenerative-related mortality, underlying cause of death was used and included the combination of dementia, Alzheimer's, Parkinson's, and motor neuron diseases. First pay code, which is defined as a worker being paid hourly or salary, and year of birth were adjusted for to minimize confounding, with baseline stratification by sex. First pay code is a measure of socioeconomic status but also a potential proxy for tobacco smoking considering work characteristic differences that drive smoking behaviors (Sorensen et al., 2004). Birth year was considered because of confounding birth cohort changes, and sex was included as it could represent many driving sex-specific differences.

670 unique job titles of all workers at all time periods were collapsed into nine job categories. This was primarily accomplished using a key that was applied to a comparable uranium processing cohort, obtained in collaboration with Oak Ridge Associated Universities (Hickey et al., 1988). 147 job titles were collapsed into categories with maximum confidence based on the key and assumptions of abbreviated job titles. Next, 272 job titles were collapsed with high confidence based on inference. This involved combining site knowledge with self-explanatory job titles or comparison to similar job titles found in a category. Lastly, the remaining job titles were assigned

based on job task as identified from artificial intelligence search engine Microsoft Copilot when searching for job titles found in the scientific occupational epidemiology literature (*Microsoft Copilot*, 2024). This task-specific information would be combined with site knowledge and compared to similar titles in a job category for assignment. 228 job titles were assigned this way with moderate confidence, leaving 22 job titles classified as "other" and only one put into a 10th category "undetermined".

There were many co-exposures available and considered for evaluation of potential confounding and effect modification. Co-exposures were initially measured as ever/never co-exposed per worker per work period, a work period being a timeframe during which a worker held a specific job title. Co-exposure assignment was based on the job exposure matrix developed by Anderson and colleagues (Anderson et al., 2012). Briefly, the job exposure matrix had been made through qualitative assessment with input from industrial hygiene measurements for many chemicals and potentially harmful substances (Anderson et al., 2012). The co-exposures considered for possible effect modification or confounding investigation were identified from the scientific literature. Appendix Figure A1, created with DAGitty, offers a simplified directed acyclic graph without consideration of other variables to show how unadjusted co-exposure confounding may occur in this context (Textor et al., 2016). The following co-exposures were selected *a priori* for analysis of confounding and effect modification: nitric acid and nitrogen dioxide [HNO3/NO2 (Chang et al., 2014; Peters et al., 2019)], machining fluids (Calvert et al., 1998), vehicle exhaust, (Costa et al., 2017; Milani et al., 2020; Shkirkova et al., 2022), welding fumes (Stampfer, 2009), trichloroethylene (DeBono et al., 2019; Dorsey et al., 2023), asbestos (Bianchi et al., 1986; Kanazawa et al., 1970), silica dust

(Rondeau, 2002; Rondeau et al., 2009), coal dust (Chang et al., 2014; Pu et al., 2023), uranium dust (Brugge & Buchner, 2011; Craft et al., 2004), and tributyl phosphate and kerosene [TBPK (Helou & Jaecker, 2014; Ritz, 1999)]. Since industrial hygiene measurements were not available, a new variable “co-exposure days” was developed for each co-exposure in attempt to develop a more granular measurement of these co-exposures. Co-exposure days represents the total number of days, expressed over a worker’s entire tenure at Fernald, that the individual had the potential to be exposed to a given non-radiological substance based on work-period specific co-exposure assignment via the job exposure matrix. This variable was calculated using the ever/never co-exposure status for a given work period for any given worker. The co-exposure days variable was used to develop a categorical assignment of co-exposure status per worker on the median value. Those without any co-exposure days were put into the “None” category, those with greater than 0 but less than or equal to the median days were considered “Low” and greater than median considered “High”. If less than 20% of the cohort was co-exposed to a given co-exposure, ever/never categories were used instead.

Statistical Analysis

Person time was approached the same as it was in Milder et al. 2024, beginning 30 days after date of hire and ended at date of death, age 95, date lost to follow-up, or December 31st, 2017, whichever came first (C. Milder et al., 2024). Descriptive analysis included frequencies of categorical variables and median and interquartile range, 25th to 75th percentile, for skewed continuous variables. Cumulative combined external and internal IR brain dose, henceforth referred to as cumulative brain dose, was visualized

by plotting dose on a violin plot, with all workers grouped by neurodegenerative-related mortality. A Kruskal-Wallis test was used to identify statistically significant differences in cumulative brain dose, across each co-exposures' and job's categories. Chi-square tests were used to evaluate if ever/never co-exposure status, for each co-exposure, varied across job categories to understand the relationship between job category and co-exposures. Cumulative brain dose by job category and ever/never co-exposure status was visualized via box plots. Kaplan-Meier survival curves were generated for each co-exposure and outcome combination to visualize survival probability over time, using attained age as the underlying timescale (Therneau & Grambsch, 2024). To explore and characterize the potential neurodegenerative-related morality for each of the nine categorical job groups without consideration of IR or co-exposures, logistic regression models were used to produce odds ratios and 95% confidence intervals (CIs). First held job category's effect on odds of neurodegenerative-related mortality was assessed. First held job category was used as job category did not change considerably over time for individual workers. The logistic regression models used the administrative services category as a referent due to their lower co-exposure experience. All logistic models were adjusted for first pay code.

Cox proportional hazards regression was used for all other primary analyses. The baseline model, which uses attained age as the underlying timescale, is given below:

$$\log\big(\lambda(t|X)\big) = \log\big(\lambda 0(t)\big) + \beta_1 X_{IR} + \beta_2 X_{first\ pay\ code} + \beta_3 X_{birth\ year}$$

In the above model, expected log hazard at time t is defined by four terms. $\log\big(\lambda 0(t)\big)$ is the baseline hazard when all other predictors are zero and is stratified by sex. $\beta_1 X_{IR}$ is

the term for cumulative annual combined external and internal IR brain dose predictor, hereafter referred to as total IR brain dose. $\beta_2 X_{first\ pay\ code}$ represents the first pay code covariate and $\beta_3 X_{birth\ year}$ is the continuous term for birth year. No dose weighting factor for the high linear energy transfer portion of the total IR brain dose was applied as it would not affect interpretation of results for our objectives. Building upon the baseline model, individual Cox models were run for both confounding and effect modification evaluation for each co-exposure. Confounding was assessed by qualitatively comparing the hazard ratio of total IR brain dose in the baseline model to total IR brain dose in models that adjusted for categorical or dichotomous co-exposure (Lash et al., 2020). To evaluate effect modification, Cox models had a product term for the categorical or dichotomous co-exposure and total IR brain dose, comparing stratified estimates to the baseline model, while also evaluating the p-value the for the product term (Knol & VanderWeele, 2012). In a validation effort, we performed a sensitivity analysis that ran the same model as the Milder et al, 2024 for neurodegenerative-related mortality, using our baseline model and adjusting for dichotomous chemical exposure and interpreting results at 100 mGy brain dose (C. Milder et al., 2024). A natural cubic spline with 3 degrees of freedom was fit to total IR brain dose in a Cox model with an underlying timescale of attained age while adjusting for similar variables in the baseline model of first pay code, birth year, and stratification of the baseline hazard by sex. This was done without consideration of other co-exposures as a sensitivity analysis to understand the dose-response shape of the relationship of interest and to replicate what was accomplished in a prior study of Fernald (Silver et al., 2013). Using a cubic spline approach allowed for the relationship to be flexible across a range of doses. All Cox

models had the proportional hazards assumption tested using the cox.zph function in the R Survival package (Therneau & Grambsch, 2024). If the assumption was not met then models were repeated with a product term between time-dependent decade of age and the term that failed the assumption, or if the product term between IR and co-exposure failed the assumption, the model additionally had baseline hazard stratification by that given co-exposure. Lastly, we performed an additional sensitivity analysis that made a false discovery rate adjustment for p-values of effect modification models via the adjustment method developed by Benjamini and Hochberg (Benjamini & Hochberg, 1995). All statistical tests used an alpha level of 0.05. Data management was completed using SAS version 9.4 (*SAS Software 9.4*, 2024) and all statistical data analyses were executed using R Statistical Software Version 4.3.2 (R Core Team, 2024).

Results

Descriptive Analysis

Descriptive characteristics for demographic, exposure, outcome, co-exposure, and collapsed job category features are detailed in Table 2.1. In consideration of demographics, the cohort was mostly white (96.3%) males (85.1%) who had hourly pay code at their first job held (59.6%). The median cumulative brain dose among all workers was 0.92 mGy (IQR 9.15 mGy). There were 211 neurodegenerative-related mortality cases, and most of the cohort was deceased at follow-up (65.1%). Median total follow-up years was 42 years, and the median attained age at start of employment was 28. For co-exposures, there were differences in the distribution of those ever co-exposed as shown in a bar chart, Appendix Figure A2. For some co-exposures, such as HNO3/NO2, nearly half the cohort was co-exposed (45.3%), for others, such as welding

Table 2.1. Demographic, exposure, outcome, and co-exposure characteristics for all 6,403 Fernald uranium processing workers

Variable	**Measure**
Categorical	**n (%)**
Sex	
Male	5450 (85.1)
Female	953 (14.9)
Race	
White	6164 (96.3)
Black	235 (3.7)
Other	4 (0.06)
First Pay Code	
Hourly	3814 (59.6)
Salary	2589 (40.4)
Vital Status at End of Follow-Up	
Alive	2112 (33.0)
Dead	4171 (65.1)
Unconfirmed	120 (1.9)
Neurodegenerative-Related [a] Cause of Death	
No	6192 (96.7)
Yes	211 (3.3)
Ever Co-Exposed:	
HNO3/NO2	2899 (45.3)
Machining Fluids	2056 (32.1)
Vehicle Exhaust	255 (4.0)
Welding Fumes	70 (1.1)
Trichloroethylene	134 (2.1)
Asbestos	225 (3.5)
Silica Dust	2082 (32.5)
Coal Dust	91 (1.4)
Uranium Dust	1015 (15.9)
TBPK	1869 (29.2)
Job Category	
Administrative Services	1205 (18.8)
Chemical Control Research and Development	719 (11.2)
Engineering and Development	297 (4.6)
Maintenance	795 (12.4)
Process Operations	1450 (22.6)
Loading and Material Handling	1237 (19.3)
Storage and Supply Services	188 (2.9)
Safety and Security	310 (4.8)
Other	78 (1.2)
Undetermined	124 (1.9)
Continuous	**Median, IQR**
Age at Start of Employment and Follow-Up	28.3 (12.6)
Age at End of Follow-Up	74.4 (18.2)
Total Follow-Up Years	42 (22.2)
Age at Death	74.0 (17.7)
Age at Neurodegenerative-Related Death[§]	82.8 (8.8)
Cumulative Brain Dose, mGy	0.92 (9.15)

[a] Neurodegenerative-related includes dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease.

Abbreviations: HNO3/NO2: nitric acid or nitrogen dioxide, TBPK: tributyl phosphate and kerosene, IQR: interquartile range, IR: ionizing radiation, mGy: milligray.

fumes, only a small percentage of the cohort was co-exposed (1.1%). The top three most common job categories were process operations (22.6%), loading and material handling (19.3%), and administrative services (18.8%). Figure 2.1 is a violin plot that displays cumulative brain dose grouped by neurodegenerative-related mortality or not. Those who experienced neurodegenerative-related death generally had slightly higher dose and those who did not had a wider range of dose, however, both were comparable. Kruskal-Wallis tests showed a significant difference in cumulative brain dose across all co-exposures' categories. The Kruskal-Wallis test for job categories also showed a significant difference in cumulative brain dose across different job categories ($p < 0.001$), Appendix Table A1 shows their summary statistics. All chi-square tests for differences of co-exposure status across job categories were significant (all p-values < 0.0001). A box plot of cumulative brain dose across those who had ever or never been co-exposed is summarized in Figure 2. Of note, those who were ever exposed to

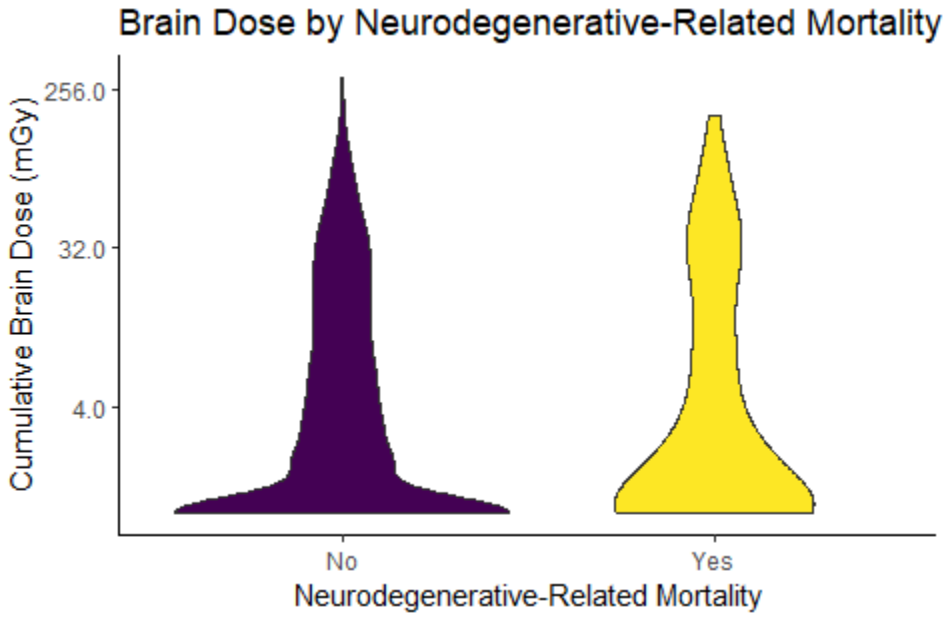

Figure 2.1. Cumulative brain dose stratified by neurodegenerative-related mortality for 6,403 Fernald uranium processing workers. *Abbreviations:* mGy: milligray.

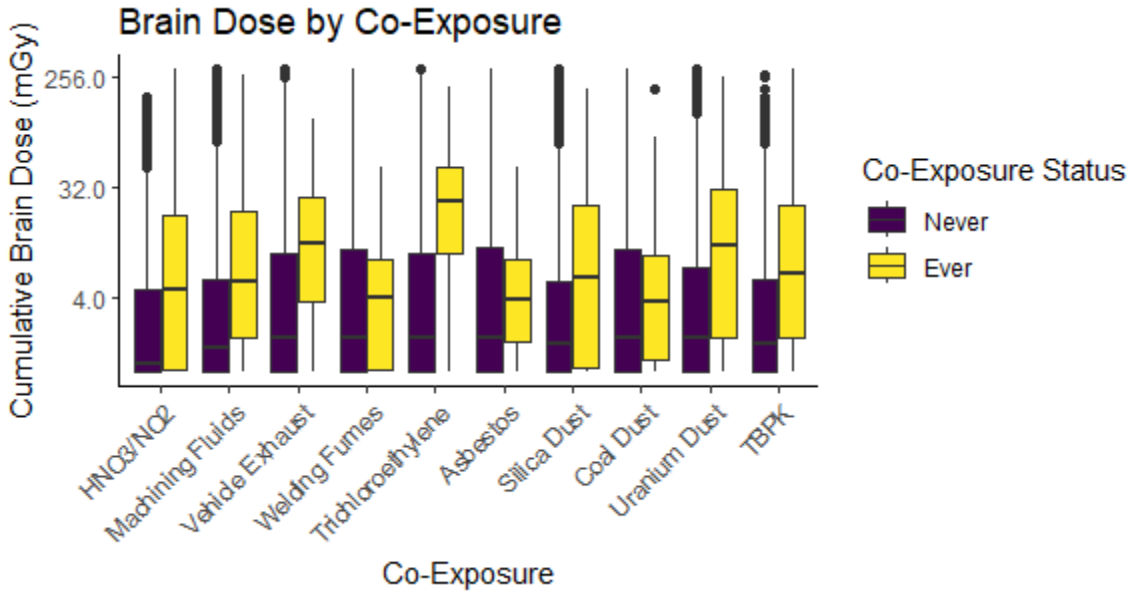

Figure 2.2. Box plot of cumulative brain dose by ever/never co-exposure status for 6,403 Fernald uranium processing workers. All Kruskal-Wallis tests for significant differences of cumulative brain dose by co-exposure status were significant: welding fumes: p = 0.0002, coal dust: p = 0.047, all other co-exposures p < 0.0001. *Abbreviations:* mGy: milligray, HNO3/NO2: nitric acid and nitrogen dioxide and nitric acid, TBPK: tributyl phosphate and kerosene

trichloroethylene experienced higher cumulative brain dose. The additional box plot of different job categories compared to the rest of the cohort showed differences in cumulative brain dose exposure experience of workers based on their jobs, summarized in Appendix Figure A3. Those who were chemical control and research and development workers compared to all other workers had higher cumulative brain dose. Survival curves that were generated for each co-exposure were inconclusive, the two that portrayed the relatively most distinctive difference in survival probability were HNO3/NO2, Figures A4 and machining fluids, A5.

Primary Analysis

Results of the broad job category logistic regression analyses exploring odds of neurodegenerative-related mortality from different job categories are summarized in Table 2.2. Results showed that compared to administrative services workers, those who

Table 2.2. Logistic regression model results for job category and neurodegenerative-related mortality for 6,403 Fernald uranium processing workers

Outcome and Job Category	OR (95% CI)
Neurodegenerative-Related Mortality [a]	
Administrative Services	1.00 (referent)
Chemical Control and Research	0.78 (0.46, 1.29)
Engineering and Development	0.87 (0.46, 1.29)
Maintenance	1.44 (0.71, 2.81)
Process Operations	1.28 (0.66, 2.39)
Loading and Material Handling	1.47 (0.73, 2.89)
Store and Supply Services	2.30 (0.97, 4.96)
Safety and Security	1.70 (0.84, 3.24)
Other	0.55 (0.03, 2.77)

Note: All estimates derived from logic models that adjusted for first pay type.
[a] Neurodegenerative-related includes dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease.
Abbreviations: OR: odds ratio, CI: confidence intervals.

worked in different job categories had differing but mostly insignificant results. Specifically, those who worked in store and supply services had the highest odds for neurodegenerative-related mortality (OR 2.30, 95% CI 0.97, 4.96). Cox model results for the baseline model and for assessing effect modification and confounding by co-exposures are summarized in Table 2.3. All results are expressed at 10 mGy IR because only 1.56% of workers experienced a cumulative brain dose greater than 100 mGy. The proportional hazards assumption was only violated for the product term in vehicle exhaust and welding fumes effect modification models, for these two models Table 2.3 reflects the updated models where adjustment was made to meet the proportional hazards assumption.

The baseline model indicated null findings for neurodegenerative-related mortality at 10 mGy total IR brain dose [hazard ratio (HR) 1.01, 95% CI 0.96, 1.06]. Across models that added co-exposure terms to assess confounding, effect estimates for total IR brain dose did not change considerably. No co-exposures displayed

Table 2.3. Confounding and effect modification by co-exposures model results for 6,403 Fernald uranium processing workers.

Outcome	HR (95%CI) Adjustment for Co-Exposure	HR (95%CI) Without Co-Exposure	HR (95%CI) With or Low Co-Exposure	HR (95% CI) High Co-Exposure	Product Term p-value for With or High Co-Exposure
Neurodegenerative-Related [a] Cause of Death	1.01 (0.96, 1.06)				
HNO3/NO2	1.03 (0.97, 1.08)	0.94 (0.82, 1.07)	1.15 (0.98, 1.35)	1.11 (0.96, 1.28)	0.16
Machining Fluids	1.01 (0.96, 1.06)	0.93 (0.85, 1.02)	1.07 (0.92, 1.25)	1.25 (1.11, 1.40)	0.0003
Vehicle Exhaust [b]	1.01 (0.96, 1.06)	1.01 (0.96, 1.06) [c]	0.96 (0.68, 1.37) [c]	-	0.83 [c]
Welding Fumes [b]	1.01 (0.96, 1.06)	NA [c, d]	NA [c, d]	-	NA [c, d]
Trichloroethylene [b]	1.01 (0.96, 1.07)	1.00 (0.95, 1.06)	1.12 (0.94, 1.33)	-	0.21
Asbestos [b]	1.01 (0.96, 1.06)	1.01 (0.96, 1.07)	0.41 (0.09, 1.94)	-	0.26
Silica Dust	1.01 (0.96, 1.06)	1.00 (0.93, 1.06)	0.94 (0.79, 1.12)	1.12 (0.99- 1.27)	0.077
Coal Dust [b]	1.01 (0.96, 1.06)	1.00 (0.93, 1.06)	1.04 (0.93, 1.16)	-	0.49
Uranium Dust [b]	1.01 (0.96, 1.06)	1.00 (0.93, 1.06)	1.04 (0.93, 1.16)	-	0.49
TBPK	1.01 (0.96, 1.07)	0.98 (0.89, 1.07)	1.07 (0.94, 1.22)	1.06 (0.94, 1.20)	0.35

Note: All models additionally adjusted for first pay type, birth year, and stratified baseline hazard by sex. All results are expressed at 10 mGy unit increase of total IR brain dose.

[a] Neurodegenerative-related includes dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease.

[b] <20% of the cohort was co-exposed to these co-exposures meaning only ever/never status was used for effect modification analysis, leading to an absence of a "high co-exposure" category.

[c] Proportional hazards assumption failed for the product term in these models, additional adjustment via baseline hazard stratification of the co-exposure was made to meet the assumption.

[d] Model did not converge due to small sample size in the "Welding Fumes" product term model (n = 70 co-exposed), causing computational issues.

Abbreviations: HR: hazard ratio, CI: confidence interval, HNO3/NO2: nitric acid and nitrogen dioxide, TBPK: tributyl phosphate and kerosene, mGy: milligray, IR: ionizing radiation.

evidence for confounding. Effect estimates varied across different co-exposure groupings in results from the models assessing effect modification. Specifically, the estimate for those in the high co-exposure group for machining fluids (HR 1.25, 95% CI 1.11, 1.40) was considerably different than those never co-exposed (HR 0.93, 95% CI 0.85, 1.02), and silica dust (HR 1.12, 95% CI 0.99, 1.27) was non-significantly different than those never co-exposed (HR 1.00, 95% CI 0.93, 1.06). For machining fluids, not only did the results indicate a change to a significant increase in risk of neurodegenerative-related death at 10 mGy total IR brain dose for those in the high co-exposure category, the p-value for the product term was also significant (machining fluids: p=0.0003). There was suggestive evidence of effect modification approaching significance for the co-exposures HNO3/NO2 (p = 0.0957) and silica dust (p = 0.0770). Figure S5 depicts the estimated dose-response relationship, from the spline model, between neurodegenerative-related mortality risk and total IR brain dose. The dose-response shape was largely null and unable to be interpreted due to wide confidence intervals indicating a lack of statistical power. In our validation sensitivity analysis, our model results, when adjusting for laboratory chemicals and expressed at 100 mGy total IR brain dose, matched those of Milder et al. (C. Milder et al., 2024). In the sensitivity analysis adjusting for false discovery rate, machining fluids remained significant (p = 0.003).

Discussion

In this retrospective cohort study, we did not find that total IR brain dose increased risk of neurodegenerative-related mortality; however, we did find that this relationship may be modified by co-exposures. Most notably IR increased risk of

neurodegenerative-related mortality among those likely highly co-exposed to machining fluids. Additionally, some job categories had elevated odds of neurodegenerative-related mortality. While this observational study has limitations that restrict causal inference, it is an initial step in addressing the considerable gap of effect modification by co-exposures in the literature of low dose IR and health research.

Our baseline IR and neurodegenerative-related disease findings have mixed alignment with previous studies. In a previous pooled cohort study of 12,403 workers, that included Fernald, standardized mortality ratios were found to be significantly elevated for dementia and Alzheimer's disease [SMR 1.29, 95% CI 1.04, 1.54; (Golden et al., 2021)]. More broadly, a systematic review and meta-analysis by Lopes et al. found consistent evidence of increased risk of Parkinson's disease morbidity and mortality from IR exposure in 4 studies [overall ERR per 100 mGy 0.11, 95% CI 0.06, 0.16; (Lopes et al., 2022)]. The systematic review and meta-analysis by Srivastava et al. found support of increased risk of dementia outcomes in 8 studies for those exposed to over 100 mSv [overall RR 1.11, 95% CI 1.04, 1.18; (Srivastava et al., 2023)]. Lastly, another systematic review and meta-analysis of 6 U.S. MPS cohorts found a significant increase in risk for Parkinson's disease [overall ERR per 100 mGy 0.17, 95% CI 0.05, 0.29; (Dauer et al., 2024)]. These studies and others disagree with our primary IR and neurodegenerative-related mortality results; however, other radiation worker cohort studies have found null results such as ours for neurodegenerative-related mortality outcomes. A U.S. MPS study of the 26,328 Los Alamos worker cohort had null findings for combined neurodegenerative-related cause of death [ERR per 100 mGy -0.01, 95% CI -0.19, 0.16; (Boice Jr., Cohen, et al., 2022)]. Another U.S. MPS cohort study of 2,514

Mallinckrodt uranium processing workers also found null results for combined neurodegenerative-related causes of death [HR per 100 mGy 0.87, 95% CI 0.57, 1.33; (C. M. Milder et al., 2023)]. Inconsistencies in comparisons with other studies may arise from greater ranges of exposure, different measures of association used, or differences in unmeasured co-exposure scenarios. Lastly, to the best of our knowledge, there are no prior investigations into effect modification of IR and neurodegenerative disease by co-exposures to compare our results to, emphasizing the importance of this study's initial step into understanding co-exposures' potential roles. The mechanism for how IR may increase risk of neurodegenerative disease is not fully understood. It is reasonable to consider the oxidative stress pathway for IR's effect, and that it may act through this pathway in the multifactorial view of neurodegeneration (Kempf et al., 2013). IR is a potential risk factor for aging through this oxidative stress pathway (Richardson, 2009). Additionally, neuroinflammation is a hallmark of Alzheimer's disease, and there exist similarities between biological mechanisms that motivate the progression of neurodegenerative diseases (Mayo et al., 2021; Pîrşcoveanu et al., 2017). The dose-response sensitivity analysis was primarily done to better understand the relationship under study and to replicate a method completed by Silver et al. in a previous study of Fernald. Despite a lack of statistical power for dose-response in the present study, Silver and colleagues found a similar shape to ours when fitting natural cubic splines to IR lung dose and lung cancer mortality (Silver et al., 2013). Our inconclusive findings would contrast with the previously mentioned Russian Mayak study in their investigation of IR and Parkinson's disease risk, where they found that linear-quadratic and linear-exponential models fit the data better than a linear model (Azizova et al., 2020).

Strengths of this study, like other studies from the U.S. MPS (Boice Jr., Cohen, et al., 2022; Dupree et al., 1987; C. M. Milder et al., 2023), start with being more generalizable to modern workers and the general population than past studies of acute high dose radiation events. By leveraging the advantages of the Fernald cohort, we were able to calculate co-exposure estimates based on previous work for all of Fernald's workers. In addition, these workers had individual level organ-specific IR dose estimates. These strong qualities combined with *a priori* identified co-exposures based on the literature elevate confidence in our results. This study joins the growing body of evidence to better capture the effects of low dose IR and help inform policy makers how radiation safety standards may need to be adapted. Our study would suggest such adaptations need to bear in mind not only radiological hazards but also concurrent non-radiological hazards, such as machining fluids. Evaluations, likely from an industrial hygiene or ergonomics perspective, should attempt to better understand why some job categories such as store and supply services are at higher risk of neurodegenerative-related mortality than others. Our study demonstrates it may be important for future investigations of radiation worker cohorts to consider the potential for machining fluids and silica dust co-exposures.

However, this study is not without limitations. First and foremost, one of the greatest weaknesses of the present study is our power, impaired by sample size. A lack of power leads to diminishing ability in assessing effect modification which could inflate estimates. This is followed by the potential for selection bias. Selection bias in our study may be present in two different ways, healthy worker survivor effect and competing events. It has been previously reported that healthy worker bias is typically stronger

than normal in radiation workers (Baillargeon & Wilkinson, 1999). Generalizability is also weakened by the relative lack of diversity in the cohort characteristics. Competing events, such as cardiovascular-related death that may preclude the time-dependent neurodegenerative-related mortality outcome of interest, also make the study of neurodegenerative-related mortality challenging. Specific to our assessment of confounding, using a qualitative approach could be considered a subjective method and a limitation. Despite our strategy of calculating co-exposure days for a more granular measurement of co-exposures, nondifferential misclassification of these co-exposures is still probable and likely of moderate magnitude which could lead to residual confounding. Given that death certificate data is used, nondifferential misclassification of the mortality outcome is also highly possible with accuracy and consistency being questionable given the neurodegenerative-related outcome (McGivern et al., 2017). This bias would influence results towards the null. Lastly, in terms of bias, there exists the chance of residual confounding as simple hourly vs salary pay may not fully capture socioeconomic status. An important unmeasured confounder may be tobacco smoking, however, such data simply does not exist for this cohort. Still, type of work organization and pay has been correlated with smoking habits (Sorensen et al., 2004), but pay type may fall short in being a true proxy for tobacco smoking.

Regardless of limitations, the present epidemiologic study investigated the dynamics between chronic, low dose IR exposure and neurodegenerative-related mortality in the circumstance of co-exposure to a large variety of non-radiological substances. Our findings indicated that some co-exposures such as machining fluids and potentially silica dust may be effect modifiers of the relationship. Furthermore, this

study found that a few job categories suffered disproportionately higher odds of neurodegenerative-related mortality. Unexpected results underscore the need for further investigation to better understand and validate the relationship between occupational exposures and health outcomes in the radiation worker context. The product of this work contributes to the literature aiming to better inform radiation safety policy for not only workers but the broader population. Our results emphasize the importance of considering co-exposures in occupational settings and offer insights that can help guide future studies and policy decisions.

CHAPTER 3: IONIZING RADIATION AND NEURODEGENERATIVE-RELATED MORTALITY: EVALUATING DATA POOLING IMPLICATIONS

Introduction

Ionizing radiation (IR) is ubiquitous within our lives with a variety of sources such as environmental radon, long duration flights, or medical diagnostics (US EPA, 2015). IR's effects on health at acute high doses are well reported (National Research Council (US) Board on Radiation Effects Research, 1998), but low chronic doses that are more applicable to the modern population are less understood. These low chronic doses may have different effects on health compared to their higher counterparts (Boice et al., 2022). Thus, the U.S. Million Person Study (MPS) was founded to investigate the effects of chronic low dose IR for improved guidance of radiation safety regarding chronic low dose IR. Cohorts of individuals exposed to IR from uranium processing for the Department of Energy (DOE), nuclear test participants, nuclear power plant workers, and more are included in the multi-cohort U.S. MPS. A major end goal of the U.S. MPS is to pool together these diverse cohorts to increase statistical power so that rare diseases and sociodemographic differences in IR and health outcomes' risk can be investigated, with the additional bonus of adding in new information (Boice et al., 2022). Part of such a goal is having strong radiation dosimetry, which has been repeatedly stressed as important for DOE facility workers (Boice et al., 2006, 2018; Leggett et al., 2005) and other populations exposed to low dose IR. From another perspective, unfortunately, not all facilities achieved such granular levels of exposure information such as the Linde cohort (Dupree et al., 1987). This disrupts the end goal of the U.S. MPS and other large-scale multi-cohort studies as data harmonization can cause

exposure assessment or covariate consolidation concerns. An evaluation of the tradeoffs has yet to be completed, particularly for the sacrifice of continuous IR measurements.

Some recent findings of increased risk of neurodegenerative-related outcomes such as Parkinson's disease have been reported in the U.S. MPS (Boice Jr., Cohen, et al., 2022; Boice Jr., Quinn, et al., 2022). The broader literature also echoes the potential for increased risk of neurodegenerative-related disease from chronic low dose IR (Pasqual et al., 2021). However, findings are inconsistent within the U.S. MPS with other studies having non-significant results for neurodegenerative-related mortality (Boice Jr., Cohen, et al., 2022; C. M. Milder et al., 2023). Such inconsistencies may be best solved through data pooling efforts where more specific neurodegenerative-related mortality outcomes can be investigated. The irregularities of IR and neurodegenerative-related mortality risk in the U.S. MPS warrant pooling of data to better investigate the relationship between low dose chronic IR and neurodegenerative-related mortality. Inconsistencies may also be explained by co-exposures to IR, like non-radiological substances, that also vary by job type and tasks performed (Dupree-Ellis et al., 2000; C. Milder et al., 2024; C. M. Milder et al., 2023; Zhivin et al., 2013). Co-exposures may act as confounders or effect modifiers of the relationship between IR and health (Lopes et al., 2022).

This study's main objectives are to evaluate risk of neurodegenerative-related mortality from categorical IR and assess confounding and effect modification by co-exposures in a pooled analysis of uranium processing workers. These objectives will be accomplished by using the Fernald Feed Material Plant, referred to as Fernald (C.

Milder et al., 2024), Linde Ceramics Plant, referenced to as Linde (Dupree et al., 1987), and Mallinckrodt Chemical Works [MCW, (C. M. Milder et al., 2023)] cohorts of the U.S. MPS. These cohorts afford a chance to investigate co-exposures due to two co-exposures in common across all three cohorts. Furthermore, due to inherent differences in data collected for the three cohorts, there exists an opportunity to highlight the potential trade-offs of merging data. This study builds upon prior research of the role of co-exposures and is the first to assess advantages and disadvantages of data pooling in occupational radiation epidemiology to the best of our knowledge.

Methods

Data Description

Data was retrieved in collaboration with Oak Ridge Associated Universities, who manages the Department of Energy's Comprehensive Epidemiologic Data Resource (*Comprehensive Epidemiologic Data Resource (CEDR)*, 2024a). This study was completed under an IRB reliance agreement between Colorado State University and the Central Department of Energy Review Board, with the Department of Energy's IRB serving as the IRB of record under HSRD ID DOE000954. All three cohorts of Fernald, Linde, and MCW have been studied previously, with work being done for the Department of Energy. The Fernald Feed Materials Plant, located in Ohio, began uranium-related operations in 1951 and ceased in 1989, focusing on materials processing for nuclear weapons and has been studied several times before (Cragle et al., 1996; C. Milder et al., 2024; Silver et al., 2013). The shared data includes information on employment and work history, pay category, IR doses, and co-exposure information for those who worked ≥ 30 days. MCW was based in Missouri and had

relevant uranium processing operations from 1942 through 1966 (C. M. Milder et al., 2023). There have been three previous mortality studies of MCW (Dupree-Ellis et al., 2000; Golden et al., 2022; C. M. Milder et al., 2023). The most recent study followed workers through December 31st, 2019, prepared data for eventual pooling efforts and expanded outcomes of interest. It includes data on pay category, IR doses, and select co-exposure status for workers who worked ≥ 30 days (C. M. Milder et al., 2023). The Linde Ceramics Plant was located in Tonowanda New York and started materials processing in 1943 and stopped operations in 1951, with the latest and first study following workers through December 31st, 1979. The retrospective mortality study of 995 white males employed ≥ 30 days investigated the association between excess observed deaths and long-term occupational exposure to uranium compounds (Dupree et al., 1987). For the present study Fernald and MCW data was shared from their most recent analysis (C. Milder et al., 2024; C. M. Milder et al., 2023). Linde's study was less recent and therefore many data elements had to be updated, building upon the shared previous data (Dupree et al., 1987). The three cohort's data were combined in three steps. Step 1 combines Fernald and Linde to maximize assessment of common co-exposures. Step 2 merges Fernald and MCW to retain the strongest form of continuous dose measurement, and Step 3 pools all three cohorts' data.

IR exposure measurement has best been described in previous literature for all cohorts. Anderson and colleagues initially calculated internal dose in Fernald using urine samples and external dose with film badges and thermoluminiscent dosimetry. Milder et al. improved dose estimates by reevaluating the dosimetry model and creating yearly organ dose estimates through 2017 (Anderson et al., 2012; C. Milder et al.,

2024). Fernald has continuous 10 year lagged annual cumulative organ-specific doses for both external and internal IR exposure. MCW's external dosimetry was measured by personal film badges, required medical chest x-ray records, and prior workplaces with film badge records, with some dose imputation and later improved with updated dosimetry by Golden et al. (Dupree-Ellis et al., 2000; Ellis et al., 2018; Golden et al., 2022). Internal IR was previously calculated using uranium urine samples, radon breath measurements, and radon ambient measurements. As with Fernald, all external and internal organ-specific doses were annualized for each worker resulting in comparable dose measurement to Fernald (C. M. Milder et al., 2023). In Linde, with the assistance of radiation and chemical hazards assessment (Hickey et al., 1988), prior authors assigned IR and non-radiological substance exposure (Dupree et al., 1987). The original study had radiation hazard assessment informed by air radon, airborne uranium monitoring, surface contamination, urinalysis, and film badge results taken mostly during 1947 and 1948. Potential annual lung dose categories were <10 mSv, 10-100 mSv, and >100 mSv, but <1000 mSv. Mean weekly film badge results above or less than the minimum detectable level, a probable level of 0.1 mSv, established dichotomous external IR exposure. With extensive assessment and careful consideration of limited data, these categories were assigned in the time-varying setting (Dupree et al., 1987). We expanded upon exposure categorization for Linde by developing a combined, both three-category potential annual lung dose and dichotomous external IR exposure, IR variable with levels of "None", "Low/Moderate", and "High" exposure to IR for Linde workers. Because dose is also a function of duration of exposure, we created an annual cumulative exposure days variable where a

worker was at “Low/Moderate” or “High” IR exposure. Using the work history characterization by Hickey et al. (Hickey et al., 1988), we assigned IR exposure category and calculated annual cumulative exposure days for all workers of Linde where data was available, lagging exposure by 10 years.

Vital status ascertainment has been described in prior literature, Fernald and Linde followed individuals up through December 31st, 2017 and MCW through December 31st, 2019. Vital status for Fernald was originally through 1989 by Cragle et al, then updated as described by Milder et al. (Cragle et al., 1996; C. Milder et al., 2024). In the original study of Linde vital status was through 1979 and determined for each worker using primarily the Social Security Administration, with underlying cause of death coded the Eight Revision of the International Classification of Diseases. In both the recent studies of Fernald and MCW (C. Milder et al., 2024; C. M. Milder et al., 2023), and the retrieved updated vital statistics for Linde, vital status was primarily ascertained from the Social Security Administration Epidemiological Vital Status Service, the National death Index, and state mortality files. Of the total 1,551 Linde workers, 1,445 workers had confirmed and known causes of death. For any causes of death prior to 1979, when underlying causes of death became readily available, a trained nosologist had coded causes of death based on death certificates. Neurodegenerative-related mortality underlying cause of death was used and included outcomes of dementia, Alzheimer’s, Parkinson’s, and motor neuron diseases. Additional important covariates existent in the data include birth year, hourly vs salary pay, job title, co-exposure details, sex, and race.

Due to inherent differences in studying the present cohorts, extensive exposure data harmonization was necessary. Step 1 combined Fernald and Linde, and step 3 combined all three cohorts, with both steps involving the categorical form of IR exposure found in Linde. For both Fernald and MCW we created a similar 3-category IR exposure variable, however, it did not have the same definition because of inherent differences in the data. The new combined IR variable was made by collapsing the 10-year lagged, internal and external combined, brain-specific annual cumulative IR measurement. Values of 0 were assigned to the "None" category, below the median values assigned to "Low/Moderate", and above the median values set to the "High" category. Then, annual cumulative exposure days were calculated the same way as they were in Linde. This approach allowed us to have a relatively consistent exposure measurement across the three cohorts for step 1 and 3 analyses. Step 2 did not require any exposure harmonization as both Fernald and MCW had continuous 10-year lagged internal and external organ-specific IR dose. No data harmonization was necessary for the outcome of neurodegenerative-related mortality.

Across all cohorts there were only two co-exposures available and in common, silica dust and uranium dust, however, step 1 that includes Fernald and Linde shared additional co-exposures. Each co-exposure was evaluated for potential to be associated with neurodegenerative-related disease or brain cancer via literature review, with co-exposures of nitric acid and nitrogen dioxide [HNO3/NO2, (Chang et al., 2014; Peters et al., 2019)], silica dust (Rondeau, 2002; Rondeau et al., 2009), and uranium dust (Brugge & Buchner, 2011; Craft et al., 2004) being selected *a priori* for analysis of confounding and effect modification. For Fernald, co-exposure assignment was based

on previous work that developed a job exposure matrix that was developed through qualitative assessment and input from sparse industrial hygiene measurements (Anderson et al., 2012). Linde's assessment of co-exposures draws from the previously described assessment that evaluated radiological hazards (Hickey et al., 1988). MCW had less, however, more granular co-exposure measurement. Uranium and silica dusts were present at MCW (Eisenbud, 1975) and measured via breathing zone sampling for dust frequently during 1942-1952, resulting in worker-specific estimates that were recorded and available in dust monitoring worksheets. Job specific daily time-weighted average dust exposures were calculated for many of the workers during this specific time period in previous study of MCW (Ellis et al., 2018; Golden et al., 2022). However, neither Fernald nor Linde have this level of granular co-exposure measurement, and data for these co-exposures was not time-varying, limiting MCW co-exposure measurement to ever/never per worker. Without exact industrial hygiene measurements for the co-exposures in Fernald and Linde, but with time-varying ever/never status, a co-exposure days variable was developed for HNO3/NO2, silica dust, and uranium dust. Co-exposure days represents the total number of days, over a worker's entire tenure at Fernald or Linde, that they had the potential to be exposed to one of the co-exposures. This was used to develop a categorical assignment of HNO3/NO2, silica dust, and uranium dust co-exposure in a similar way to combined IR categorization. Those with no co-exposure days were assigned the "None" category, those with less than the median days were "Low" co-exposed, and those greater than the median co-exposure days were "High" co-exposed. To harmonize data for step 2 and 3, both including MCW, co-

exposure status for silica and uranium dusts was collapsed to ever/never for each worker.

First pay code, which is defined as a worker being paid hourly or salary, birth year, sex, and cohort were considered important for confounding adjustment. In this study first pay code is a measure of socioeconomic status but also a possible proxy for tobacco smoking (Sorensen et al., 2004). First pay code was not available for the Linde cohort, and only skill level at first job held was previously used (Dupree et al., 1987). However, because first pay code was heavily dependent on job title, we used univariate data imputation for first pay code for all but 2 individuals missing job title information. All of Linde's job titles had a match in the Fernald dataset, allowing us to use the SuperLearner R package to train a prediction model on Fernald job title data and predict first pay code for the Linde cohort (Polley et al., 2024). In updating Linde data, we added individuals that were not white males that had not been previously analyzed. The original cohort included 1,550 individuals, with the updated cohort having 1413 individuals. Reasons and number of individuals excluded are summarized in Figure B1. Birth year was considered for adjustment because of confounding temporal changes, sex because of many potential sex-specific differences, and cohort due to probable confounding differences across facilities.

Statistical Analysis

Person time for all cohorts began 30 days after date of hire and ended at date of death, age 95, date lost to follow-up, or December 31st, 2017, whichever came first. Descriptive analyses included frequencies of categorical variables and median and interquartile range for continuous variables, separated by both individual cohort and by

analysis steps 1, 2, and 3. A density plot of cumulative exposure years was created for both step 1 and step 3 data to visualize frequency of cumulative IR exposure. For a visual description of categorical combined IR and neurodegenerative-related mortality, a grouped bar chart was plotted for individual cohorts and all cohorts combined using step 3 data. Additionally, to explore cumulative brain dose by neurodegenerative-related mortality, a violin plot was developed for step 2 continuous IR data. Bivariate analyses differed by analysis steps but overall explored correlations between IR exposure, co-exposures, and neurodegenerative-related mortality. Step 1 employed only chi-square tests between categorical combined IR and the three multi-categorical co-exposures of HNO3/NO2, silica dust, and uranium dust and neurodegenerative-related mortality and these same co-exposure variables. Step 2 used Kruskal-Wallis tests between cumulative IR brain dose and co-exposures of ever/never silica and uranium dusts and chi-square tests between ever/never silica and uranium dusts and neurodegenerative-related mortality. Lastly, step 3 repeated all chi-square tests of Step 1 but with co-exposures of ever/never silica and uranium dusts.

As previously mentioned, steps 1, 2, and 3 were separated to maximize power for different parts of answering the overall research question. Across all steps of the primary analysis, Cox proportional hazards regression models were fit using attained age as the underlying timescale were employed, with the baseline model given below:

$$\log\big(\lambda(t|X)\big) = \log\big(\lambda 0(t)\big) + \beta_1 X_{IR} + \beta_2 X_{first\ pay\ code} + \beta_3 X_{birth\ year} + \beta_4 X_{cohort}$$

The expected log hazard at time *t* is defined by five terms. $\log\big(\lambda 0(t)\big)$ is the baseline hazard and is stratified by sex, and $\beta_1 X_{IR}$ is the term for ionizing radiation which varies based on step of the primary analysis. $\beta_2 X_{first\ pay\ code}$ represents the dichotomous first

pay code term, $\beta_3 X_{birth\ year}$ represents the continuous birth year term, and $\beta_4 X_{cohort}$ is the term for cohort. The baseline model and its interpretation varied from step to step due to two different measures of IR, however, the outcome for all steps was neurodegenerative-related mortality. Step 1 and 3 used the categorical combined IR variable that had the "None" category as the referent and additionally adjusted for annual cumulative IR exposure days. Step 2 simply used the continuous annual cumulative combined internal and external IR brain dose variable, hereafter referred to as total IR brain dose. Results for step 2 were expressed at 10 mGy of IR brain dose. Building from these baseline models for steps 1, 2, and 3 individual Cox models were run for evaluation of both confounding and effect modification for the given co-exposures in each step. Confounding was assessed via additional adjustment for the co-exposure. Qualitative comparison of the regression coefficients and hazard ratios (HRs) of the IR term in these individual models to the baseline model for a given step was used to evaluate presence of confounding (Lash et al., 2020). Effect modification was also assessed by building from the baseline model, including a product term between the IR term and a given co-exposure. The co-exposure category specific IR effect estimates of these models were compared to baseline and the p-value for the product term was appraised to detect evidence of effect modification (VanderWeele, 2012). In step 1 confounding and effect modification models used the three-category variables for HNO3/NO2, silica dust, and uranium dust co-exposure, in steps 2 and 3 ever/never status was used for silica dust and uranium dust co-exposure. 95% confidence intervals (CIs) were generated and reported as a measure of precision.

We generated meta-analytic estimates to assess the implications of pooling complex data together compared to other strategies of aggregating data. In order to perform qualitative comparison, we calculated meta-analytic estimates only for the cohorts used in the pooled analysis. We drew upon results from the most recent study of Fernald and MCW to obtain HRs and 95% CIs for those cohorts (C. Milder et al., 2024; C. M. Milder et al., 2023). To obtain updated Linde-specific overall neurodegenerative-related mortality results we isolated the cohort data from step 3 of our analysis and re-ran step 3 primary analysis models on Linde alone, using the high categorical IR result in meta-analytic estimate calculation. To have comparable estimates and variances across the 3 studies, we expressed findings of Fernald and MCW at 175 mGy. This number, converted from 17.5 rem/year assuming a dose weighting factor of 1, was previously reported as the likely mid-point for the potential annual lung dose of those in the high category of internal IR exposure in the previous study of Linde (Dupree et al., 1987). We used the Metafor R package to calculate an overall meta-analytic estimate (Viechtbauer, 2024). We fitted a random-effects model with the rma function to allow the exposure-response to differ by cohort. The overall estimate of the meta-analysis was then qualitatively compared to the overall findings of our Step 3 pooled primary analysis with special consideration of different direction or significance of the effect. In a sensitivity analysis to better understand the relationship between continuous total IR and neurodegenerative-related mortality we fitted a natural cubic spline with 3 degrees of freedom to total IR brain dose in the step 2 baseline model. We performed another sensitivity analysis to better understand the direction and magnitude of potential misclassification of IR when the total IR brain dose is collapsed

down into 3 categories. To do this we combined only Fernald and MCW and repeated the same step 3 primary analysis models in the absence of the likely less reliable categorical combined IR data of Linde. The results of these sensitivity analysis models were then qualitatively compared to step 3 model results to ascertain the potential impact of exposure misclassification. All primary analysis Cox models had the proportional hazards assumption tested using the coxph function in the R Survival Package (Therneau & Grambsch, 2024). All statistical tests used an alpha level of 0.05. Data management was done using SAS version 9.4 (*SAS Software 9.4*, 2024) and statistical data analyses were performed using R Statistical Software Version 4.3.2 (R Core Team, 2024).

Results

Descriptive Statistics

When using Fernald job title data to predict first pay code for the Linde cohort, the area under the curve (AUC) across 5 different seeds was consistently > 0.95. Descriptive analysis results for all separate cohorts are summarized in Table 3.1, and descriptive analysis results for separate primary analysis steps 1, 2, and 3 are summarized in Appendix Table B1. The combined step 3 primary analysis had a total of 437,150 person-years across 10,330 workers. Across the cohorts, most workers were white (Fernald: 85.1%, Linde: 79.9%, MCW: 100%) males (Fernald: 96.3%, Linde: 96.7%, MCW: 100%) who were paid hourly (Fernald: 59.6%, Linde: 69.5%, MCW: 82.6%) and deceased at end of follow-up (Fernald: 65.1%, Linde: 93.6%, MCW: 84.0%). Among the three cohorts, MCW had the highest proportion of neurodegenerative-related mortality within its cohort (Fernald: 3.3%, Linde: 5.4%, MCW:

Table 3.1. Demographic, exposure, outcome, and co-exposure characteristics for separate cohorts of Fernald, Linde, and MCW, from step 3, n = 10,330

Variable	Fernald	Linde	MCW
Categorical	**n (%)**	**n (%)**	**n (%)**
Sex			
Male	5450 (85.1)	1129 (79.9)	2514 (100.0)
Female	953 (14.9)	284 (20.1)	N/A
Race			
White	6164 (96.3)	1367 (96.7)	2514 (100.0)
Black	235 (3.8)	44 (3.1)	N/A
Other	4 (0.06)	2 (0.1)	N/A
First Pay Code			
Hourly	3814 (59.6)	982 (69.5)	2076 (82.6)
Salary	2589 (40.4)	431 (30.5)	438 (17.4)
Vital Status at End of Follow-Up			
Alive	2112 (33.0)	87 (6.2)	387 (15.4)
Dead	4171 (65.1)	1323 (93.6)	2113 (84.0)
Unconfirmed	120 (1.9)	3 (0.2)	14 (0.6)
Neurodegenerative-Related [a] Cause of Death			
No	6192 (96.7)	1337 (94.6)	2354 (93.6)
Yes	211 (3.3)	76 (5.4)	160 (6.4)
Ever Co-Exposed			
Silica Dust	2082 (32.5)	1013 (71.7)	1317 (52.4)
Uranium Dust	1015 (15.9)	1114 (78.8)	1855 (73.8)
IR Category at First Work Period			
None	563 (8.8)	431 (28.2)	92 (3.7)
Low/Moderate	2924 (45.7)	428 (28.0)	6 (0.2)
High	2910 (45.5)	670 (43.8)	2401 (96.1)
Continuous	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Birth Year	1929 (17)	1913 (16)	1922 (16.0)
Follow-Up (Years)	42.4 (22.3)	41.3 (27.2)	46.5 (25.1)
Age at Start of Follow-Up	28.3 (12.6)	30.9 (16.4)	28.4 (12.5)
Age at End of Follow-Up	74.4 (18.1)	75.1 (20.2)	77.0 (16.7)
Date of Termination (Year)	1966 (22.2)	1946 (1.8)	1958 (10.8)
Years Worked	5.7 (13.8)	0.7 (1.8)	4.1 (8.0)
Cumulative Exposure Years	5.0 (13.0)	1.0 (3.0)	4.0 (8.0)

[a] Neurodegenerative-related includes dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease.

Abbreviations: MCW: Mallinckrodt Chemical Works, N/A: not applicable, IQR: interquartile range, IR: ionizing radiation, mGy: milligray.

6.4%). In consideration of co-exposures, Linde had more co-exposure for both silica dust, 71.7%, and uranium dust, 78.8%, than either Fernald or MCW. At first job held, Linde had the highest proportion of workers in the "None" combined IR category (28.2%), Fernald had the most workers in the "Low/Moderate" combined IR category (45.7%), and MCW had the most in the "High" combined IR category (96.1%). Median

years of follow-up were comparable across cohorts, as was age at start of follow-up and age at end of follow-up. There were more considerable differences across cohorts for median birth year, years worked, and cumulative exposure years. Figure 3.1 is a violin plot that summarizes cumulative brain dose by neurodegenerative-related mortality for step 2 data, cumulative brain dose was comparable between those with neurodegenerative-related mortality and all other workers. Figure 3.2 is a density plot of cumulative exposure years for step 3 data showing a heavy right skew with vast majority of workers having fewer than 20 cumulative exposure years. Figure B2 is a panel figure that displays ionizing radiation category by neurodegenerative-related mortality across cohorts, in panel D as ionizing radiation category increases, so does the number of workers and subsequent number of neurodegenerative-related mortality

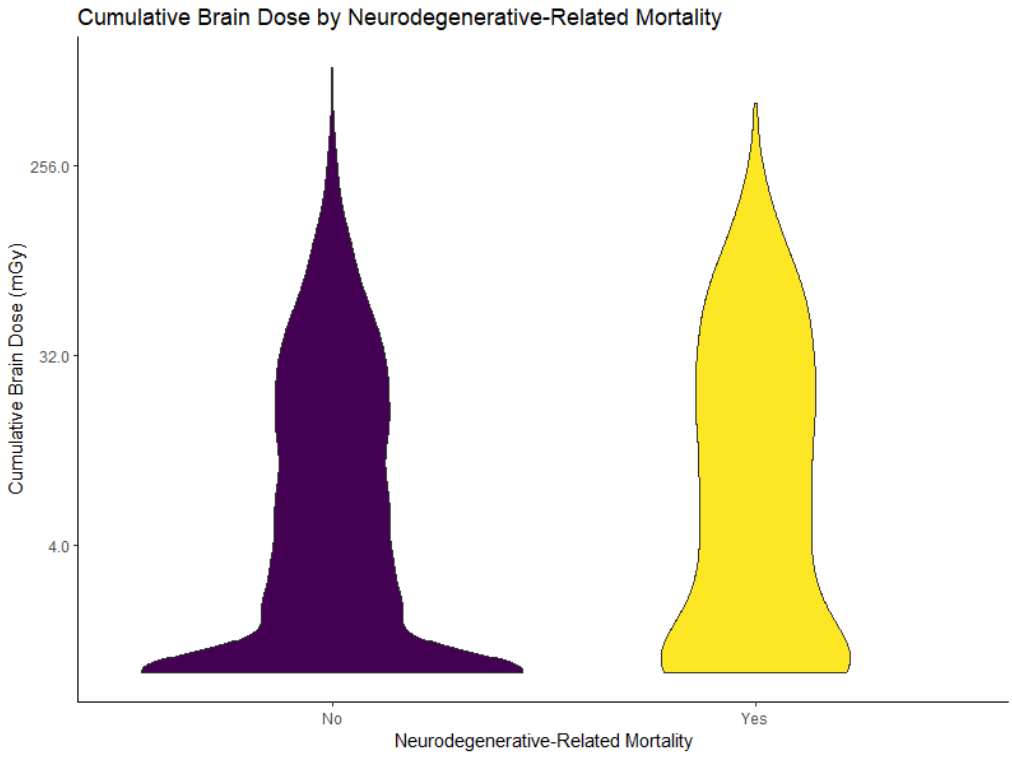

Figure 3.1. Step 2, 8,916 Fernald and MCW workers, cumulative brain dose stratified by neurodegenerative-related mortality for pooled. *Abbreviations:* mGy: milligray, MCW: Mallinckrodt Chemical Works.

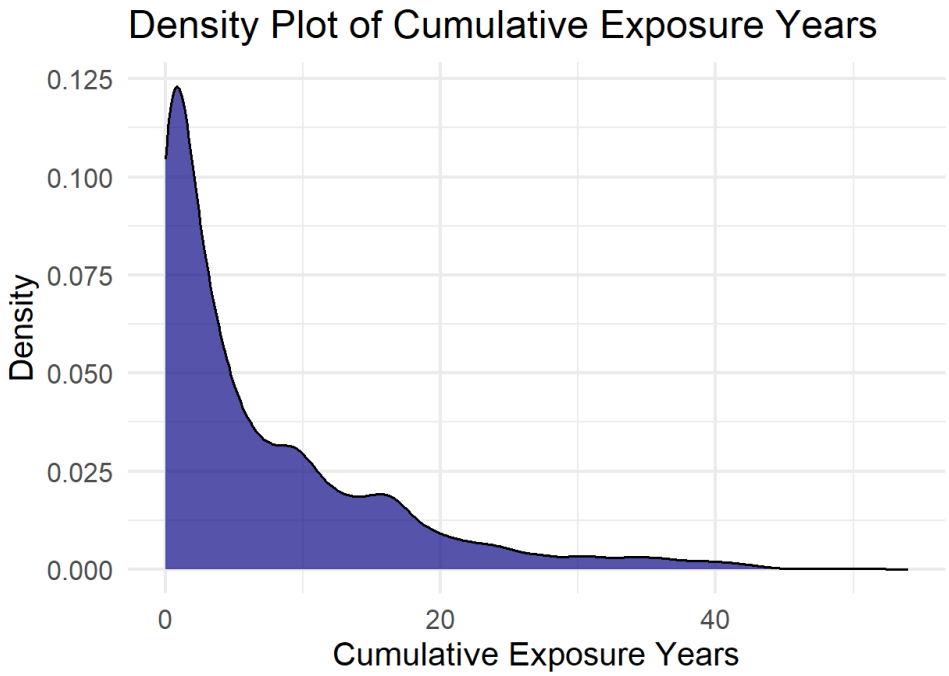

Figure 3.2. Step 3 cumulative exposure years density plot for pooled Fernald, Linde, and MCW cohorts, n = 10,330.

cases. Chi-square tests revealed significant differences between combined categorical IR and HNO3/NO2 (tested only in step 1), silica dust, and uranium dust (steps 1 and 3; all p-values < 0.0001). In step 2 the chi-square test for neurodegenerative-related mortality and silica dust was non-significant (p = 0.2788), however, all other chi-square tests between co-exposures and neurodegenerative-related mortality were significant (step 2 uranium dust p = 0.035, all other p-values < 0.0001). Kruskal-Wallis tests in step 2 revealed significant differences in cumulative IR brain dose and both co-exposures of silica and uranium dusts (p < 0.0001).

Primary Analysis

Table 3.2 shows overall, confounding, and effect modification results for pooled Fernald and Linde cohorts. Overall results indicated a significant protective effect amongst those exposed to low/moderate IR compared to no IR exposure (HR 0.64, 95% CI 0.46, 0.90). The overall effect of high categorical IR was closer to the null and

Table 3.2. Step 1 overall, confounding, and effect modification results for Fernald and Linde cohorts, n = 7,815.

Model	HR (95%CI) Overall and Adjustment for Co-Exposure	HR (95%CI) Without Co-Exposure	HR (95%CI) With Low Co-Exposure	HR (95% CI) With High Co-Exposure	Product Term p-value for High Co-Exposure
Overall					
Low/Moderate IR	0.64 (0.46, 0.90)	N/A	N/A	N/A	N/A
High IR	0.88 (0.62, 1.26)	N/A	N/A	N/A	N/A
HNO3/NO2					
Low/Moderate IR	0.68 (0.48, 0.97)	0.66 (0.43, 1.01)	0.62 (0.35, 1.88)	0.78 (0.28, 2.72)	0.5148
High IR	0.97 (0.68, 1.39)	1.00 (0.64, 1.56)	0.88 (0.43, 2.09)	1.19 (0.36, 3.43)	0.7580
Silica Dust					
Low/Moderate IR	0.66 (0.47, 0.93)	0.66 (0.45, 0.98)	0.46 (0.24, 1.86)	1.17 (0.30, 4.09)	0.3884
High IR	0.92 (0.64, 1.32)	0.84 (0.55, 1.29)	0.75 (0.34, 2.22)	1.78 (0.41, 5.03)	0.2354
Uranium Dust					
Low/Moderate IR	0.64 (0.45, 0.90)	0.61 (0.41, 0.90)	0.85 (0.32, 2.65)	0.71 (0.27, 2.49)	0.7877
High IR	0.87 (0.61, 1.24)	0.81 (0.54, 1.23)	0.88 (0.34, 2.58)	1.24 (0.40, 3.11)	0.4125

Note: All models had the outcome of neurodegenerative-related (dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease) mortality and additionally adjusted for first pay type, birth year, annual cumulative exposure days, cohort and stratified baseline hazard by sex. All models' proportional hazards assumptions were met.

Abbreviations: HR: hazard ratio, CI: confidence interval, IR: ionizing radiation, HNO3/NO2: nitric acid and nitrogen dioxide.

nonsignificant. In this analysis we found no evidence of confounding by any co-exposures. Effect modification results were largely null for all 3 co-exposures. Table B2 displays step 2 overall, confounding, and effect modification results for pooled Fernald and MCW cohorts. The overall model had null findings for neurodegenerative-related mortality at 10 mGy (HR 1.01, 95% CI 0.99, 1.03). There was no evidence of confounding by either silica dust or uranium dust. Effect modification results were also null, with some variation in the effect estimate for silica dust, however the p-value for interaction was nonsignificant (p = 0.3519). Table 3.3 summarizes overall, confounding, and effect modification results for all Fernald, Linde, and MCW pooled cohorts. The overall model indicated null results between neurodegenerative-related mortality and low/moderate categorical IR (HR 0.95, 95% CI 0.73, 1.24) and high categorical IR (HR 1.05, 95% CI 0.80, 1.37) compared to the none category. Similar to the previous analysis steps, we found no evidence of confounding by either silica dust or uranium dust. The effect of low/moderate IR across silica or uranium dust status did not change considerably, neither did the effect change for high IR category across uranium dust co-exposure status. We did find a nonsignificant increase in the effect of high IR amongst those who were co-exposed to silica dust (HR 1.26, 95% CI 0.65, 1.74) compared to the baseline result for high IR, however, the product term p-value was still nonsignificant (p = 0.1721). All Cox models' proportional hazards assumptions were met. Meta-analytic estimate results are summarized by a forest plot, Figure 3.3. The overall random effects model estimate suggested null effect (HR 0.95, 95% CI 0.75, 1.20). Compared to the step 3 primary analysis overall findings for high categorical IR, this meta-analytic result had improved precision with a consistent null finding. However, while both step 3

Table 3.3. Step 3 overall, confounding, and effect modification results for all Fernald, Linde, and MCW cohorts, n = 10,330.

Model	HR (95%CI) Overall and Adjustment for Co-Exposure	HR (95%CI) Without Co-Exposure	HR (95%CI) With Co-Exposure	Product Term p-value for Co-Exposure
Overall				
Low/Moderate IR	0.95 (0.73, 1.24)	N/A	N/A	N/A
High IR	1.05 (0.80, 1.37)	N/A	N/A	N/A
Silica Dust				
Low/Moderate IR	0.93 (0.71, 1.22)	0.90 (0.66, 1.23)	0.95 (0.58, 1.68)	0.8595
High IR	1.07 (0.81, 1.41)	0.91 (0.63, 1.30)	1.26 (0.65, 1.74)	0.1721
Uranium Dust				
Low/Moderate IR	0.95 (0.72, 1.27)	1.04 (0.72, 1.48)	0.89 (0.52, 1.79)	0.5698
High IR	1.05 (0.79, 1.41)	0.99 (0.67, 1.46)	1.08 (0.55, 1.90)	0.7435

Note: All models had the outcome of neurodegenerative-related (dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease) mortality and additionally adjusted for first pay type, birth year, annual cumulative exposure days, cohort and stratified baseline hazard by sex. All models' proportional hazards assumptions were met.
Abbreviations: HR: hazard ratio, CI: confidence interval, N/A, not applicable, mGy: milligray, IR: ionizing radiation.

primary analysis high categorical IR and overall meta-analytic estimates and confidence intervals indicated null findings, the meta-analytic findings swapped direction. If compared to step 3 primary analysis low/moderate categorical IR, findings were more consistent in directionality. Results of the sensitivity analysis for a dose-response plot to better understand the shape of the effect showed null results and can be found in Appendix Figure B2. Table B3 summarizes our sensitivity analysis of using step 3 data but with only pooled Fernald and MCW data. Results indicated an elevated, but still nonsignificant, risk of neurodegenerative-related mortality compared to overall results from step 3's primary analysis. This elevated effect was consistent across confounding results, however, there was still no evidence for confounding. For effect modification in this sensitivity analysis, product term p-values were consistent with those in step 3 primary analysis and the effects of low/moderate and high IR across status of silica and uranium dust co-exposure were comparable with step 3 primary analysis results.

Discussion

In our retrospective study we did not find that categorical low/moderate or high IR increased risk of neurodegenerative-related mortality, nor did continuous total IR brain dose in the pooling of cohorts with quantitative data. Across all three primary analysis steps we did not find evidence for confounding or effect modification by co-exposures, however effect modification results were likely hampered by sample size. In this more extreme, because categorical IR exposure, example of trade-offs for pooling data we found that the categorized data pooled analysis high categorical IR estimate was fairly comparable to the meta-analytic estimate with a small reduction in precision. This study contributes important insights into the data pooling goals of large multi-cohort studies

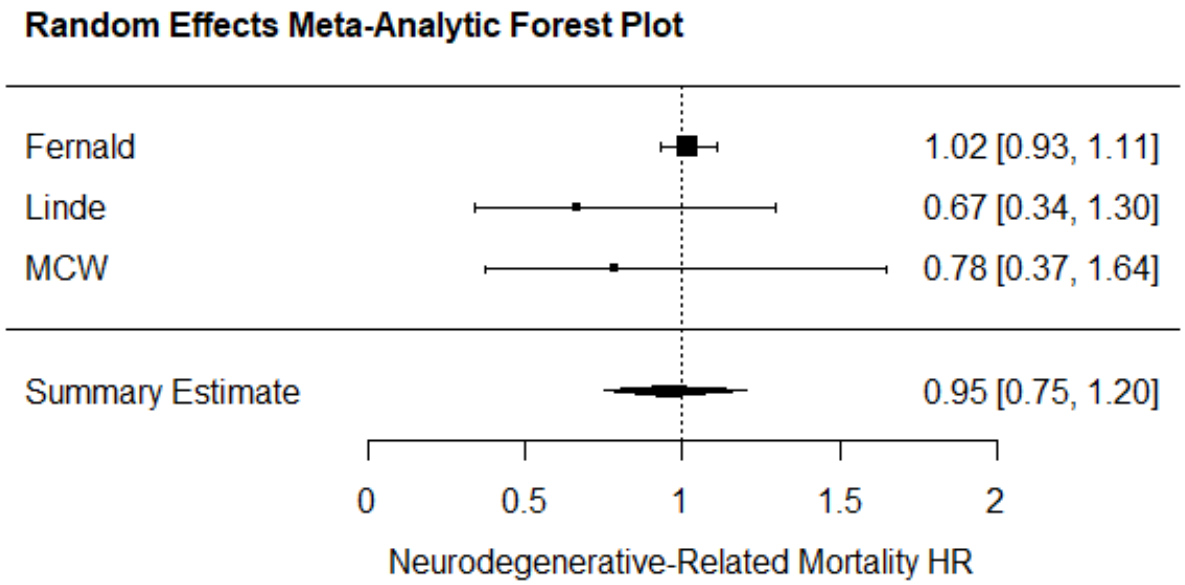

Figure 3.3. Random effects forest plot for Fernald, Linde, and MCW studies. *Abbreviations:* MCW: Mallinckrodt Chemical Works, RE: random effects, HR: Hazard Ratio.

such as the U.S. MPS, giving initial evidence on the trade-offs of pooling vs meta-analytic approaches in the exaggerated example of including a cohort with limited categorical IR measurement. Furthermore, it adds more understanding of the role that some select co-exposures may play in radiation worker cohorts.

Our pooled analysis and meta-analysis findings have varied consistency with previous large-scale studies of IR and neurodegenerative disease; however, comparison is made difficult by different outcome definitions. Perhaps the most comparable analysis to ours is the pooled cohort study by Golden et al. In their study pooling Fernald, MCW, Port Hope, and Middlesex cohorts they identified a significantly elevated SMR for Dementia and Alzheimer's disease among males [SMR 1.29, 95% CI 1.29, 1.04 (Golden et al., 2021)]. The elevated SMR appeared to be mostly driven by Fernald, however, in the most recent analysis of Fernald there were null results for combined Dementia, Alzheimer's, Parkinson's and motor neuron disease mortality risk at 100 mGy in a dose-response analysis [HR 1.19, 95% CI 0.67, 2.11 (C. Milder et al., 2024)]. Additionally, the previous study of MCW also reported null findings for neurodegenerative-related mortality at 100 mGy [HR 0.87, 95% CI 0.5, 1.33 (C. M. Milder et al., 2023)]. Dauer and colleagues produced a meta-analysis of Parkinson's disease recently of only U.S. MPS studies, having a more equivalent population to our study but including none of our selected cohorts. Their summary estimate indicated a significant excess relative risk (ERR) at 100 mGy brain dose for Parkinson's disease (ERR 0.17, 95% 0.05, 0.29). Of note, all but one of the included studies had elevated ERR but wide confidence intervals including the null, emphasizing the utility of the meta-analysis approach (Dauer et al., 2024). Another systematic review and meta-analysis by

Lopes et al. that investigated Parkinson's disease morbidity and mortality from IR exposure across 4 studies found increased ERR per 100 mGy [overall ERR 0.11, 95% CI 0.06, 0.16 (Lopes et al., 2022)] The last notable and relevant systematic review and meta-analysis by Srivastava and colleagues found more consistent evidence of increased relative risk (RR) of dementia-related, equivalent to neurodegenerative-related, mortality using a random effects inverse-variance model [RR 1.11, 95% CI 1.01, 1.22 (Srivastava et al., 2023)]. These three systematic reviews and meta-analyses contrast from our meta-analytic estimate that found null results, however, our estimate is limited due to sample size and is likely driven to null by our cohorts having nonsignificant findings for neurodegenerative-related mortality. One explanation for the potential difference would be confounding or effect modification by unmeasured co-exposures in other cohorts.

The discussion of performing pooled analyses in contrast to meta-analysis is not new. Broadly, data pooling is preferred in occupational studies as new research questions become possible such as effect modification by demographics, new analytic approaches can be brought forth with increased power like observing a wider range of exposure response, and general causal inference is strengthened, at the potential cost of overshadowing individual cohort effects, which can be addressed (Checkoway, 1991). Much prior work in radiation epidemiology has called for more pooling efforts to better understand a variety of research questions, from sociodemographic differences to investigating concerns of effect modification or confounding by environmental or occupational co-exposures (Blettner, 2015; Boice et al., 2022; Samet, 1997). The complete role of co-exposures still remains understudied and there exists support that

they may threaten validity via confounding or effect modification (C. M. Milder et al., 2023; Schubauer-Berigan et al., 2020). However, pooling efforts to evaluate confounding or effect modification via co-exposures are hindered by a lack of consistent co-exposure measurement, or, in the case of the present study when consistent co-exposure measurement exists other data such as the IR measurement is inconsistent. Compared to chapter 2's study of only Fernald Table 2's effect modification results had wide confidence intervals, and the addition of Linde's workers did not appreciably influence results. In an older study by Gilbert et al. that detailed pooling methods while comparing drawbacks of different approaches for 3 nuclear worker cohorts, they also found that very few IR exposure categories was far from optimal, however, a larger number of categories can still yield results close to continuous data (Gilbert et al., 1990). Given the observed challenges of categorical IR such as much widened confidence intervals and the previous study of having too few IR categories, we would not recommend the pooling of the Linde cohort in future IR focused analyses. In the context of this research and prior work, pooling cohorts remains a lofty but demanding goal and meta-analyses serve as a key, albeit limited, intermediate step to aggregating data.

Strengths of this study begin with having improved generalizability to modern workers and the general population due to lower doses, similar to other studies in the U.S. MPS (Boice et al., 2023; Boice Jr., Cohen, et al., 2022; Golden et al., 2021), than past study of acute high dose radiation events. Another strength is that we identified co-exposures *a priori* based on literature review. While the categorical form of IR introduced some challenges, it enabled us to pool together three uranium processing

cohorts that boasted a large sample size and many person-years of follow-up. Linde may have restricted the pooled analysis with this categorical IR measurement, but the cohort gave us the opportunity to investigate data pooling trade-offs in a more extensive circumstance by that same nature. Furthermore, our approach of calculating exposure days and co-exposure days allowed us to capture IR exposure more accurately even with only having categories of IR exposure and it enabled us to have a more granular measurement of co-exposures in step 1 analysis. Our study helps inform researchers and future study design on the implications of pooling highly diverse cohorts together. Our findings demonstrate uncertainty in the benefit of harmonizing data that is strongly different across cohorts. Precision was stronger in our meta-analytic approach, likely in how it handled cohort effect and variability between cohorts, yet it did not allow for assessment of co-exposure's potential role. Ultimately, given our uncertainty in estimates we would recommend future studies to replicate the comparisons made here but to exclude cohorts that are firmly divergent such as Linde when it comes to certain analyses. Such future research would continue to better the field's understanding of data aggregation techniques in more modest information loss circumstances where heterogeneity by different designs, methods, and measurement is less (Blettner et al., 1999).

This study is not without weaknesses. The greatest limitation of the present study is the extent to which data needed to be harmonized, particularly of IR exposure measurement. While Linde did bring more diversity into the pooled analysis, the collapsing of Fernald and MCW's continuous IR measurement cost a great deal of information. Because of the crude categorical IR measurement, we would expect a

moderate magnitude of misclassification of the multi-categorical IR exposure despite our effort to better capture IR exposure with annual cumulative exposure days, which could contribute to why some protective results were found. Our sensitivity analysis using only Fernald and MCW's categorical data would support that this bias influenced results towards the null, however, confidence intervals are overlapping. When comparing this sensitivity analysis to step 2 results with continuous IR measurement, a small bias away from the null is observed. Furthermore, the categorical form of IR introduced decreased power to answer our research questions, particularly of effect modification, in our categorical pooled analyses. Our neurodegenerative-related mortality outcome was based on death certificate data, which likely brought about nondifferential misclassification bias that would push results further towards the null (McGivern et al., 2017). While Linde helped introduce new information, the pooled analysis still had largely white male workers, impacting the generalizability of this study. Competing events, a form of selection bias, are likely present given that previous research supports elevated cardiovascular-related death in radiation worker cohorts as covered in the previous publication of Fernald (C. Milder et al., 2024). Given the time-dependent nature of neurodegenerative-related mortality, competing events would be a considerable factor. Residual confounding by socioeconomic status may exist due to only having hourly vs salary pay. Lastly, our meta-analysis portion of our study has several imitations. With only three studies, there is a great limit to statistical power, the impact of individual studies is great, and the heterogeneity and CI calculation is likely deficient. Additionally, because of the inherent difference in the individual analysis of Linde compared to Fernald and MCW the interpretation of the meta-analytic estimate is

limited, despite our efforts at standardizing the effect across cohorts. However, the meta-analytic estimate was not intended to be interpreted alone, only as contrast to the comparable high categorical IR pooled analysis finding.

In this study we evaluated the implications of data pooling of Fernald, Linde, and MCW cohorts to investigate the association between IR exposure and neurodegenerative-related mortality as well as the potential for confounding or effect modification by co-exposures. We did not observe an increased risk of neurodegenerative-related mortality from categories of IR exposure, nor did we find evidence of confounding or effect modification by HNO3/NO2, silica dust, or uranium dust. Our findings underscore the potential trade-offs inherent in pooling highly heterogeneous data with the overall goal of trying to increase sample size to understand the role of co-exposures. The Linde cohort had extensive co-exposure information but introduced categorical IR exposure measurement which likely brought about misclassification bias attenuating potential associations in baseline models as well as co-exposure models. Our meta-analytic comparison provided additional perspective that was representative of overall IR results but could not assist in capturing co-exposure function. Our research highlights the need for a balanced approach in data harmonization and shows the value in both pooled and meta-analytic frameworks in occupational radiation epidemiology. More investigations into the role of co-exposures are warranted in individual studies so that systematic reviews and meta-analyses can account for these factors. Future studies will likely benefit from pooling cohorts with more consistent data, while also considering present co-exposures, to better understand neurodegenerative-related risks with chronic low-dose IR exposure.

CHAPTER 4: ASSESSING SELECTION MECHANSIMS IN THE RELATIONSHIP OF IONIZING RADIATION AND NEURODEGENERATIVE-RELATED MORTALITY AMONG URANIUM PROCESSING WORKERS

Introduction

Ionizing radiation is an exposure common in day-to-day life between environmental and medical sources (US EPA, 2015). Health risks of acute high doses of IR are well understood (National Research Council (US) Board on Radiation Effects Research, 1998), however, the long-term effects of chronic low-dose exposure remain an area of less certainty, particularly for those who are occupationally exposed. Workers in industries such as uranium processing, nuclear power, and military operations experience prolonged low-dose IR exposure that is different from both high dose events and the general population's routine exposure (Boice et al., 2022). Recognizing this, large scale multi-cohort studies such as the U.S. Million Person Study (MPS) have been established to better investigate the health outcomes of protracted low dose occupational IR exposure. Some recent findings suggest an association between chronic low dose IR and neurodegenerative diseases like Parkinson's disease, though results remain inconsistent (Azizova et al., 2020; Boice Jr., Cohen, et al., 2022; Dauer et al., 2024; C. M. Milder et al., 2023; Pasqual et al., 2021; Srivastava et al., 2023). With neurodegenerative diseases affecting millions in the U.S. and placing significant burden on healthcare systems and caregivers (*Neurodegenerative Diseases*, 2022; Rushford & Harvey, 2016), understanding potential occupational contributors is increasingly important. However, studying occupational cohorts present distinct methodological challenges.

Traditionally selection mechanisms are primarily thought of as differential loss to follow up in occupational cohort studies (Hernán et al., 2004), the design of much of occupational radiation epidemiology research. However, occupationally IR exposed workers in many cohorts of the U.S. MPS do not experience substantial loss to follow-up (Boice Jr., Cohen, et al., 2022; C. Milder et al., 2024; C. M. Milder et al., 2023). Other more relevant and concerning forms of selection mechanisms would be the healthy worker survivor effect (HWSE) and competing events. HWSE has been acknowledged in occupational epidemiology for a considerable time and can be explained in occupational studies as unhealthy individuals tend to depart work earlier and accrue less exposure than their healthier coworkers (Buckley et al., 2015). The impact of HWSE has been noted to be particularly strong in previous study of radiation workers, calling for further study to understand the confounding role employment duration may play in occupational radiation epidemiology (Baillargeon & Wilkinson, 1999).

Competing events, are a form of selection bias that occur when the primary outcome of interest is precluded by the occurrence of the competing outcome which may be critical when considering the latency of IR and the time for neurodegenerative-related disease development (Mansournia et al., 2022). Underutilized causal inference approaches have been available for an extensive time to help address these biases (Robins, 1986). Previous research has shown considerable change in estimates from applying these evolving methods. One notable example was when risk was observed to be higher than originally thought when the HWSE was controlled for in a study of radon and lung cancer among Colorado Plateau uranium miners (Keil et al., 2015).

The primary goal of this research is to estimate the potential impact of a hypothetical intervention aimed at mitigating occupational IR exposure on the risk of neurodegenerative-related mortality, while addressing issues of HWSE and competing events. To meet this end we apply the parametric g-formula, an estimation approach from the causal inference literature that extends standardization to account for time-varying challenges (Keil et al., 2014) such as IR exposure and employment duration in the Fernald cohort of the U.S. MPS (C. Milder et al., 2024). Fernald Feed materials Plant was a Department of Energy uranium processing facility primarily producing high-purity uranium metal (Silver et al., 2013). By simulating an intervention scenario where IR exposure is reduced earlier in a worker's employment, we aim to evaluate how the change could influence neurodegenerative mortality risk while addressing the potential for HWSE and competing events. Our study builds upon prior occupational radiation epidemiology research to assess potential threats to validity in the field and to possibly offer alternative insights into inconsistencies for IR and neurodegenerative-related disease findings.

Methods

Data Description

Data for the Fernald cohort was obtained in collaboration with Oak Ridge Institute for Science and Education Comprehensive Epidemiologic Data Resource (ORISE, *Comprehensive Epidemiologic Data Resource (CEDR)*, 2024). The present study operated under an IRB reliance agreement between Colorado State University and the Central Department of Energy Review Board, HSRD ID DOE000954. ORISE initially obtained employment, radiological exposure information, and vital status data on

Fernald employees from 1951 through 1989 in a study that assessed 4,014 white males (Cragle et al., 1996). Silver and colleagues built upon Cragle et al.'s mortality study to include a total of 6,409 workers and added on work history and vital status information through 2004 (Silver et al., 2013). A data sharing agreement was developed with the National Institute for Occupational Safety and Health and provided IR organ-specific doses, pay category of workers, and other occupational exposure data. This dataset of 6,403 Fernald workers who worked at least 30 days from 1951 through 1985 was then used by Milder et al. for the most recent mortality study of the cohort, extending follow-up through 2017 (C. Milder et al., 2024). The current study relies on cohort data used by Milder et al.

IR dosimetry for the Fernald cohort has been previously described (Anderson et al., 2012; C. Milder et al., 2024). Briefly, area and personal monitoring data was used to estimate 10-year lagged annual cumulative organ-specific doses from external and internal IR exposures. Internal dose was first calculated by Anderson and colleagues with positive uranium concentrations and chronic inhalation assumptions (Anderson et al., 2012), Milder et al. reevaluated the uranium dosimetry model and created yearly organ dose estimates from date of first uranium intake through follow-up of 2017 (C. Milder et al., 2024). Personal film badges and thermoluminiscent dosimetry measured external exposure to IR (Anderson et al., 2012), Milder et al. further developed external dosimetry by estimating cumulative annual absorbed dose to 15 organs and adding in dose received at prior workplaces (C. Milder et al., 2024).

Neurodegenerative-related mortality includes underlying cause of death for combined dementia, Alzheimer's, Parkinson's, and motor neuron disease outcomes.

This outcome data was retrieved from vital status ascertainment via the National Death Index, the Social Security Administration, and Pension Benefits, Inc. Death certificates used International Classification of Diseases revision at time of death, and where underlying causes of death were unavailable prior to 1979 a trained nosologist coded causes of death from death certificates. Vital status was initially established through 1989 by Cragle and colleagues, but later updated through December 31st, 2017, by Milder et al. with only 22 (0.36%) individuals without confirmed vital status (Cragle et al., 1996; C. Milder et al., 2024).

IR has continuously growing evidence of having an association with an increased risk of cardiovascular disease (CVD) mortality (Baselet et al., 2016; Boice Jr., Quinn, et al., 2022). Furthermore, the previous mortality study of the Fernald cohort found a significant increase in risk of CVD mortality at 100 mGy IR (HR 1.27, 95% CI 1.07-1.50; C. Milder et al., 2024). For these reasons we determined that CVD mortality may present as a considerable competing event that is also affected by exposure against our primary outcome of neurodegenerative-related mortality. CVD mortality data is also derived from underlying causes of death in the same way neurodegenerative-related mortality data was obtained. Other data of year of birth, sex, and first pay code were adjusted for to address potential confounding. Type of pay, hourly or salary and referred to as first pay code, at first job held is a measure of socioeconomic status. Birth year is important because of potential confounding birth cohort differences, and sex is also included as it can represent many driving sex-specific differences. Lastly, a work status variable was generated to indicate which years workers were actively employed.

Hypothetical Intervention

In order to test intervention scenarios for the parametric g-formula, we developed hypothetical interventions to mitigate IR exposure and estimate the intervention's effect on risk of neurodegenerative-related mortality. The purpose of these hypothetical interventions was to test certain numerical reduction's effect, assuming successful intervention, on risk of neurodegenerative-related mortality. We used this approach to emulate more realistic interventions that may have real-world applicability in the Fernald context where doses were already considered low at the time and dose limits may not have certain applicability. An interdisciplinary approach was considered necessary to develop the interventions for the Fernald cohort. Four total informational interviews with experts in ergonomics, industrial hygiene and health physics were conducted to facilitate discussion and idea generation for feasible hypothetical interventions given the historical context of the Fernald plant. These experts were primarily queried on potential intervention strategies that may have been effective. Each informational interview began with reviewing general Fernald plant operational history and safety details, including the type, sources, and levels of IR exposure present. Then a structured questionnaire, see Appendix Methods C1, written prior to each meeting was applied with a degree of flexibility, allowing discussion to meet the end goal of eliciting ideas on intervention strategies. Throughout this process the hierarchy of controls was brought to mind for the likely most effective intervention approaches (Castro & A.B. (Butch), 2003). When all qualitative information and ideas were collected they were combined with both historical knowledge of Fernald (Kent et al., 2017; Smith et al., 2014, 2016) and the radiation safety policy literature to draft hypothetical interventions (Frane & Bitterman, 2024).

Final intervention scenarios were designed to have a measurable impact on IR exposure for workers in the historical cohort, theoretically reducing risk of IR-related health outcomes.

We developed two dynamic hypothetical interventions that could achieve an aggressive and modest reduction to IR to apply within the parametric g-formula. The first is an engineering control, using containment devices around industrial operations processing uranium primarily designed to reduce airborne radioactive material. The primary source intended to be controlled for is the abundant preventable dust inhalation exposure from production of uranium metal products (Kent et al., 2017; Smith et al., 2014). Briefly the core processes targeted by this intervention would have started with uranium milling operations that can generate a considerable amount of dust. Impure materials were then dissolved in nitric acid to produce a crude product for solvent extraction purification. This product, uranyl nitrate solution, was then concentrated via evaporation and heated to uranium trioxide, “orange salt”. Uranium trioxide was then converted to uranium tetrafluoride, “green salt” (Smith et al., 2014), which was then blended with magnesium metal granules in a closed reduction pot and heated to produce uranium masses called “derbies”. Lastly these derbies were remelted in a vacuum induction furnace and poured into graphite molds to form ingots (Smith et al., 2016). The engineering control would primarily be containment devices around these dust producing and heating processes. This intervention aims for an aggressive 80% reduction in IR exposure for all workers during occupational tenure. While a higher reduction would be expected the practicality of containment device maintenance, overall compliance, other sources of IR existing, and scale of operations would be limiting

factors. Our second hypothetical intervention is broader and a blend of administrative control approaches. In the administrative controls hypothetical intervention we proposed worker rotation, hazards training, error management, and safety culture improvements. Worker rotation would present as a system of rotating workers out of high exposure categories to reduce individual doses with stronger training programs to ensure rotation does not result in a simple shifting of distribution of dose among workers. This worker rotation intervention would help prevent individual workers from accumulating particularly high doses of IR and co-exposures from working in one specific process for most of their tenure. Human factors and work design centered error management updates would further help reduce small-scale errors that unnecessarily increase exposure. More specifically, this would take the form of more proactive measures such as reporting near misses or minor exposure events that could then be intervened upon in future safety measures in a continual cycle of a self-improving safety system. Additionally, here work design changes would lead to increasing distance and decreasing time with respect to IR sources. Lastly, safety culture improvements could yield increased uptake of all existing and hypothetically proposed interventions, further reducing IR exposure. Such an intervention has a modest 20% reduction in IR exposure for all workers during occupational tenure, but only after the first 5 years of startup in consideration of administrative start-up time.

Statistical Analysis

Person time was calculated in the same way it was by Milder and colleagues, beginning 30 days after date of hire and ending at date of death, age 95, date lost to follow-up, or December 31st, 2017, whichever was first (C. Milder et al., 2024).

Descriptive analyses included frequencies for categorical variables and median and interquartile range for skewed continuous variables. Cumulative combined external and internal IR brain and heart doses, referred to as cumulative brain or heart dose, were visualized by plotting dose on a violin plot grouped by mortality of that outcome or not. Kaplan-Meier survival curves were generated for duration of employment, using time worked in years as the timescale, stratified by median dichotomized cumulative IR brain to visualize how employment duration may vary by IR brain dose (Therneau & Grambsch, 2024).

We employed the parametric g-formula to estimate the effect of IR exposure interventions on the risk of neurodegenerative-related mortality. We estimated this risk under six scenarios including three interventions, “natural course”, “engineering control”, and “administrative control”, and for each intervention adopting two approaches of modeling CVD mortality or not modeling CVD mortality. The parametric g-formula and its application has been described in detail in prior literature. In brief the method is a generalization of standardization for time-varying settings of exposures and covariates and requires the assumptions of positivity (every individual has a non-zero probability of receiving exposure), conditional exchangeability (no unmeasured confounders at all time points), counterfactual consistency, (every individual’s counterfactual outcome under their observed exposure history is equal to their observed outcome), and correct model specification (Neophytou et al., 2016; Robins, 1986; Taubman et al., 2009). Risk of neurodegenerative-related mortality under each intervention is estimated as a weighted sum, or integral, of the probability of neurodegenerative-related mortality,

conditional on exposure and covariate histories across all possible IR exposure and covariate trajectories.

Our analysis applies parametric models for neurodegenerative-related mortality conditional on prior time-varying IR dose and covariate histories and stagnant baseline covariates, as well as models for all time-varying variables, in this case being IR exposures and work status. Neurodegenerative mortality was assumed to be a survival outcome specification, meaning that the estimated probability of the event of interest occurring over time was modeled while accounting for time-event data and relied on a pooled logistic model. Parametric models were specified for neurodegenerative-related mortality, CVD mortality in the approach that considered competing events, work status, annual brain dose, and annual heart dose. All models had predictors of row, a measure of time with a natural cubic spline of 3 degrees of freedom, and baseline birthyear, year at hire, sex, and first pay code. Time-varying work status was additionally predicted by previous year's work status, 10-year lagged cumulative average annual brain dose, and 10-year lagged cumulative average annual heart dose. Annual brain and heart doses also were predicted by prior year's respective doses. The neurodegenerative-related mortality model and CVD mortality competing event model were likewise also predicted by 10-year lagged cumulative average annual brain and heart doses respectively and prior year's work status. In consideration of IR exposure and potential adverse neurodegenerative effects, dose was lagged by 10 years. 10-year lagged cumulative average brain and heart dose variables were calculated via a built-in "lagavg" function, and other lagged variables via the "lagged" function, both part of the gfoRmula R package (McGrath et al., 2020). In regard to our competing event approach, when CVD

mortality is not modeled in the approach without competing events considered, observed cases of CVD mortality in the data are treated as uninformative right-censored observations. However, when CVD mortality is modeled in our competing event considering approach, a risk for it is predicted which assists in estimation of the overall cumulative incidence of neurodegenerative-related mortality (Cole et al., 2013; McGrath et al., 2020). A Monte Carlo estimator estimates the overall risk by averaging over many possible exposure and covariate histories. This is accomplished by synthetic sampling, also known as pseudo-sampling, based on the observed dataset population. In the present analysis we used synthetic sampling for a sample of 10,000. Workers with exactly 10 observations/years of follow-up presented technical issues with lagging methods and therefore were dropped from analysis reducing the sample size from 6,403 to 6,146, a 4% reduction without loss of any neurodegenerative-related mortality cases. Under no intervention the simulation used values predicted via these models for a natural course. Engineering control intervention reduced annual brain and heart dose by 80% for all observations of a worker's tenure, and administrative control intervention attenuated annual brain and heart dose by 20% for all observations of a worker's tenure after 1956, assuming a 5-year delay in adaptation and participation of administrative controls. 95% confidence intervals for overall parametric g-formula estimates were obtained via bootstrapping, using 1,000 bootstrap samples. Cumulative incidence estimates for each year of follow-up were used to create cumulative incidence curves, for each intervention and competing event modeling circumstance. Cumulative incidence for overall observed and simulated data under no intervention were also plotted and compared to assess model prediction abilities. All statistical tests used an

alpha level of 0.05. Data management was completed using SAS version 9.4 (*SAS Software 9.4*, 2024) and all statistical data analyses were executed using R Statistical Software Version 4.4.1 using the gfoRmula package (McGrath et al., 2020; R Core Team, 2024).

Results

Descriptive Analysis

Descriptive results for the demographic, exposure, outcome, and competing event data are detailed in Table 4.1. Of the 6,146 Fernald uranium processing workers,

Table 4.1. Demographic, exposure, outcome, and competing event characteristics for 6,143 Fernald uranium processing workers.

Variable	**Measure**
Categorical	**n (%)**
Sex	
Male	5243 (85.31)
Female	903 (14.69)
Race	
White	5918 (96.29)
Black	224 (3.64%)
Other	4 (0.07)
First Pay Code	
Hourly	3653 (59.44)
Salary	2493 (40.56)
Vital Status at End of Follow-Up	
Alive	2112 (34.36)
Dead	4012 (65.28)
Unconfirmed	22 (0.36)
Neurodegenerative-Related [a] Cause of Death	
No	5935 (96.57)
Yes	211 (3.43)
Cardiovascular Disease Cause of Death	
No	4890 (79.56)
Yes	1256 (20.44)
Continuous	**Median, IQR**
Birthyear	1929 (17)
Age at Hire	28 (12)
Age at End of Follow-Up	75 (17)
Year of Hire	1955 (7.24)
Year of Termination	1965 (19.21)
Years Worked	5.52 (14.02)
Follow-Up Years	43.45 (22.0)
Cumulative IR Brain Dose (mGy)	1.27 (10.05)
Cumulative IR Heart Dose (mGy)	1.43 (11.19)

[a] Neurodegenerative-related includes dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease.
Abbreviations: IQR: interquartile range, IR: ionizing radiation, mGy: milligray.

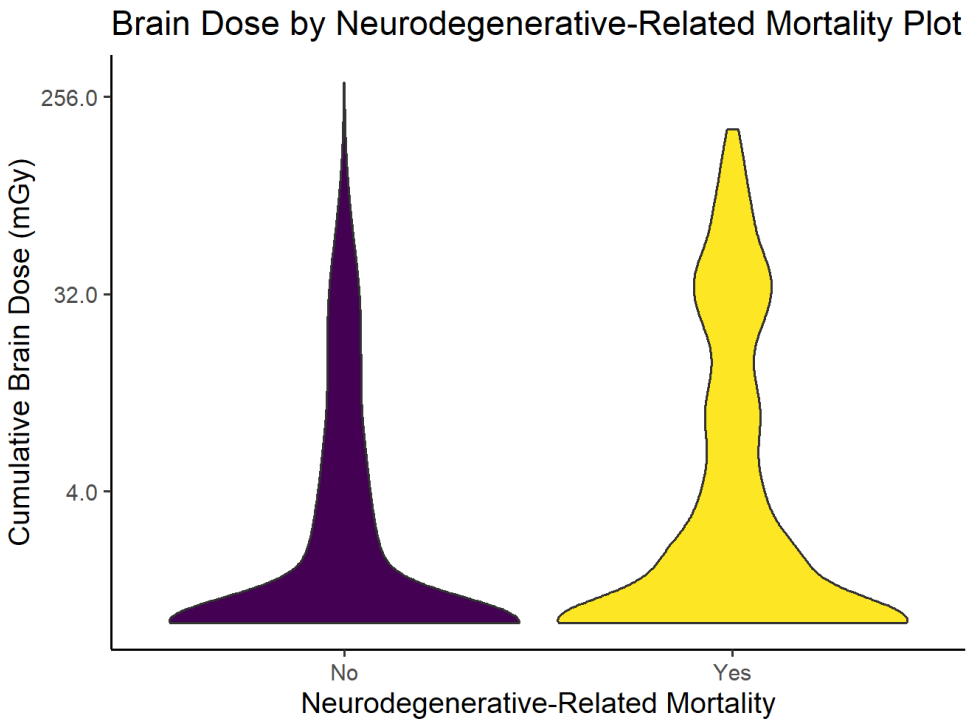

Figure 4.1. Cumulative brain dose stratified by neurodegenerative-related mortality for 6,143 Fernald uranium processing workers. Neurodegenerative-related includes dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease. *Abbreviations:* mGy: milligray.

the majority were white (96.29%) males (85.31%) who were paid hourly (59.44%) and deceased at end of follow-up (65.28%). There were 211 (3.43%) cases of neurodegenerative-related mortality and 1,256 (20.44%) cases of CVD mortality. The median year of hire was early at 1955 (IQR 7.24), with a median year of termination of 1965 (IQR 19.21), and median years worked were 5.52 (IQR 14.02). Cumulative IR brain dose was 1.27 mGy (IQR 10.05) and cumulative IR heart dose was comparable at 1.43 mGy (IQR 11.19). Figure 4.1 illustrates cumulative brain dose by neurodegenerative-related mortality, showing that those who suffered neurodegenerative-related mortality generally had higher cumulative brain dose. Similarly, Figure C1 shows a likewise trend for cumulative heart dose by CVD mortality. Lastly, our Kaplan-Meier survival curves for employment duration stratified by median

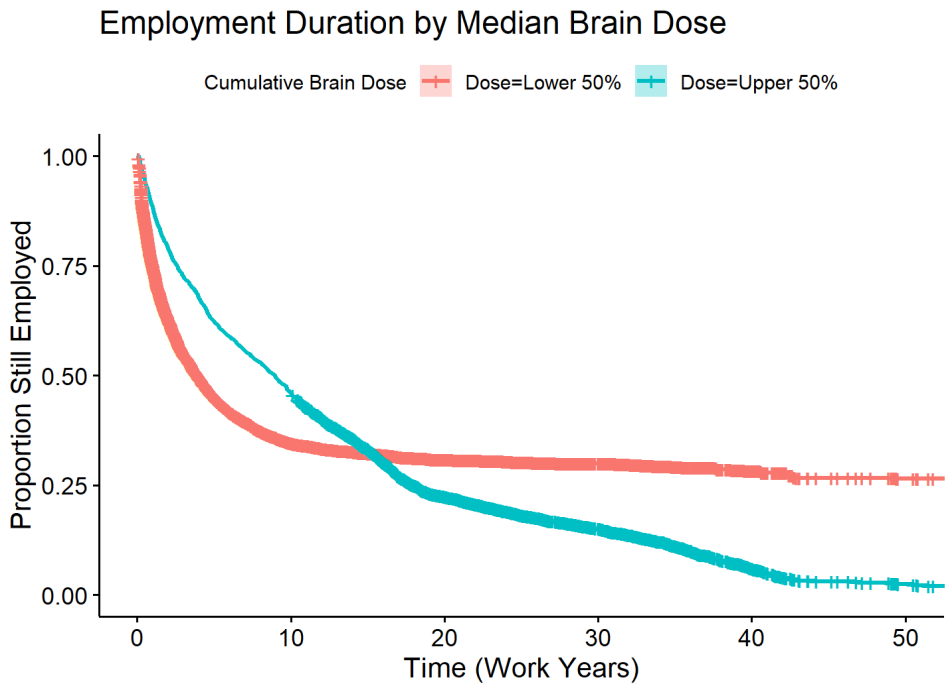

Figure 4.2. Kaplan-Meier survival curves showing work tenure in years of 6,143 Fernald uranium processing workers and proportion still employed across different work tenure lengths, stratified by dichotomized, at the median, cumulative brain dose.

cumulative IR brain dose are shown in Figure 4.2. These curves indicate that those in the upper half of cumulative IR brain dose initially had a higher proportion of workers employed until approximately 15 years of tenure, after which these workers began to be less likely to remain employed compared to those in the lower half of cumulative IR brain dose.

Primary Analysis

Observed vs predicted cumulative incidence of neurodegenerative-related mortality among the 6,146 Fernald uranium processing workers, with modeling for competing events is shown in Figure 4.3. The same results are shown in the scenario of not modeling for competing events in Figure C2. Cumulative incidence differed between both figures, but each had an exponential shape. When modeling for competing events we found that cumulative incidence of neurodegenerative-related mortality was

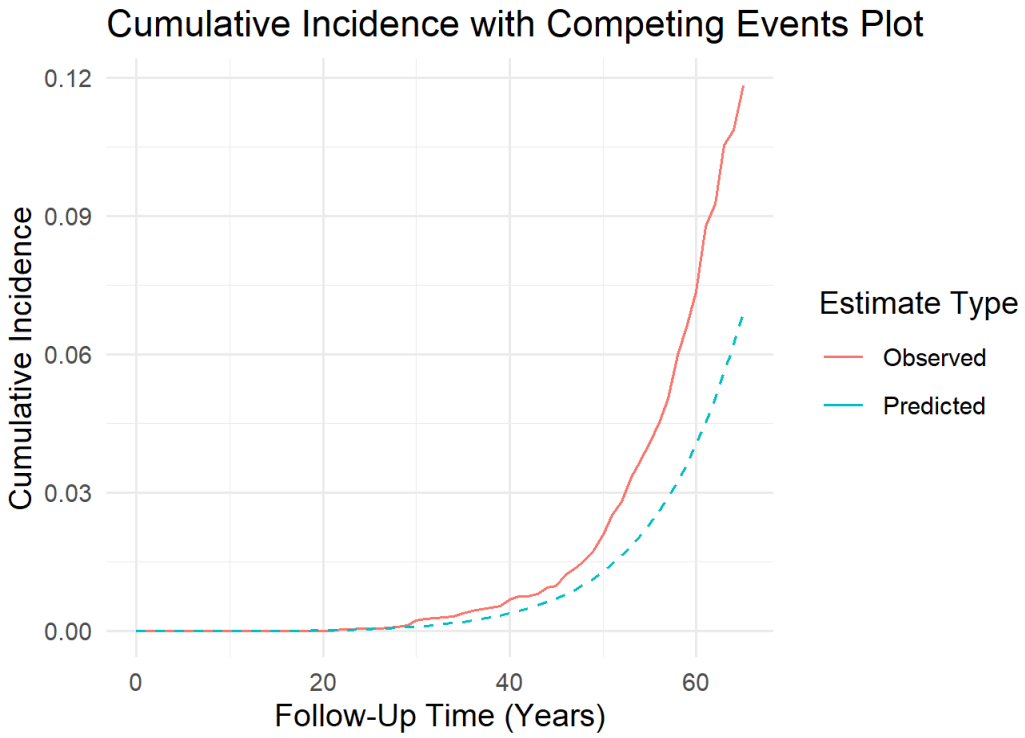

Figure 4.3. Cumulative incidence of neurodegenerative-related mortality over time, expressed in work years or row for 6,143 Fernald uranium processing workers. Results represent parametric g-formula modeling for competing events output based on 1,000 bootstrap samples.

attenuated compared to the observed data, indicating evidence of CVD operating as a competing event of the relationship between IR and neurodegenerative-related mortality. The larger discrepancy between predicted and observed in Figure 4.3 indicated potential overestimation of risk of CVD leading to lower risk of neurodegenerative-related mortality. Cumulative incidence plots with interventions, with modeling for competing events are shown in Figure 4.4 and without competing events found in Figure C3. Both plots are indicative of largely null intervention effects as cumulative incidence did not change considerably by different hypothetical intervention scenarios. Table 4.2 displays the simulated cumulative incidence under natural course and both interventions, risk ratios (RR) compared to natural course, risk differences (RD) compared to natural course, and proportion of person years that were intervened

Table 4.2. Parametric g-formula survival results for neurodegenerative-related mortality with and without competing event modeling under several interventions for 6,143 Fernald uranium processing workers.

Intervention	Cumulative Incidence (%)	RR (95% CI)	RD (95% CI)	% Person Time Intervened Upon
Without Competing Events Modeling				
Natural Course [a]	16.99			
Engineering Control [b]	17.43	1.03 (0.99, 1.09)	0.004 (-0.002, 0.012)	85.65
Administrative Control [c]	17.14	1.01 (1.00, 1.03)	0.001 (-0.0006, 0.004)	73.88
With Competing Events Modeling				
Natural Course [a]	6.87			
Engineering Control [b]	7.14	1.04 (0.99, 1.11)	0.003 (-0.0006, 0.006)	85.59
Administrative Control [c]	6.96	1.01 (1.00, 1.04)	0.0009 (-0.0002, 0.002)	72.87

Note: see manuscript for full model specification details. All results represent parametric g-formula using 10,000 synthetic samples and 1,000 bootstrap samples. Interventions were as follows:
[a] Simulated natural course scenario, where the g-formula simulates what was observed under no intervention using exposure and covariate histories predicted with the given dataset.
[b] Simulated engineering control intervention scenario, where all absorbed dose during working tenure is reduced by 80%.
[c] Simulated administrative control intervention scenario, where all absorbed dose during working tenure and after the year 1956 is reduced by 20%.
Abbreviations: RR: risk ratio, CI: confidence interval, RD: risk difference.

upon for both interventions. Natural course cumulative incidence without modeling competing events (16.99%) was considerably higher than natural course cumulative incidence when modeling for competing events (6.87%), further indicating CVD's competing event role. In both scenarios interventions non-significantly slightly increased cumulative incidence, with RR and RD confidence intervals always including the null.

Discussion

In our application of the parametric g-formula in a cohort of uranium processing workers we did find evidence of significant bias contributions from CVD as a competing event for the relationship between IR and neurodegenerative-related mortality. While we

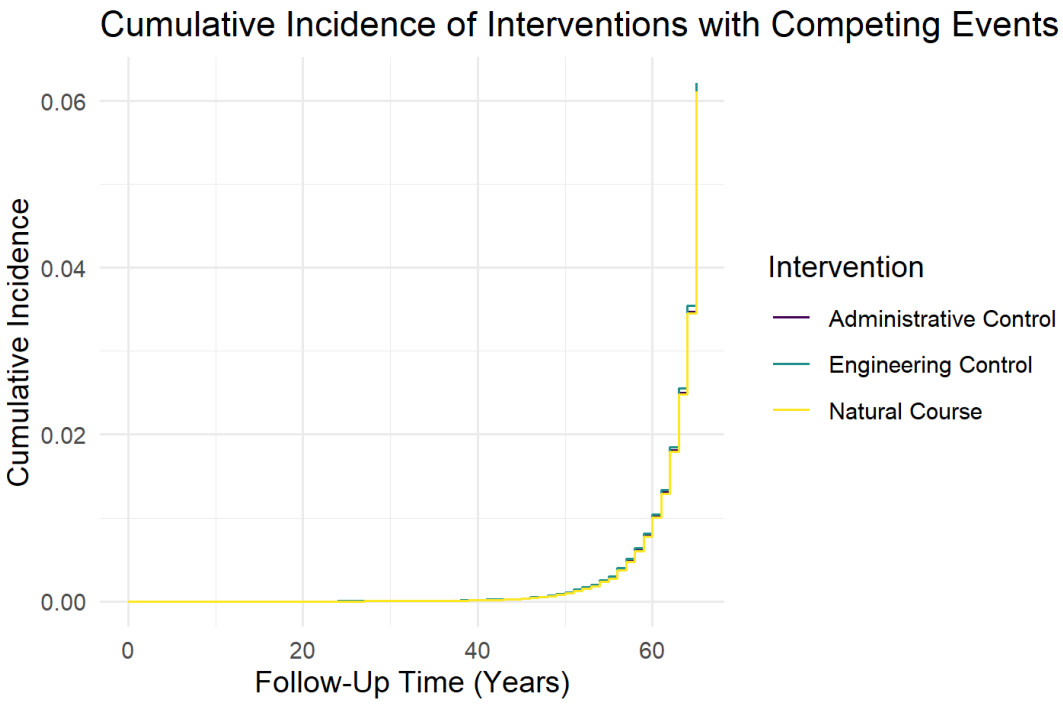

Figure 4.4. Cumulative incidence of neurodegenerative-related mortality over time by intervention group, expressed in work years/row for 6,143 Fernald uranium processing workers. Results represent parametric g-formula modeling for competing events output based on 1,000 bootstrap samples. Interventions are as follows: simulated natural course scenario, where the g-formula simulates what was observed under no intervention using exposure and covariate histories predicted with the given dataset; simulated engineering control intervention scenario, where all absorbed dose during working tenure is reduced by 80%; simulated administrative control intervention scenario, where all absorbed dose during working tenure and after the year 1956 is reduced by 20%.

did find evidence of the potential for HWSE in survival curves of employment duration, hypothetical intervention scenarios did not appreciably change cumulative incidence of neurodegenerative-related mortality. This result would indicate that for the relationship of interest HWSE may not be a key factor. These results add to the growing literature that applies the parametric g-formula to evaluate the impact of occupational exposures and to assess nuances such as HWSE and competing events. In occupational radiation epidemiology our relatively novel approach assesses the potential for bias by two distinct sources that in an effort to contribute to understanding the inconsistent

association found between occupational IR and neurodegenerative-related mortality across the literature.

Uranium mining, milling, and processing are distinct operations, however routes of exposure and sources of exposure may have some overlap aiding literature comparison (Boice Jr et al., 2008; *Conventional Uranium Mills*, 2021; US EPA, 2018). The most relatable example to our findings for HWSE would be the study of HWSE in the 4,124 worker Colorado Plateau Uranium Miner Cohort. This study by Keil et al. examined radon exposure, a form of IR, and lung cancer deaths using a similar approach of hypothetical interventions applied with g-estimation of structural nested models. In their cohort study they estimate the time ratio, relative change in median remaining survival time. The time ratio was made to compare models that adjust for HWSE, by adjusting for time-varying confounding of current and past employment status and history of prior exposure, and do not adjust for HWSE. They found a 39% difference between adjustment and non-adjustment, and while not directly comparable, it is indicative of much stronger HWSE among uranium miners, to our negligible differences between natural course and intervention scenarios in uranium processing (Keil et al., 2015). Another more recent study, that of 93,918 South Korean medical radiation workers, used a similar approach by employing g-estimation that could adjust for prior radiation exposure and time-varying employment status. Similar to the Colorado Plateau Uranium miners, they observed a 51% higher risk for all deaths when comparing g-estimation HRs to a standard model (Lee et al., 2024). Within the U.S. MPS, previous study of healthy worker survivor effect among the 44,154 worker Hanford nuclear facility cohort examining all-cause standardized mortality ratios

according to length of employment also found strong evidence for HWSE. The survival advantage was particularly strong among those with tenure more than 30 years and hired before age 40 (Baillargeon & Wilkinson, 1999). Due to the sparsity of assessment of HWSE in occupational radiation epidemiology, other studies that may have comparable findings to ours are lacking. These 3 studies' results contrast to our HWSE findings, possibly indicating that HWSE may be of greater concern for other health outcomes outside of neurodegenerative-related mortality as our survival curves in Figure 4.2 suggest it may still exist. It is possible that a true HWSE may be observed for more specific neurodegenerative disease outcomes, such as Parkinson's disease that could be considered to have the strongest literature support at this time (Azizova et al., 2020; Dauer et al., 2024). Furthermore, outcome misclassification may also contribute to obfuscation of a HWSE.

While some work has been done to investigate HWSE in radiation epidemiology, even less has been accomplished to assess the role of competing events outside of its use as a decision to treat tool in medical contexts (de Gonzalez et al., 2015; Hinnen et al., 2011; Ramin et al., 2021; Wu et al., 2021). Using the same Fernald cohort data, the previous mortality study of Fernald evaluated CVD and ischemic heart disease mortalities in two extreme assumptions of where 1) all employees who died of competing causes were not censored until end of follow-up and 2) those who died of competing causes would have died of CVD/ischemic heart disease on that same day anyways. Milder et al. highlighted how these different assumptions drastically changed the potential range of risk of these outcomes at 100 mGy IR (C. Milder et al., 2024). Often in previously mentioned and other study's application of the parametric g-formula

competing events models are fit for proper specification in their causal framework and to most accurately represent effect of interventions for public health implications (Cole et al., 2013; Edwards et al., 2014; Neophytou et al., 2016; Taubman et al., 2009). Other more theoretical literature provides details to the importance of competing event analysis, arguments for or against certain methods, and more examples of its utility in understanding etiologic questions with intervenable endpoints (Austin et al., 2016; Coemans et al., 2022; Lau et al., 2009; Mansournia et al., 2022). In our evaluation of competing events for neurodegenerative-related mortality we find that CVD mortality serves as a competing event, which may have public health implications. In the hypothetical scenario that an intervention, targeting something that does not also impact risk of neurodegenerative-related mortality, reduces risk of the CVD mortality competing event, then individuals would live longer and contribute more time at risk of neurodegenerative-related mortality. An example of implications related to radiation exposure is shown in prior literature, with one study of 14,800 U.S. based cervical cancer patients receiving radiotherapy. In this study competing events of death and second malignancies are modeled for, revealing how single site second malignancies were of significantly higher risk (Wu et al., 2021). Future studies that aim to understand how IR increases risk of neurodegenerative-related mortality or reduce that risk via interventions should consider modeling for competing events as Austin et al. emphasizes that conventional survival analysis methods may be inappropriate in the context of competing events (Austin et al., 2016). Furthermore, studies of neurodegenerative-related mortality should carefully consider how competing events

may impact generalizability to other populations that may not share the same risk factors for CVD as IR exposed workers.

Strengths of this study start with the relatively novel contribution to the occupational radiation epidemiology literature. The use of the parametric g-formula appropriately adjusts for time-varying confounders, addressing a key limitation to standard approaches in occupational radiation epidemiology where employment status and exposure levels can change over time. This method introduces more causal inference tools to the field, helping account for issues such as competing events or in relevant cases where HWSE may be of concern. Another strength of the parametric g-formula is that it is less prone to violations of positivity compared to methods such as inverse probability weights. Lastly, the parametric g-formula allows for direct estimation of absolute risk under hypothetical interventions that were specifically designed to have been feasible interventions. Objective, complete, individual-level, organ-specific IR exposure data is another strength of our study, allowing for reassurance of low exposure misclassification. The Fernald cohort also benefits from long follow-up with over 99% known causes of death, allowing for a more comprehensive assessment of long-term health outcomes such as neurodegenerative-related mortality.

The parametric g-formula has unique strengths but is not without limitation. The causal inference technique is more sensitive to the assumption of correct model specification, an assumption that is never fully testable (Keil & Richardson, 2017). Limitations of our data, such as a lack of smoking information which could be an unmeasured confounder, may contribute to model misspecification in our study. Furthermore, this would threaten the conditional exchangeability assumption behind the

causal inference method. Pay type was adjusted for both socioeconomic reasons and as a potential proxy for smoking data in regard to this concern (Sorensen et al., 2004). However, residual confounding could also exist from only having hourly vs salary pay type as a measure of socioeconomic status. A considerable compounding factor for the threat of this unmeasured confounding would be that the parametric g-formula requires numerous models that may further propagate biases over a long-follow up period (Neophytou et al., 2016). Another major limitation regarding the g-formula use would be the “g-null paradox” which describes that it may be impossible to correctly specify the model for the g-formula if the causal null hypothesis is true (Eisen A. et al., 2012). There exists stronger evidence across the literature behind neurodegenerative-related mortality risk from protracted low dose occupational IR (Dauer et al., 2024; Lopes et al., 2022; Srivastava et al., 2023). Lastly, as shown in Figure 3 predicted vs observed curves indicate that we may be overestimating competing event risk and therefor the true competing event role may not be as strong as our evidence suggests. Other cohort specific limitations would be generalizability, outcome misclassification, weaknesses in our hypothetical interventions, and sample size as having only 6,143 individuals is less than ideal. The Fernald cohort is predominantly white males which is not representative of more diverse modern day work forces, limiting generalizability. However, generalizability is still stronger than studies of acute high dose radiation events (Boice et al., 2022). Non-differential outcome misclassification is highly likely given the source of mortality data is from historical death certificates (McGivern et al., 2017). This bias would likely attenuate associations towards the null and may contribute to the lack of significant neurodegenerative-related mortality risk from protracted low dose IR. Finally,

we expect there to be weaknesses in our hypothetical intervention development due to only having four expert informational interviews. Three of the consulted experts were from one institution, which could introduce an institutional bias in the approach, and only one expert had personal experience with Fernald. The limited insight into Fernald operations was addressed via review of the extensive documentation of Fernald's operations by the National Institute for Occupational Safety and Health's dose reconstruction project's technical basis documents for Fernald (Kent et al., 2017; Smith et al., 2014, 2016). We find it unlikely that this weakness would change our results, given that even when one of our interventions issued a considerable reduction in IR dose we still did not find evidence of HWSE for neurodegenerative-related mortality. An alternative explanation for this null finding could be that Fernald workers already had relatively low doses compared to other occupationally IR exposed workers.

This study applied the parametric g-formula to examine the impact of key selection mechanism biases such as HWSE and competing events on occupational IR exposure and neurodegenerative-related mortality by applying hypothetical interventions. Our findings suggest that CVD mortality acts as a competing event for neurodegenerative-related mortality in the Fernald cohort, influencing observed estimates. However, hypothetical interventions aimed at reducing IR exposure did not meaningfully alter cumulative incidence, indicating limited evidence of intervention effectiveness in this context. Our results contribute to the ongoing discussion of IR-related neurodegenerative risks and emphasize the importance of considering competing risks in occupational radiation epidemiology. Future research should continue refining and applying causal inference approaches such as the parametric g-

formula and explore broader intervention strategies to mitigate potential long-term health effects of protracted low dose IR in other historical worker cohorts.

CHAPTER 5: CONCLUSIONS

Summary

Much of what is understood regarding the adverse effects of ionizing radiation (IR) on health is derived from the Life Span Study (LSS) of Japanese atomic bomb survivors (*Life Span Study (LSS) – Radiation Effects Research Foundation (RERF)*, 2024), such findings may not be generalizable to worker and general populations exposed to chronic low doses of IR. The U.S. Million Person Study (MPS) aims to address this gap in knowledge through rigorous worker cohort study and methodical data pooling. Recent studies of chronic low dose IR and neurodegenerative-related mortality suggest an associated risk, which is particularly concerning given the burden of neurodegenerative disease across the globe with an estimated 10 million new dementia cases every year (*ADI - Dementia Statistics*, 2024). However, the relationship between IR and neurodegenerative-related mortality is not consistent across the literature which could be explained by threats to validity underlying the etiological question in such studies. This project introduces novel techniques to investigate, evaluate, and improve the validity of studies of IR and neurodegenerative disease. In our first aim we highlighted how while IR did not significantly increase risk of neurodegenerative-related mortality, some co-exposures, such as machining fluids, may act as an effect modifier of IR and neurodegenerative-related mortality risk among Fernald uranium processing workers, weakening generalizability of findings to other populations. Aim two expanded to pool two additional worker cohorts exposed to IR and found no evidence of confounding or effect modification by silica or uranium dusts and

additionally found a meta-analysis of those same cohort studies had comparable overall results to the pooled analysis results. Our third aim assessed how selection mechanisms of healthy worker survivor effect (HWSE) and competing events impacted the relationship of interest, finding that while healthy HWSE may not impact the IR and neurodegenerative-related disease, cardiovascular disease (CVD) mortality acted as a competing event that emphasizes a need to apply more sophisticated survival analyses. The culmination of these dissertation aims have resulted in contributions that may help explain inconsistencies in IR and neurodegenerative-related mortality findings and describes solutions in research methodology in the field of occupational radiation epidemiology.

Individual Project Conclusions

Aim 1: Assess modification and confounding of IR and neurodegenerative-related mortality's relationship by co-exposures and characterize exposure and mortality experience by job category.

The rationale behind this aim stemmed from the understanding that workers in occupational settings are often exposed to a mix of radiological and non-radiological hazards, which may confound or modify the relationship between IR and adverse health outcomes. This study used the 6,403 uranium processing workers of Fernald Feed Materials Plant, referred to as Fernald. We found that when comparing hazard ratios (HRs) and 95% confidence intervals (CIs) of overall IR and neurodegenerative-related mortality at 10 mGy brain dose (milligray; HR 1.01, 95% CI 0.96, 1.06) to the estimate among those highly co-exposed to machining fluids (HR 1.25, 95% CI 1.11, 1.40) that machining fluids modified the relationship of IR and neurodegenerative-related mortality,

even showing a shift to significantly increased risk. Additionally, our study revealed that certain job categories such as store and supply services have elevated odds of neurodegenerative-related mortality compared to administrative workers.

This aim was limited by sample size, selection bias, and potential misclassification of co-exposures and neurodegenerative-related mortality. However, it had notable strengths including the use of individual level, organ-specific IR dose estimates and the calculation of co-exposure estimates for all workers in the Fernald cohort. The most significant contribution of this aim was addressing the gap in literature regarding effect modification of co-exposures on the relationship between chronic low dose IR and neurodegenerative-related mortality. Our research of effect modification by co-exposures in occupational radiation epidemiology is a first in the field, and with significant results it punctuates the need for further evaluation of co-exposure's role in IR and adverse health amongst occupational radiation studies. Our findings suggest that studies of IR and neurodegenerative-related mortality should consider the presence of co-exposures to IR and how co-exposures may impact generalizability and risk assessment within subgroups.

Aim 2: Evaluate concerns of confounding and effect modification for the relationship between IR exposure and neurodegenerative-related mortality in a pooled analysis of cohorts and assess overall conclusions in comparison with meta-analytic estimates.

In our second aim we evaluated confounding and effect modification potential by co-exposures in a pooled analysis of three cohorts and compared overall analogous pooled results with meta-analytic estimates to evaluate future research strategies of the field. This approach was taken to address inconsistencies in prior research and to

leverage increased statistical power of combined data, but also in consideration that future efforts to evaluate IR and neurodegenerative-related mortality may hinge upon resource-intensive pooling efforts. The study pooled data from the Fernald, Linde Ceramics Plant, hereafter called Linde, and Mallinckrodt Chemical Works (MCW) cohorts, requiring intensive data harmonization. We found consistent results with Aim 1 of no increased risk of neurodegenerative-related mortality at low/moderate IR category (HR 0.95, 95% CI 0.73, 1.24) or high IR category (HR 1.05, 95% CI 0.80, 1.37) and that this association was not confounded or modified by silica or uranium dusts. Additionally, it was found that the meta-analytic estimate of these same cohort's individual studies had a congruous summary estimate null finding compared to the step 3 primary analysis finding for high categorical IR (HR 0.95, 95% CI 0.75, 1.20).

A key limitation in this second aim was the need for extreme forms of data harmonization. This was noted with the categorization of continuous IR measures. Inclusion of the Linde cohort with its categorical IR measurement restricted the pooled analysis. The study's strengths included a large sample size of 10,330 uranium processing workers, many person-years of follow-up and leveraging cohorts of workers tasked with similar operations. A significant contribution was providing insight on the trade-offs of data pooling versus meta-analytic approaches. The findings suggest a balanced approach for future research is needed in data harmonization. Our results would recommend that pooled analyses are needed to improve statistical power for evaluation of co-exposures that are not consistently reported across the literature, but that meta-analyses have strong value in radiation epidemiology where resources may be scarce to pool data diverse cohorts together.

Aim 3: Develop a hypothetical intervention to mitigate exposure and estimate its effect on risk of neurodegenerative-related mortality while managing issues of HWSE using causal inference methodology.

Aim 3 mitigated occupational IR exposure with potential intervention end points in Fernald to evaluate HWSE and assessed CVD mortality as a competing event. These goals were pursued in response to the methodological gap in occupational radiation epidemiology, where worker cohorts likely experience HWSE and competing events like CVD mortality may differentially preclude neurodegenerative-related mortality with respect to exposure. Both selection mechanisms would threaten validity of the study of neurodegenerative-related mortality and possibly contribute to inconsistent findings in the literature. Addressing these challenges, we applied the parametric g-formula, a causal inference estimation approach that extends standardization to time-varying settings. To apply the g-formula with interventions to determine HWSE, we developed two hypothetical intervention endpoints with possible real-world implementation examples. The first was an aggressive engineering control reducing IR exposure for all workers during tenure by 80%, the second a blend of administrative controls for a modest 20% reduction of IR exposure for all workers after 5 years of startup. Results determined that for the study of IR and neurodegenerative-related mortality HWSE may not be a key function as cumulative incidence did not change considerably between natural course (16.99%), engineering control (17.43%), and administrative control (17.14%), however, assessment of time to leaving work by exposure status was indicative of HWSE. Furthermore, there was evidence of CVD acting as a competing

event for neurodegenerative-related mortality, however, this does not necessarily mean that our estimates of the intervention's effect are biased.

Aim 3's strengths included relatively novel contribution to the occupational radiation epidemiology literature by employing the parametric g-formula to address time-varying concerns and the direct estimation of absolute risk under hypothetical interventions. Limitations, however, include weaknesses of the parametric g-formula such as sensitivity to the assumption of correct model specification, and other general cohort limitations previously mentioned for Fernald. Despite limitations, a significant contribution of Aim 3 was the application of the parametric g-formula to examine the impact of key selection mechanism issues of HWSE and competing events on occupational IR exposure and neurodegenerative-related mortality. Findings suggest that CVD mortality acts as a competing event for neurodegenerative-related mortality, but may not be a significant source of bias here. Depending on the magnitude of effect and distribution of CVD and neurodegenerative-related mortality in other contexts, the competing event may offer another explanation for inconsistencies amongst published research of IR and neurodegenerative-related mortality.

Overall Contributions and Impact

This project contributes to the field of occupational radiation epidemiology by addressing critical gaps in understanding what could be a complex relationship between IR exposure and neurodegenerative disease, while improving methods for future studies. There remains a need for continued research on the effects of chronic low-dose IR by large multi-cohort efforts such as the U.S. MPS. This project supports chronic low dose IR research by introducing novel techniques and investigating the internal and

external validity of prior and future studies of chronic low dose IR and neurodegenerative disease. The most significant contribution of this research lies in evaluating the role of co-exposures as effect modifiers and/or confounders, enhancing understanding of data aggregation approaches, and addressing selection mechanism concerns. Co-exposures, such as machining fluids, may modify the relationship between IR and neurodegenerative-related mortality in historical worker cohort studies. Our second aim contributes insight on the trade-offs of data pooling versus meta-analytic approaches, especially when including a cohort with limiting exposure measurement. Competing events to neurodegenerative-related mortality such as CVD mortality may mask true risk of neurodegenerative-related mortality from chronic low dose IR and there exist viable methods to address competing events. Ultimately, this body of work highlights nuances in the relationship between chronic low dose IR and neurodegenerative disease that offer explanations into inconsistent findings.

Future research should focus on replicating the approaches in this project in different contexts. These studies should consider the potential for co-exposures and where possible continue to evaluate the role of effect modification or confounding by co-exposures. Pooled analysis approaches may be resource intensive but will be necessary for increased power to evaluate co-exposure role, however, meta-analyses may offer comparable insights. The application of the parametric g-formula used here exemplifies an option for addressing selection mechanisms and can enhance causal inference. Research endeavors to come should investigate the long-term health effects of IR beyond mortality outcomes and foster interdisciplinary collaborations to advance methodological innovations. The knowledge and methods derived from this project have

the potential to transform how chronic low dose IR research is conducted, improving our understanding that underlies actions to improve health and well-being of the general population and modern-day workforce.

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APPENDIX A: SUPPLEMENTARY MATERIALS FOR CHAPTER 2

Table A1. Summary statistics of cumulative brain dose by job category for 6,403 Fernald uranium processing workers.

Job Category	Median Total IR Brain Dose, mGy (IQR)	Mean Total IR Brain Dose, mGy (SD)
Administrative Services	<0.01 (0.51)	1.13 (4.34)
Chemical Control Research and Development	0.46 (2.71)	2.59 (5.63)
Engineering and Development	0.01 (1.05)	1.54 (6.68)
Maintenance	1.86 (8.19)	7.08 (12.8)
Process Operations	1.9 (33.6)	26.5 (39.0)
Loading and Material Handling	4.57 (20.7)	14.5 (21.8)
Storage and Supply Services	<0.01 (1.83)	4.38 (13.6)
Safety and Security	0.34 (1.84)	3.22 (10.4)
Other	<0.01 (0.12)	0.88 (3.84)
Undetermined	4.14 (11.2)	11.0 (24.4)

Note: Kruskal-Wallis test p-value for significant differences across categories: < 0.0001.
Abbreviations: IR: ionizing radiation, mGy: milligray, IQR: interquartile range, SD: standard deviation.

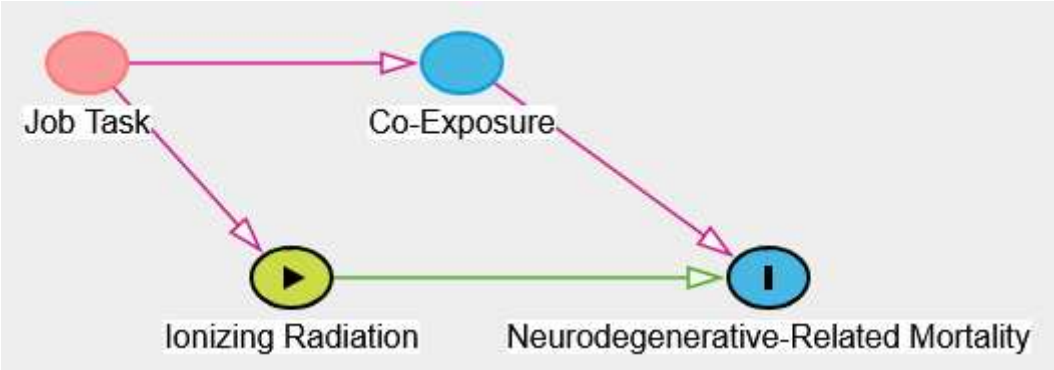


Figure A1. Directed acyclic graph of the potential pathway for confounding of the relationship of IR and neurodegenerative-related mortality in the context of co-exposures, without consideration of other potential causal relationships. The green circle represents the primary exposure and the blue circle with the roman numeral in the center represents the primary outcome, while the other blue circle is an ancestor of the outcome. The red circle is both an ancestor of the primary exposure and outcome. Pink arrows represent biasing pathways, and the green arrow represents the causal pathway of interest.

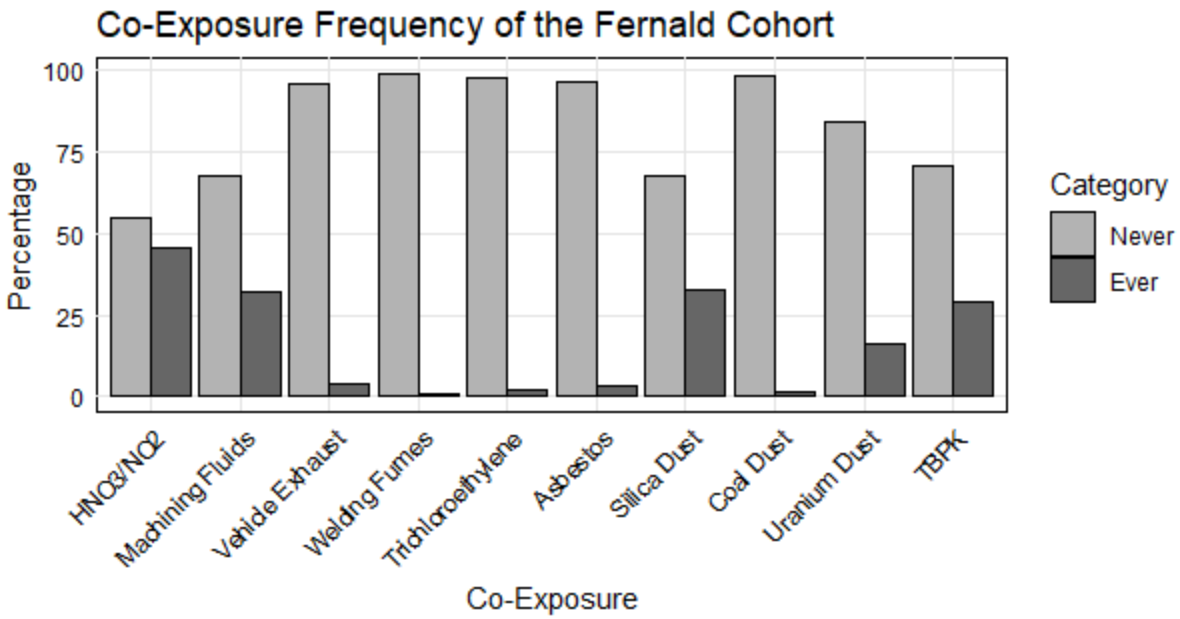
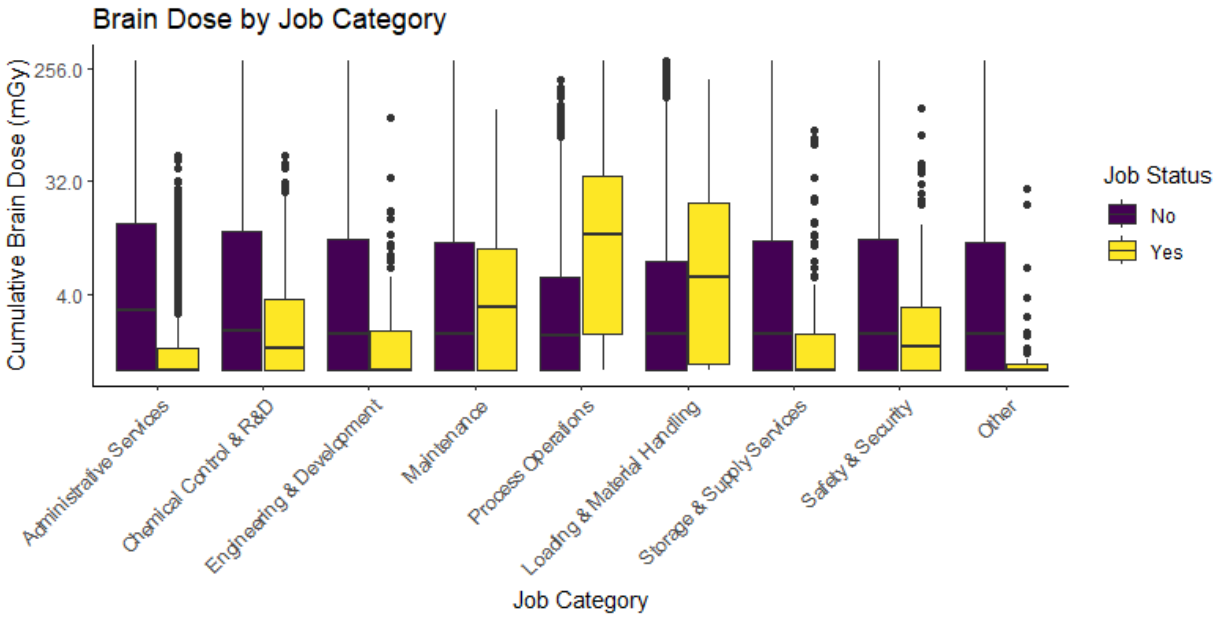


Figure A2. Bar plot of ever/never co-exposure frequencies for 6,403 Fernald uranium processing workers. *Abbreviations:* HNO3/NO2: nitric acid and nitrogen dioxide, TBPK: tributyl phosphate and kerosene.



F**igure A3.** Cumulative brain dose by job category box plot for 6,403 Fernald uranium processing workers. *Abbreviations:* R&D: research and development.

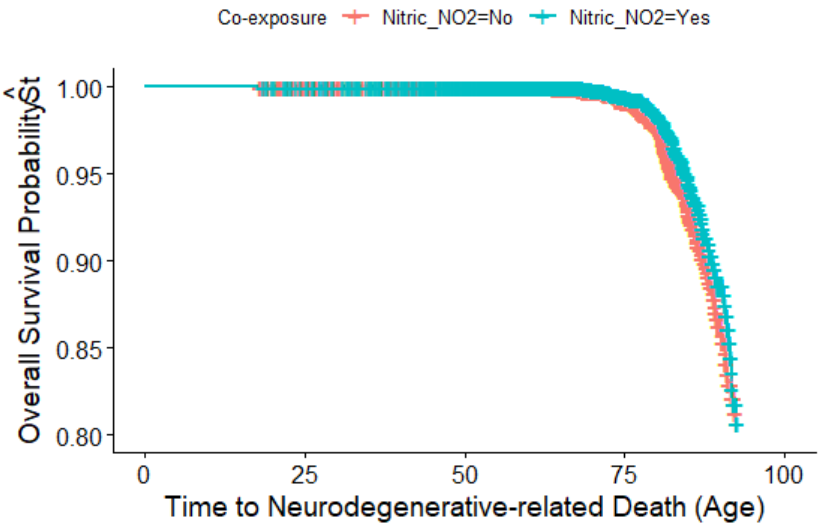


Figure A4. Survival probability plot of 6,403 Fernald workers either co-exposed to HNO3/NO2 or not, using attained age as the time variable. *Abbreviations:* Nitric_NO2: nitric acid and nitrogen dioxide.

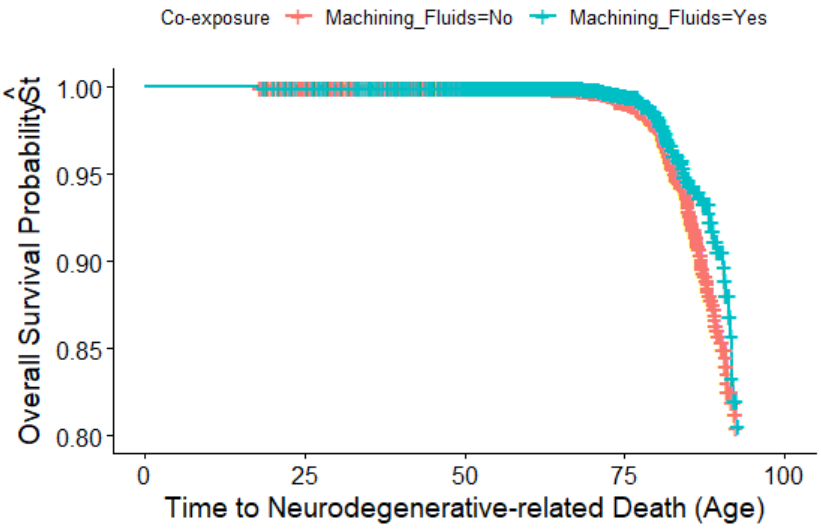


Figure A5. Survival probability plot of 6,403 Fernald workers either co-exposed to machining fluids or not, using attained age as the time variable. *Abbreviations:* Nitric_NO2: nitric acid and nitrogen dioxide.

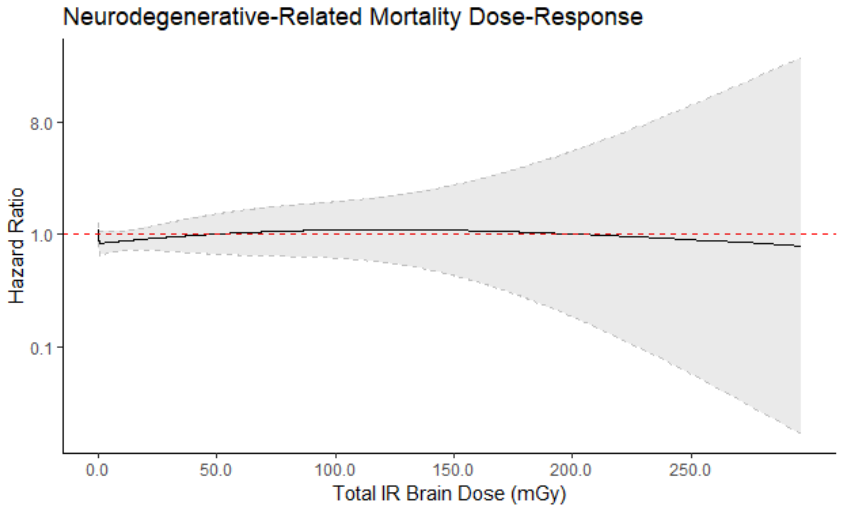


Figure A6. Dose-response plot of total IR brain dose vs hazard ratio for neurodegenerative-related mortality in the 6,403 Fernald uranium processing workers, a hazard ratio of 1 is marked with the hashed red line. *Abbreviations:* IR: ionizing radiation, mGy: milligray.

APPENDIX B: SUPPLEMENTARY MATERIALS FOR CHAPTER 3

Table B1. Demographic, exposure, outcome, and co-exposure characteristics for separate analysis steps 1, 2, and 3, n = 10,330.

Variable	**Step 1**	**Step 2**	**Step 3**
Categorical	**n (%)**	**n (%)**	**n (%)**
Sex			
Male	6578 (84.2)	7964 (89.3)	9092 (88.0)
Female	1237 (15.8)	953 (10.7)	1237 (12.0)
Race			
White	7530 (96.4)	8678 (97.3)	10044 (97.2)
Black	279 (3.6)	235 (2.6)	279 (2.7)
Other	6 (0.08)	0 (0.0)	6 (0.06)
First Pay Code			
Hourly	4796 (61.4)	5890 (66.1)	6872 (66.5)
Salary	3019 (38.6)	3027 (33.9)	3457 (33.5)
Vital Status at End of Follow-Up			
Alive	2199 (28.1)	2499 (28.0)	2586 (25.0)
Dead	5493 (70.3)	6284 (70.5)	7606 (73.6)
Unconfirmed	123 (1.6)	134 (1.5)	137 (1.33)
Neurodegenerative-Related [a] Cause of Death			
No	7528 (96.3)	8546 (95.8)	9882 (95.7)
Yes	287 (3.67)	371 (4.6)	447 (4.3)
Ever Co-Exposed			
HNO3/NO2	3963 (50.7)	N/A	N/A
Silica Dust	3095 (39.6)	3399 (38.1)	4412 (42.7)
Uranium Dust	3196 (40.9)	3937 (44.2)	5051 (48.9)
Cohort:			
Fernald	6403 (81.9)	6403 (71.8)	6403 (62.0)
Linde	1413 (18.1)	N/A	1413 (13.7)
MCW	N/A	2514 (28.2)	2514 (24.3)
IR Category at First Work Period			
None	994 (12.5)	N/A	1086 (10.4)
Low/Moderate	3354 (42.3)	N/A	3358 (32.2)
High	3583 (45.2)	N/A	5981 (57.4)
Continuous	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Birth Year	1926 (19)	1927 (17)	1925 (18)
Follow-Up (Years)	42.3 (22.7)	43.7 (23.2)	43.4 (23.5)
Age at Start of Follow-Up	28.7 (13.1)	28.3 (12.6)	28.6 (13.0)
Age at End of Follow-Up	74.5 (18.4)	75.2 (17.9)	75.2 (18.1)
Date of Termination (Year)	1962 (19.3)	1963 (13.7)	1961 (14.6)
Years Worked	3.8 (11.9)	5.1 (11.8)	3.9 (10.1)
Cumulative Exposure Years	4 (10.9)	N/A	4 (10.0)
Cumulative IR Brain Dose (mGy)	N/A	2.75 (17.4)	N/A

[a] Neurodegenerative-related includes dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease.

Abbreviations: HNO3/NO2: nitric acid or nitrogen dioxide, N/A: not applicable, IQR: interquartile range, MCW: Mallinckrodt Chemical Works, IR: ionizing radiation, mGy: milligray.

Table B2. Step 2 overall, confounding, and effect modification results for Fernald and MCW cohorts, n = 8,916.

Model	HR (95%CI) Overall and Adjustment for Co-Exposure	HR (95%CI) Without Co-Exposure	HR (95%CI) With Co-Exposure	Product Term p-value for Co-Exposure
Overall	1.01 (0.99-1.03)			
Silica Dust	1.02 (0.99-1.04)	1.04 (0.98-1.11)	0.97 (0.91-1.04)	0.3519
Uranium Dust	1.01 (0.96-1.03)	1.02 (0.96-1.08)	0.99 (0.92-1.06)	0.8141

Note: All models had the outcome of neurodegenerative-related (dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease) mortality and additionally adjusted for first pay type, birth year, annual cumulative exposure days, cohort and stratified baseline hazard by sex. Results are expressed at 10 mGy of IR. All models' proportional hazards assumptions were met.
Abbreviations: HR: hazard ratio, CI: confidence interval, HNO3/NO2: nitric acid and nitrogen dioxide, mGy: milligray, IR: ionizing radiation.

Table B3. Step 3 overall, confounding, and effect modification results for only Fernald and MCW cohorts, n = 8,916.

Model	HR (95%CI) Overall and Adjustment for Co-Exposure	HR (95%CI) Without Co-Exposure	HR (95%CI) With Co-Exposure	Product Term p-value for Co-Exposure
Overall				
Low/Moderate IR	1.05 (0.78-1.43)	N/A	N/A	N/A
High IR	1.09 (0.80-1.50)	N/A	N/A	N/A
Silica Dust				
Low/Moderate IR	1.01 (0.75-1.37)	1.00 (0.70-1.41)	0.95 (0.53-1.84)	0.8796
High IR	1.09 (0.80-1.49)	0.96 (0.65-1.42)	1.25 (0.61-1.85)	0.3224
Uranium Dust				
Low/Moderate IR	1.03 (0.74-1.42)	1.13 (0.77-1.66)	0.90 (0.52-1.80)	0.4540
High IR	1.06 (0.76-1.48)	1.02 (0.67-1.55)	1.03 (0.54-1.87)	0.9885

Note: All models had the outcome of neurodegenerative-related (dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease) mortality and additionally adjusted for first pay type, birth year, annual cumulative exposure days, cohort and stratified baseline hazard by sex. All models' proportional hazards assumptions were met.
Abbreviations: HR: hazard ratio, CI: confidence interval, HNO3/NO2: nitric acid and nitrogen dioxide, mGy: milligray, IR: ionizing radiation.

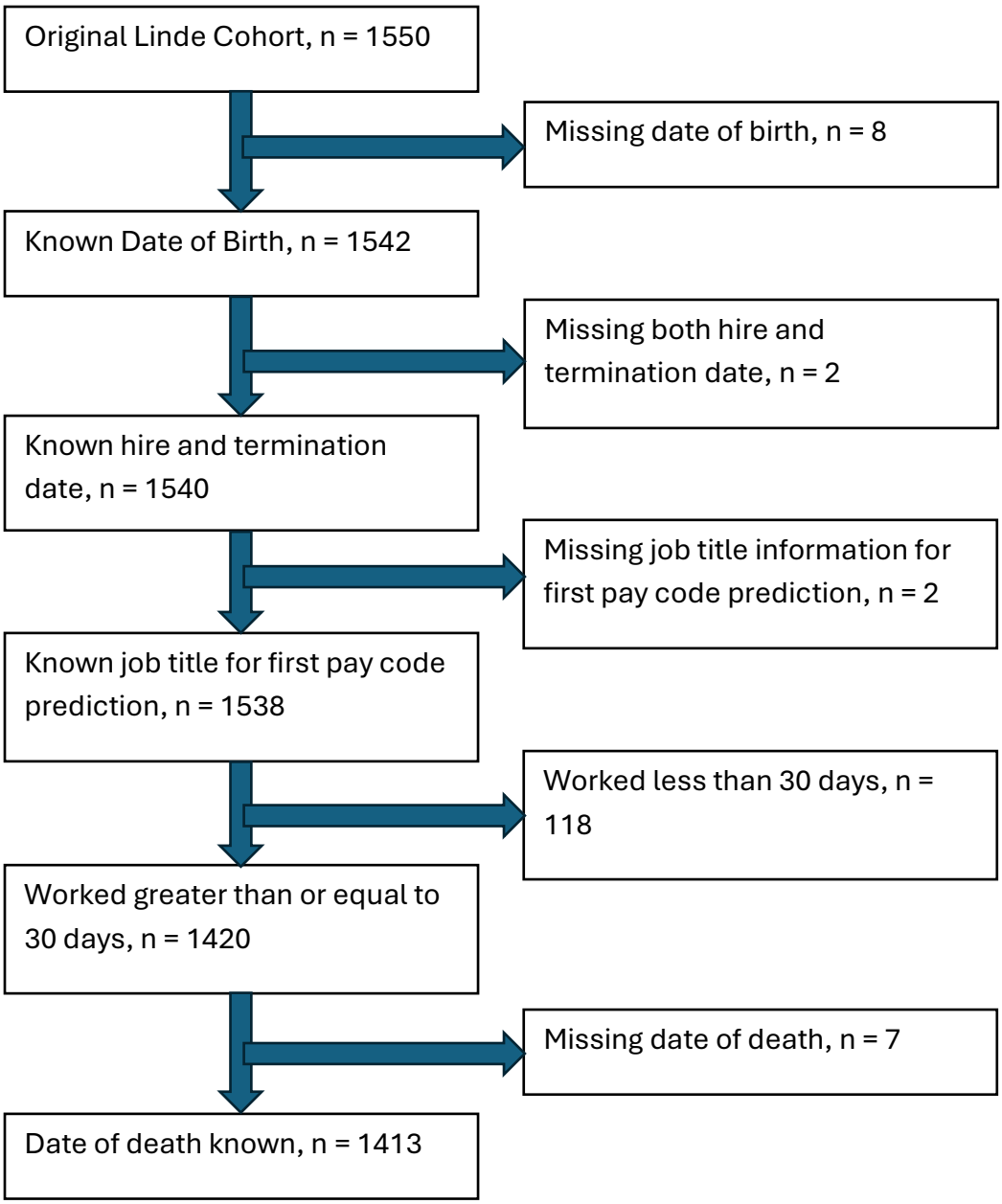


Figure B1. Linde cohort individuals dropped from analysis due to missing data or exclusion criteria.

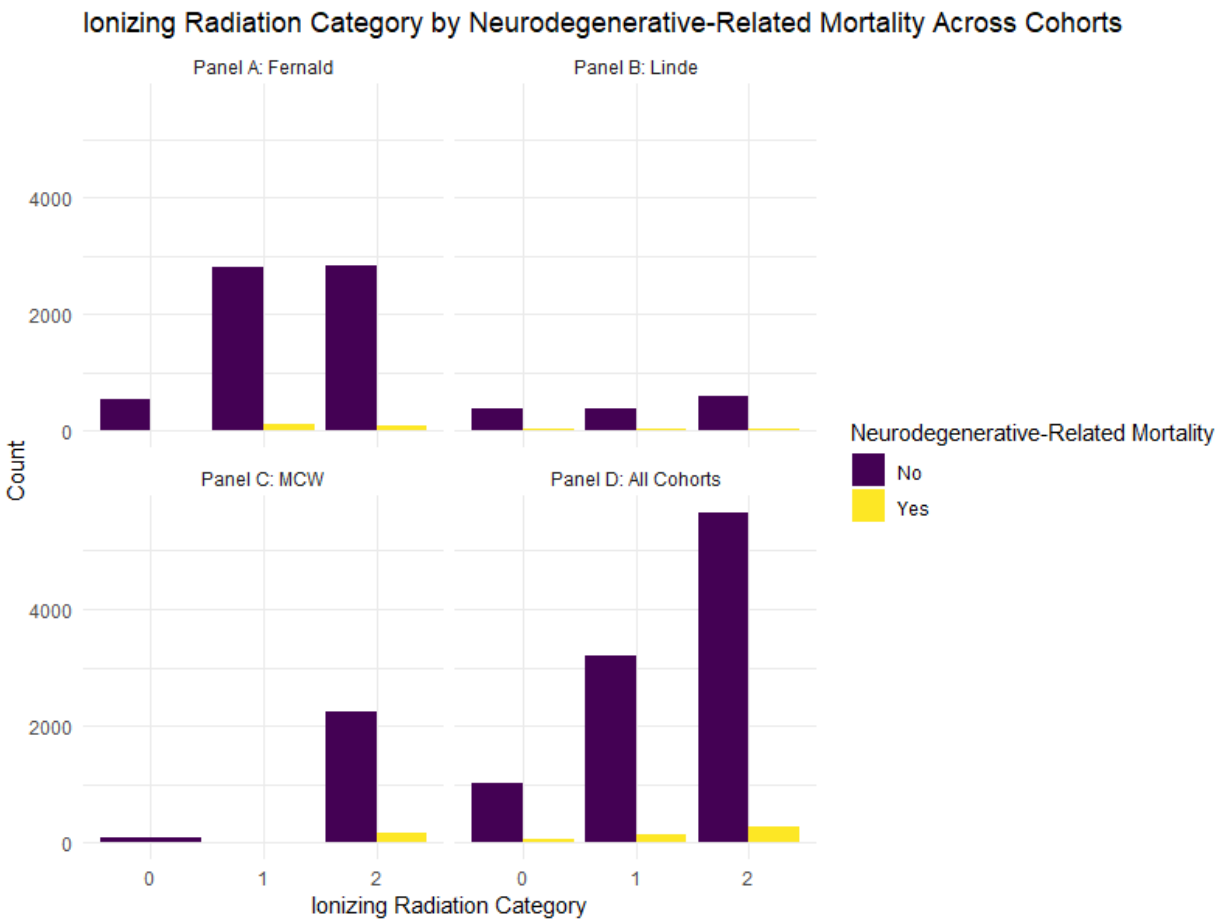


Figure B2. Step 3 combined ionizing radiation category at first job held distribution by neurodegenerative-related mortality within ***A.*** Fernald, ***B.*** Linde, ***C.*** Mallinckrodt, and ***D.*** all cohorts pooled together, n = 10,330. *Abbreviations:* MCW: Mallinckrodt Chemical Works.

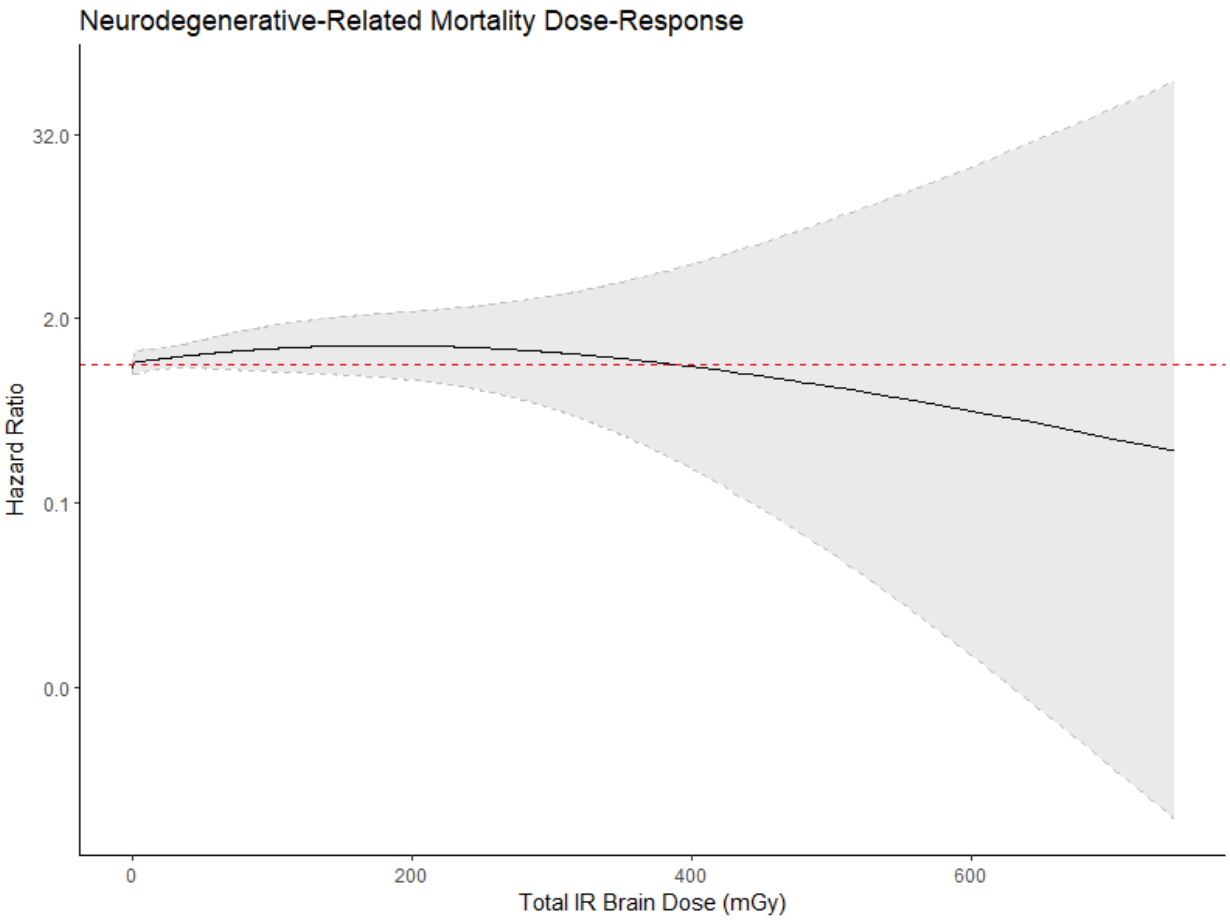


Figure B3. Step 2 pooled Fernald and MCW dose-response plot of total IR brain dose vs hazard ratio for neurodegenerative-related mortality, n = 8,916, a hazard ratio of 1 is marked with the hashed red line. *Abbreviations:* IR: ionizing radiation, mGy: milligray.

APPENDIX C: SUPPLEMENTARY MATERIALS FOR CHAPTER 4

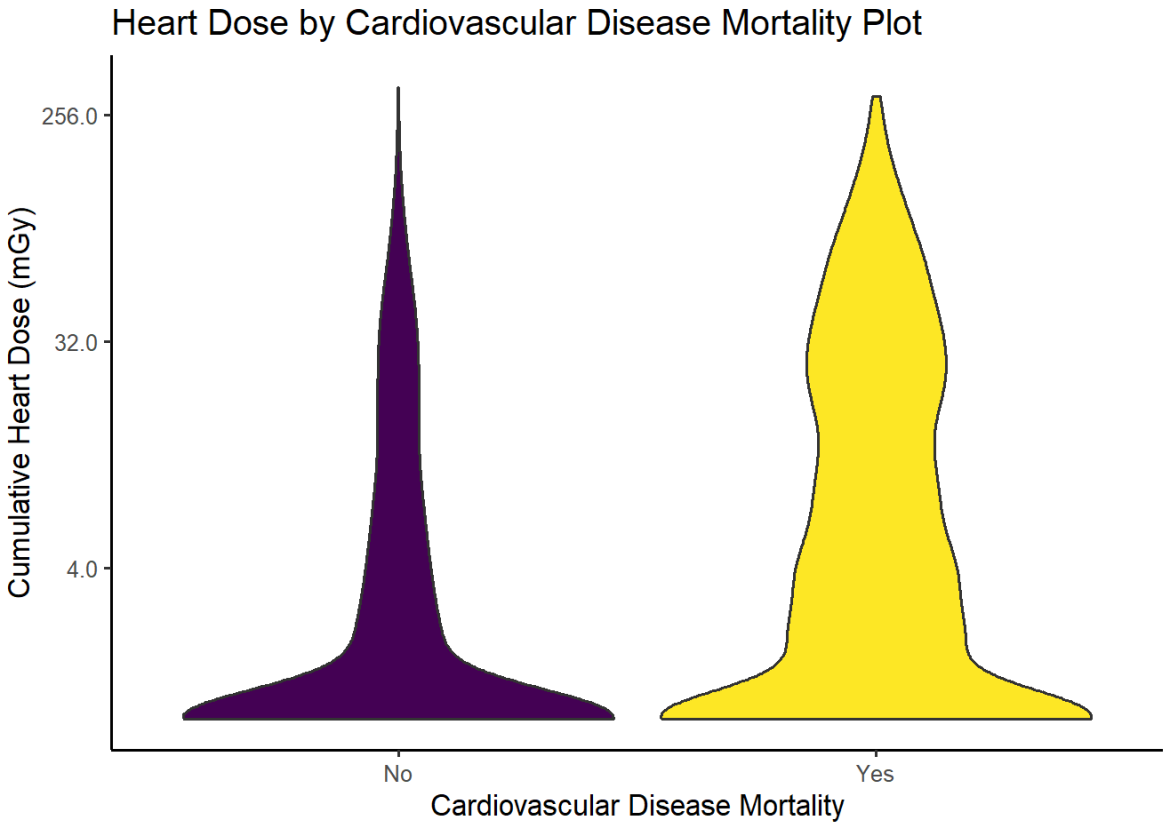


Figure C1. Cumulative brain dose stratified by neurodegenerative-related mortality for 6,143 Fernald uranium processing workers. *Abbreviations:* mGy: milligray.

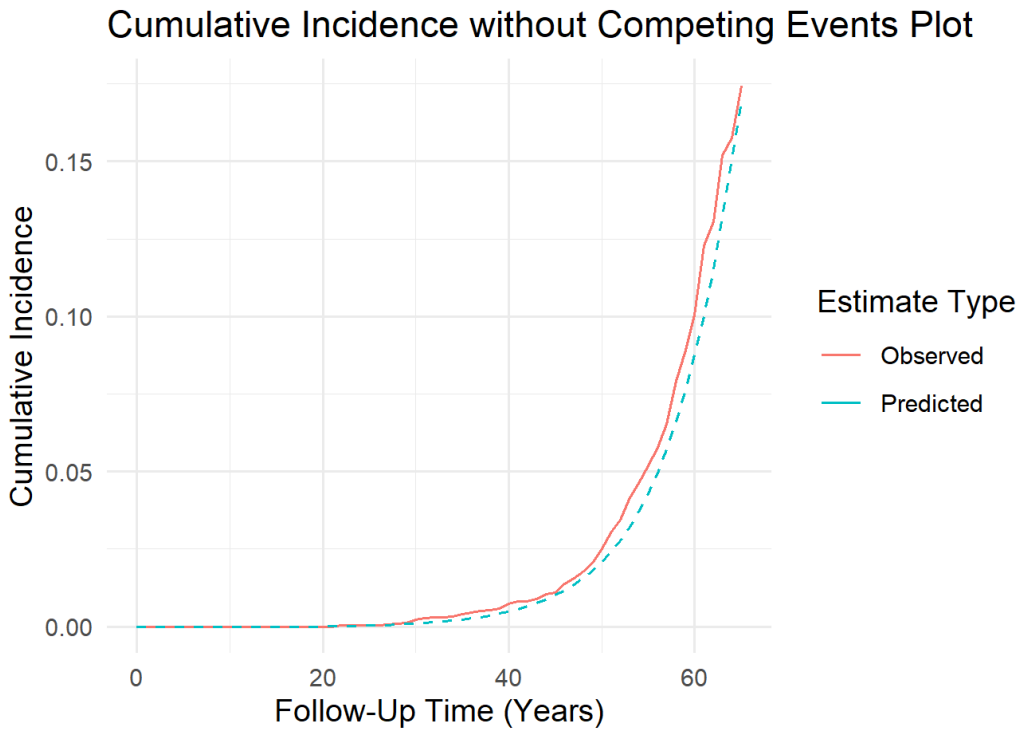


Figure C2. Cumulative incidence of neurodegenerative-related mortality over time, expressed in work years/row for 6,143 Fernald uranium processing workers. Results represent parametric g-formula output without modeling for competing events based on 1,000 bootstrap samples.

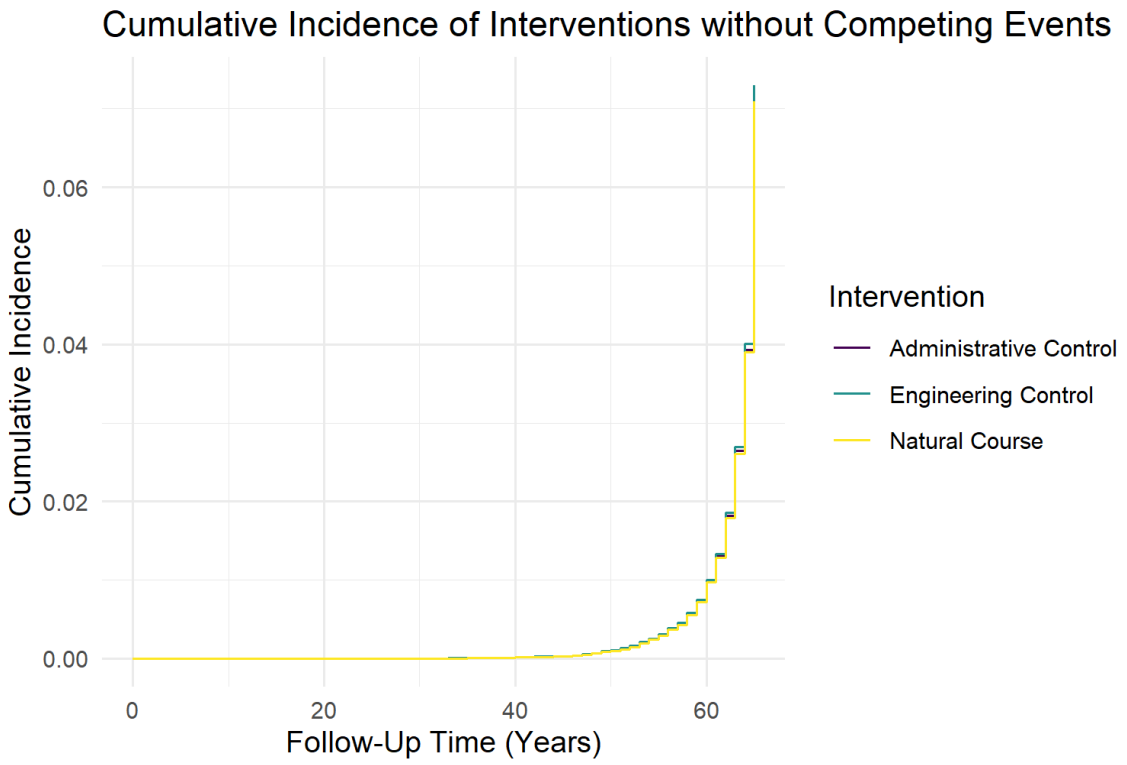


Figure C3. Cumulative incidence of neurodegenerative-related mortality over time by intervention group, expressed in work years/row for 6,143 Fernald uranium processing workers. Results represent parametric g-formula without modeling for interventions output. Interventions are as follows: simulated natural course scenario, where the g-formula simulates what was observed under no intervention using exposure and covariate histories predicted with the given dataset; simulated engineering control intervention scenario, where all absorbed dose during working tenure is reduced by 80%; simulated administrative control intervention scenario, where all absorbed dose during working tenure and after the year 1956 is reduced by 20%.

Methods C1. Supplementary Hypothetical Intervention Questionnaire

1. In an environment like Fernald, what types of interventions would you prioritize to reduce workers' exposure to ionizing radiation? Consider the feasibility of these interventions given the safety climate at the time, but the technological improvements available now.
2. What controls would you propose to limit exposure to non-radiological co-exposures, (e.g., welding fumes, silica dust, HNO3/NO2), in consideration of effective, low-tech solutions?
3. Given available PPE today, what improvements or specific types of equipment could have better protected workers from inhaling radioactive particles or toxic fumes?
4. How might engineering controls, such as improved ventilation or enclosure of certain processes, have feasibly reduced airborne contaminants and radiation exposure? Are there any specific design features that come to mind?
5. What role could automation, remote handling, or shielding have played at this time if they were implemented?
6. What administrative controls or procedural changes could have reduced cumulative exposure to hazards across an employee's tenure at Fernald? Would job rotation or more frequent shift breaks have been feasible solutions?
7. Are there any specific monitoring or tracking systems that could have been implemented from either today or from back then?
8. What changes to incident reporting and follow-up could have helped manage both immediate and cumulative risks from exposure incidents, such as near misses? Would reassignment after high exposure incidents be ideal?
10. How might additional safety training have helped workers recognize and minimize their exposure to both radiological and non-radiological hazards? Consider the era and what safety measures may have been missing that are present today.
11. In terms of reducing environmental contamination, what containment or waste disposal practices today would have been feasible at Fernald?