

Assessment of bias associated with person-year
grouping methods in individual and pooled
epidemiological cohorts from the Million Person Study

by

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Abstract

Radiation epidemiology has progressed from analyses of accidental and wartime exposures to today's studies of low-dose exposures resulting primarily from occupational settings and medical interventions. In the age of low-dose, chronic radiation exposure studies, it is imperative that cohorts are large enough to detect radiation-related health outcomes with precision. Statistical software capabilities for studies of this type have recently been improved to support cohorts with over 50 million person-years of data. Prior to these advancements, follow-up records in large datasets had been grouped into uniform intervals, reducing the size to accommodate software limitations. For example, if grouping into two-record intervals, an individual's history consisting of with 30 years of annual follow-up would be represented by 15 records. The resulting data are less granular and potentially misrepresent exposure and outcome measures.

Enhanced software capabilities permit survival analysis regressions on unprecedentedly large datasets. Full-size and grouped datasets can now be rapidly processed and results can be compared in an effort to characterize grouping-related bias. Three of the largest Million Person Study cohorts are analyzed. Individual cohort, pooled, and meta-analysis risk estimates are presented for ungrouped and grouped data. Grouping is performed three different ways to identify where biases are most likely introduced. Additionally, grouping bias is assessed for simulated data where the expected risk estimate is known. By utilizing these various methods, generalizations can be made on the expected magnitude of grouping bias. Findings reveal observable bias associated with person-year grouping, dependent on grouping method and cohort characteristics. The impact of these findings is assessed and recommendations are made for ongoing radiation epidemiology studies.

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Chapter 1

Introduction & Background

1.1 History of Radiation Protection and Epidemiology

At the turn of the 20th century, arguably the most rapid period of advancement in physical sciences took place. In 1895, Wilhelm Röntgen discovered x-rays and harnessed them to image the human body ([Roentgen, 1895](#)). By the year 1900, radioactivity was discovered independently by Henri Becquerel for uranium ([Becquerel, 1896](#)) and then Marie and Pierre Curie for radium and polonium ([Curie, 1898](#)), J.J. Thomson discovered electrons ([Thomson, 1897](#)), and Ernest Rutherford discovered alpha and beta radiation ([Rutherford, 1899](#)). Before World War I, Max Planck discovered photons ([Planck, 1900](#)), Albert Einstein quantized light through the discovery of the photoelectric effect ([Einstein, 1905](#)), Rutherford discovered the atomic nucleus ([Rutherford, 1911](#)), and Niels Bohr introduced quantized energy states of atomic electrons ([Bohr, 1913](#)), significantly enhancing our understanding of atomic structure. Building upon these ideas, advancements by Werner Heisenberg and Erwin Schrödinger in the 1920s established a mathematical framework for quantum mechanics ([Heisenberg, 1925](#); [Schrödinger, 1926](#)). The dramatic increase in understanding of our physical world during this time opened a new realm of technological possibilities. However, dangers in the application of these physical phenomena were quickly evident.

Biological consequences of radiation exposure were observed throughout this period of discovery, including the amputation of both arms and 1904 death of Clarence Dally, an assistant of Thomas Edison’s x-ray experiments ([The New York Times, 1904](#)). Informal exposure recommendations were developed, such as a limit of 3,000 rad (30 gray) per year, based on observable changes to a photographic plate ([Inkret et al., 1995](#)). In 1915, the British Röntgen Society, established fewer than 20 years earlier, passed a resolution for radiation protection, followed by the introduction of a “tolerance dose” of 70 rem (0.7 sievert) per year in 1924. The tolerance dose was about one-tenth of the observed skin erythema (reddening) dose and was intended to be sustainable without harmful effects ([Mutscheller, 1925](#)). This marked the first of many efforts to establish radiation exposure limits with the aim of preventing adverse biological effects.

In the late 1920s, the International Commission on Radiation Units and Measurements (ICRU) and the International Commission on Radiological Protection (ICRP) were founded. At this point, the Röntgen (R) was established as the primary unit for exposure. The Röntgen is defined as the quantity of x-ray or gamma radiation required to produce 2.58×10^{-4} coulombs of charge per kilogram of air under standard conditions. Shortly after, the U.S. National Council on Radiation Protection and Measurements (NCRP) and United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) were established. These organizations have since provided numerous evidence-based recommendations to regulatory bodies, policymakers, and the radiation protection community. Each organization began to produce independent recommendations on dose quantities and limits. Initially, each organization’s recommendations did not differ substantially from the British Röntgen Society’s tolerance dose.

In December of 1938, a vastly consequential scientific breakthrough occurred when Otto Hahn and Fritz Strassmann experimentally discovered nuclear fission ([Hahn and Strassmann, 1939](#)). The process was promptly characterized theoretically by Lise Meitner and Otto Frisch ([Meitner and Frisch, 1939](#)). Nuclear fission’s chain-reactive nature quickly gave rise to fear of Adolf Hitler’s possession of nuclear weapons. In 1939, Albert Einstein wrote a letter to President Franklin D. Roosevelt warning the Administration of the potential

power of fission chain reactions and encouraged investment into U.S. nuclear weapons research ([Einstein, 1939](#)). This prompted a scientific arms race in which—by 1944—Manhattan Project sites were established for uranium enrichment (Oak Ridge), plutonium production (Hanford), and weapons development (Los Alamos). Each site had its own division of the Manhattan Project’s Medical Section, led collectively by radiologist Stafford Warren. In 1945, following the Trinity test explosion, atomic bombs were dropped on Hiroshima and Nagasaki, leading to Japan’s surrender and the end of World War II. Deriving some good from a tremendously tragic event, the Atomic Bomb Casualty Commission (ABCC) (now Radiation Effects Research Foundation (RERF)) was established as a Japanese-U.S. joint effort to study the long-term effects of radiation exposure among Japanese atomic bomb survivors. The RERF Life Span Study (LSS) has provided invaluable information on the health risks associated with radiation exposure ([Ozasa et al., 2012](#)).

After World War II, heightened interest in nuclear power production prompted the creation of the U.S. Atomic Energy Commission (AEC) in 1946, which oversaw the development and control of atomic energy for civilian and military applications. Due to conflicting goals of both regulating and promoting nuclear energy, the AEC was later replaced by the U.S. Nuclear Regulatory Commission (NRC) and other agencies focused on promoting these technologies. Health physics—an alternate name for the study of biological effects of radiation exposure—saw great advancements throughout the 1950s. The Tripartite Conferences were held between the U.S., Canada, and the U.K. to better develop concepts in health physics. The units rad and rem for absorbed dose (D) and dose equivalent (H), respectively, were introduced. The rem (radiation equivalent man) is the absorbed dose multiplied by a radiation quality factor (QF), accounting for differential effects on the human body based on linear energy transfer (LET, here L), which varies by radiation type (Eq. 1.1). Quality factor is typically 1 for photons and electrons, and up to 20 for neutrons and other charged particles.

$$H = D \times QF(L) \tag{1.1}$$

Additionally, the Tripartite Conferences introduced the concept of relative biological effec-

tiveness (RBE). In simple terms, the RBE is a ratio of absorbed doses that produce the same biological endpoint, using a reference radiation and a comparison radiation ([Alpen, 1998](#)). Further concepts aiding dosimetry were introduced during this time, including depth dose and a reference anatomical human.

Also shortly after the War's end, American geneticist Hermann Muller was awarded the 1946 Nobel Prize in Physiology or Medicine for inducing gene mutations in fruit flies by x-ray irradiation ([Muller, 1927](#)). Importantly, he observed that there was no threshold dose required to induce these effects in fruit flies. In 1956, the National Academy of Sciences' (NAS) Biological Effects of Atomic Radiation (BEAR) I genetics panel proposed the linear no-threshold (LNT) model, suggesting that radiation-associated risks increase linearly with dose and can be present at any level of exposure ([NAS, 1956](#)). This model helped introduce the concept of stochastic radiation exposure effects, which was supported by the appearance of excess solid cancers in atomic bomb survivors throughout the 1960s ([Beebe et al., 1962, 1971; Jablon et al., 1964, 1965](#)).

In 1966, ICRP Publication 9 addressed these new ideas ([ICRP, 1966](#)). Paragraph 7 states that there is no practical alternative to a linear relationship and that assuming doses act cumulatively is unlikely to lead to underestimation of risks. Paragraph 52 famously recommends that “all doses be kept as low as is readily achievable, economic and social consequences being taken into account.” The “as low as readily achievable” phrasing was changed to “as low as reasonably achievable” (ALARA) in ICRP Publication 26, emphasizing that exposures should be optimized rather than minimized ([ICRP, 1977](#)). ICRP Publication 103 discusses the three principles of the System of Radiological Protection extensively ([ICRP, 2007](#)). Their interpretations have been debated over time, particularly the interpretation of the optimization principle. Once a net benefit is determined (satisfying justification), the net benefit should be maximized (optimization). This principle is sometimes misinterpreted, leading to exposure minimization, which is rarely supportive of maximizing the net benefit. For example, in a nuclear power plant maintenance scenario, excessive restriction of time in an exposure zone could result in higher risk of faulty repair. In optimizing planned exposures, all factors pertaining to the benefits and risks of the exposure must be fully considered and

appropriately quantified. ICRP 103 descriptions of the three principles of the System of Radiological Protection are displayed in Figure 1.1.

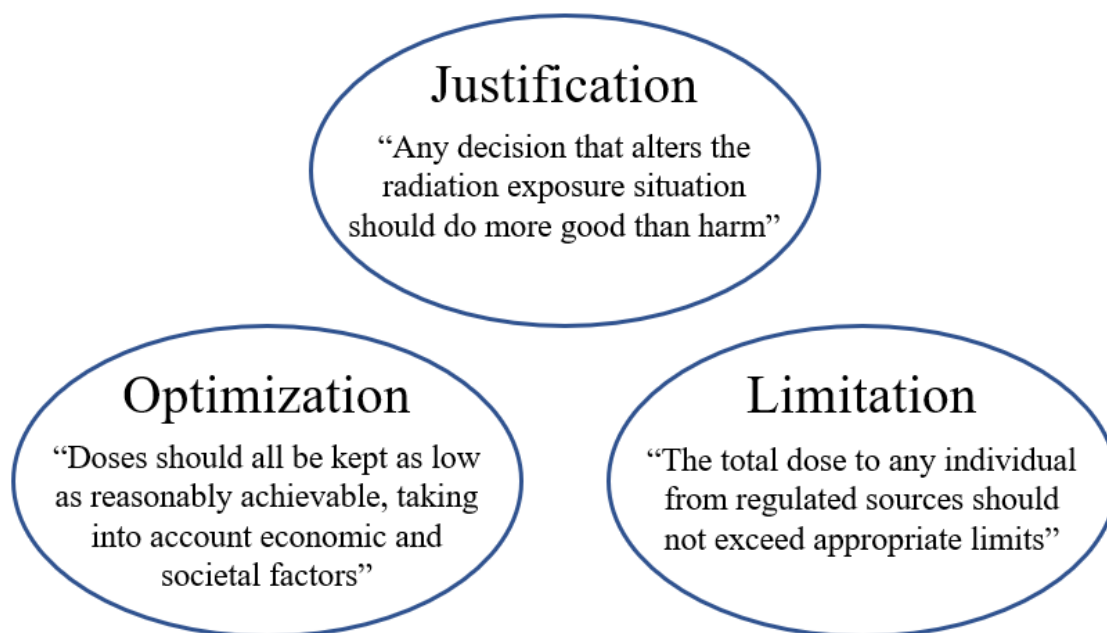


Figure 1.1: *ICRP 103 descriptions of the three fundamental principles of the System of Radiological Protection (ICRP, 2007).*

The landmark 1977 ICRP Publication 26 contained additional important developments for radiation protection. Exposure units rad and rem were replaced by gray (Gy) and sievert (Sv), following the 1975 adoption of these units by the French General Conference on Weights and Measurements (CGPM) (CGPM, 1975). Occupational exposure limit recommendations were reported as 50 mSv per year—identical to the 1966 ICRP 9 recommendations. However, the new recommendations were developed using a risk-based approach, incorporating results from studies of stochastic radiation effects. This differed from previous recommendations, which focused on exposure thresholds designed to prevent deterministic effects, now known as tissue reactions.

Lastly, the effective dose equivalent (H_E) was introduced, taking into account relative organ radiological sensitivities with tissue weighting factor (w_T). Essentially, the effective dose equivalent is the weighted average of dose equivalents (H_T) received by the major body

organs and tissues (Eq. 1.2).

$$H_E = \sum_T w_T \overline{QF_T} D_T = \sum_T w_T H_T \quad (1.2)$$

The 1980s featured key advancements and painful reminders of the potential dangers of harnessing radiation. The 1980 NAS Biological Effects of Ionizing Radiation (BEIR) III report addressed population effects from low levels of ionizing radiation exposure—a pursuit ahead of its time (NAS, 1980). Natural exposure limitation and radioactive waste disposal were addressed in ICRP 39 and 46, respectively (ICRP, 1984, 1985). On April 26, 1986, the No. 4 reactor of the Chernobyl Nuclear Power Plant exploded, leading to widespread fear and distaste for nuclear science applications (Lindell and Perry, 1990). About a year later, a capsule of cesium-137 was stolen in Brazil, leading to four deaths and even greater public concern (Petterson, 1988). It was clear that higher safety standards needed to be applied to radiation-related applications. In response, the International Atomic Energy Agency (IAEA) hosted many safety-related conventions and published a series of International Nuclear Safety Advisory Group (INSAG) reports, two of which were dedicated to the Chernobyl accident (INSAG, 1986, 1992).

In 1990, ICRP Publication 60 emphasized individualized dose limits and protection guidelines for workers, public, and sensitive groups (ICRP, 1991). The occupational dose limit changed substantially from 50 mSv per year in any year to 20 mSv per year averaged over any five-year period, with no more than 50 mSv in any year. The public 1 mSv per year limit was retained. Recommendations on emergency exposure situations and ethical responsibilities reflected the recent public exposure incidents. Dose quantities were again restructured, introducing the effective dose E , which accounts for multiple types of radiation R imparted to a single organ or tissue T (Eq. 1.4). Here, H_T is the newly-defined equivalent dose (Eq. 1.3) and the quality factor is replaced with a radiation weighting factor (w_R). Also given emphasis in ICRP 60 is the depth dose $Hp(10)$ —the personal dose equivalent at a depth of 10 mm in soft tissue. This quantity serves as an estimate of effective dose that can be easily

implemented in personal dosimetry.

$$H_T = \sum_R w_R D_{T,R} \quad (1.3)$$

$$E = \sum_T w_T \times \left(\sum_R w_R D_{T,R} \right) = \sum_T w_T H_T \quad (1.4)$$

In 1993, NCRP Report 116 recommended a stochastic public exposure limit of 1 mSv per year lifetime average (effective dose) and deterministic public exposure limits of 50 mSv to any tissue and 15 mSv to the lens of the eye in any one year (equivalent dose) (NCRP, 1993). For workers, the stochastic one-year limit was 50 mSv and an average of 20 mSv over any five-year period, while deterministic worker limits were simply 10 times greater than the public limits. The exposure limit recommendations of ICRP 60, NCRP 116, and BEIR V were notably influenced by the atomic bomb survivor LSS results, marking the first epidemiologically-driven radiation protection guidelines. The 1988 LSS Report 11 contained results for follow-up through 1985, with significant excess relative risks reported for many cancers including leukemia, lung, and breast cancers (Shimizu et al., 1988). The LSS was an incredibly powerful study for its time, allowing radiation protection authorities to assign risks of specific health outcomes to exposures of various magnitudes. However, important limitations have prompted investment into additional radiation epidemiology studies. A central issue to the atomic bomb survivor cohort is that exposures were received acutely (i.e., all at once) and mostly at high doses (> 100 mGy). Today, most exposure scenarios are low dose and low dose rate. Thus, there has been a special focus on monitoring those exposed to chronic, low doses of ionizing radiation.

In the early 21st Century, a new round of recommendations came from NAS, ICRP, and NCRP. First, in 2006, the NAS BEIR VII Phase 2 report was released. BEIR VII reported not only new limits, but also recommendations for risk modeling based on the LSS cohort (NAS, 2006). Recommended excess relative risk (ERR) and excess absolute risk (EAR) models supported LNT and included effect modification by sex, attained age, age at exposure, and occasionally time since exposure. One year later, ICRP Publication 103

expanded on many past topics such as ALARA, exposure classifications, and the use of the LNT model for regulatory purposes (ICRP, 2007). Additional refinements were made to tissue weighting factors and effective dose. In 2009, NCRP published Report 160, which detailed the magnitude and sources of U.S. population radiation exposures (NCRP, 2009). The U.S. average annual radiation dose was reported to be 6.2 mSv, primarily from natural background and recent increases in the use of medical imaging procedures (Smith-Bindman et al., 2008).

In March 2011, an intense earthquake and tsunami struck Fukushima, Japan, causing three core meltdowns and many explosions within the Fukushima Daiichi Nuclear Power Plant. Although many deaths occurred as a result of the natural disaster, observed health effects associated with radiation exposure are limited (Tsuboi et al., 2022). In light of this incident, the U.S. House of Representatives held a joint subcommittee hearing to examine nuclear energy safety, risk assessment, public health protection, and associated scientific and technical policy issues (U.S. House of Representatives, 2011). At this hearing, radiation epidemiologist John Boice addressed the need for a large study of U.S. workers that will aid our understanding of the health consequences of chronic, low-dose radiation exposure. Such a study would allow the U.S. to develop protection standards directly applicable to U.S. public and worker populations.

Just one year later, funding was granted to fully establish the Million U.S. Radiation Worker and Veteran Study, now known as the Million Person Study (MPS) (Boice, 2012). The MPS population is 10 times larger than the LSS and is comprised of many existing cohorts exposed chronically to ionizing radiation (Boice, 2024). Once cohorts are assembled and analyzed individually, they can be pooled for greater statistical power, resulting in precise and generalizable radiation risk estimates. The MPS is actively publishing results, including initial pooled-cohort risk estimates (Boice, 2024).

Other modern radiation epidemiology studies are underway, providing valuable comparisons to the MPS and LSS results. The International Nuclear Workers Study (INWORKS) is a large, multi-cohort study consisting of radiation workers from France, the United Kingdom, and the United States (Leuraud et al., 2015; Richardson et al., 2025). The Pooled

Uranium Miner Analysis (PUMA) consists of seven uranium miner cohorts from around the world, providing unique results on radon and radon-progeny exposures (Rage et al., 2020). PUMA results are not as easily compared to other studies, as exposures include high-LET exposures resulting from radionuclide intake. Methods are constantly refined within each study, which is discussed further in Section 1.2. Risk estimates are strengthened over time as active cohorts accrue continued follow-up. Recently-published lung cancer mortality risk estimates from select studies are presented for comparison in Table 1.1.

Table 1.1: *Recently published lung cancer mortality risk estimates from prominent epidemiology cohorts. The LSS reports a sex-averaged ERR per 100 mGy for never-smokers at age 70 from age at exposure 30. Never-smoker population size cannot be derived from information in (Cahoon et al., 2017). The MPS reports a sex-adjusted ERR at 100 mGy. INWORKS reports a sex-stratified Poisson maximum likelihood excess relative rate per 100 mGy. Both MPS and INWORKS make indirect adjustments for smoking by socioeconomic status and year of birth.*

Cohort	Reference	Size	ERR at 100 mGy ^a (95% CI)
LSS	(Cahoon et al., 2017)	—	0.08 (0.06; 0.11)
MPS	(Boice et al., 2022b)	367,727	0.02 (-0.03; 0.07)
INWORKS	(Richardson et al., 2025)	309,932	0.07 (0.01; 0.12) ^b

^a Risk estimate specifics differ for each cohort, as detailed in the table caption.

^b Approximate Wald-type 95% confidence interval, assuming a normally distributed point estimate. Converted from a likelihood-based 90% confidence interval (0.02; 0.12) reported in (Richardson et al., 2025).

As for recent committee publications, the ICRP leaned into philosophical, ethical, and policy-related topics with Publication 138, while NCRP Report 180 focused on the modern application of technical methodologies described in ICRP 103 (ICRP, 2018; NCRP, 2018c). With improved epidemiology leading to more accessible low-dose risk estimation, the LNT model has become a contentious topic. As a result, many organizations have taken stances on the matter, including NCRP Commentary 27 and the UNSCEAR 2020/2021 report, both supporting LNT for regulatory purposes (NCRP, 2018b; UNSCEAR, 2022). Views on the LNT model and other radiation protection standards will surely evolve as further scientific findings arise. Ultimately, it is evident that over the years, advancements in radiological protection have enabled safer and more plentiful benevolent uses of nuclear technologies.

1.2 Challenges & Direction

Radiation-associated risk estimation often requires many assumptions, making methodological decisions crucially important. Committee-level publications have thoroughly documented potential and active methods used in a variety of radiation protection applications. Of these methods, it is difficult to create a hierarchy because their overall impact and validity are not easily determined. Due to its broad relevance, a good place to start is the dose rate effect. In radiation epidemiology, the impact of dose rate is of great concern when translating risks estimated from near-instantaneously exposed atomic bomb survivors to populations exposed today at low dose rates. Adjustment for dose rate has been quantified by a dose and dose-rate effectiveness factor (DDREF), with a value of 2.0 in ICRP 60 and then 1.5 in BEIR VII preferred solid cancer risk models, indicating a greater risk at higher dose rates (ICRP, 1991; NAS, 2006). However, DDREF values are considerably uncertain and may vary by dose and LET, as made clear in BEIR VII. Interestingly, high dose rate medical interventions are being developed. FLASH radiotherapy involves administering doses at ultra-high dose rates (≈ 40 Gy/s) with the intention of reducing normal tissue damage (Kim and Zou, 2023). A review on radiation dose rate effects highlighted the significant uncertainties regarding dose rate’s influence on biological outcomes and encouraged enhanced experimental design and a focus on low dose rate exposures, as they are most generalizable to today’s populations (Lowe et al., 2022).

Determining the biological effectiveness of different types of radiation presents another challenge. A fundamental pertinent concept is relative biological effectiveness (RBE)(Eq. 1.5), defined briefly in Section 1.1. An RBE value compares the doses of two radiation types needed to achieve a specific biological endpoint (e.g., 50% cell survival, lung tumor incidence). A common reference radiation in experimental radiobiology is filtered 250 kilovolts peak (kVp) x-rays (i.e., beam contains photons with energies up to 250 kiloelectron volts (keV)). When comparing to another type of radiation, it is important to fix factors such as dose rate and dose location, so that the effect of dose magnitude is properly isolated. Regulatory dose quantities such as equivalent dose and effective dose incorporate biological effectiveness

through a simplified quality factor, or more recently a radiation weighting factor (see Eqs. 1.1, 1.2, 1.3, 1.4). Recommended values of these factors have been updated over time by the ICRP and other organizations, reflecting available biological and epidemiological research. However, significant uncertainty exists around the accuracy of these values, as recognized by many radiation protection professionals (Cucinotta, 2015; Fisher and Fahey, 2017; ICRP, 2007; NAS, 2006). Thus, researchers must consider the limitations of these values when radiation quality is relevant to their study.

$$RBE_{effect} = \frac{D_{reference}}{D_{comparison}} \Big|_{effect} \quad (1.5)$$

Epidemiologic results may not be explained by well-developed biological mechanisms. A relevant example is the observed association of radiation exposure with Parkinson’s disease (Dauer et al., 2024). Without a biological mechanism supporting the observations, it is currently difficult to confidently assign causality. However, data-driven observations in epidemiology are still useful and can have immense impacts on disease prevention. A classic example is English physician John Snow successfully stopping a cholera outbreak in 1854 London by identifying that cholera deaths were clustered around a water pump in the city (Snow, 1856). After removing the pump handle, the number of new cases dropped sharply. Notably, this occurred prior to the acceptance of the germ theory of disease and identification of cholera’s bacterial form, demonstrating that effective public health action can be based on patterns in data alone. Still, a harmonious relationship between biological and epidemiological evidence is ideal. Integrating multiple lines of evidence is especially important when evaluating the effects of radiation on the human body, given the stochastic nature of many of these effects and their dependence on factors such as dose rate, radiation type, and individual susceptibility.

Additional challenges exist in the modeling of radiation-associated human health risks. As discussed in Section 1.1, the LNT model, although often critiqued, is widely-accepted as the best choice for regulatory applications. This model is not applied to all radiation-associated outcomes. For example, tissue reactions such as cataracts and skin erythema are

predominantly experienced above a dose threshold (Fry, 2001; Thome et al., 2018). Arguments are made for alternative models, including hormesis models suggesting a protective effect of low dose radiation exposures (Iavicoli et al., 2023; Mothersill and Seymour, 2022). As substantial and replicated evidence does not exist for an alternative model, the LNT model is still most practical for virtually all radiation protection purposes, as originally recommended in ICRP Publication 9 (ICRP, 1966).

To accurately assess the relationship between dose and outcome risk, confounding factors must be adjusted for within radiation risk models. A confounder is a variable associated with both the exposure and outcome. Without adjustment for confounders, the exposure of interest will be estimated to have an artificially stronger or weaker correlation to the outcome. An example is silica dust inhalation as a confounder for lung cancer mortality in uranium miner studies (Kreuzer et al., 2024). Although radiation is the exposure of interest, silica dust—a known carcinogen—was often inhaled by miners. Since silica dust exposure is related to both radiation exposure (in the workplace) and the outcome of interest, silica dust exposure is a confounder for the relationship between radiation exposure and lung cancer mortality. Uranium miner studies have adjusted for silica dust exposure using industrial hygiene data or stratification by job type, tenure, or calendar period. Conveniently, when adding adjustments for confounders to statistical models, it is often clear when the adjustments significantly improve model fit. Smoking is also an important confounder in radiation epidemiology. Unfortunately, individual-level smoking data are not often available in large epidemiology cohorts. In this case, surrogate measures can be used to indirectly adjust for smoking (see Section 2.5).

Modeling the latency period between exposure and potential outcome is another prominent challenge. Immediately after a radiation exposure, it is typically not possible to detect cancer-related outcomes of interest. In radiation epidemiology studies, a 10-year latency period is often assumed for solid cancers. This is commonly referred to as a lag time and incorporated into risk models by “lagging” dose data by the approximate latency. So, with a 10-year lag time, an exposure at age 45 would appear in the lagged dataset as an exposure at age 55. Lag time choice is influenced by mechanistic understanding and sometimes model

fit metrics. Uncertainties related to this adjustment are not typically considered, likely due to high variation in true latency periods. Recent research has characterized biologically-based latency functions, arguing that their approach may be more appropriate than fixed lag times ([Little et al., 2024](#)). Notably, it is indicated that prostate and thyroid cancer may have a longer minimum latency period, possibly exceeding 20 years. Lag times in radiation epidemiology may need refinement since risk would be misrepresented for outcomes with latency periods that vary greatly from current assumptions. More work must be done to characterize latency periods between radiation exposures and common radiation-associated health outcomes.

At the 2025 NCRP Annual Meeting, which had a special focus on the MPS, radiation epidemiologists interacted with representatives from U.S. regulatory bodies such as the Department of Energy (DOE), Environmental Protection Agency (EPA), and NRC. Communication gaps between epidemiologists and policymakers became evident during the meeting. For example, confusion arose surrounding “internal” analyses performed for risk estimation. General audiences are likely most familiar with clinical trials and case-control studies, in which control groups are well-defined. In a cohort study, identifying an appropriate control group can be challenging, as cohorts are frequently assembled based on exposure status. When conducting Poisson regression (see Section [2.1.3](#)), a baseline model representing an unexposed population must be defined. The baseline serves as a control and could be comprised of a low-dose exposure category (e.g., 0-5 mGy) or only zero-dose individuals. In contrast, Cox proportional hazards regression (see Section [2.1.2](#)) does not require specification of a baseline model. Thus, an “internal” or “within-cohort” analysis can be conducted, in which zero- and low-dose individuals who experience the outcome of interest will inherently drive risk estimates toward the null. In certain settings, it is important to clearly articulate this nuanced approach to risk estimation.

Another communication challenge lies in the subtle difference between “ERR at 100 mGy” and “ERR per 100 mGy.” This example serves as a strong argument for more unified parlance across radiation epidemiology. Here, the conceptual distinction is clearer than the terminology suggests. An ERR per 100 mGy indicates a linear model, such that the ERR

scales proportionally with dose. The ERR at 100 mGy does not imply linearity, so risk at another dose value must be calculated according to the model form. Although it is rarely a topic of discussion in academic publications, an effort to better communicate methods and results in radiation epidemiology would elevate the field’s quality and reach.

An emerging methodological challenge in radiation epidemiology is dose uncertainty estimation. Each cohort within the MPS has a unique dosimetry system, sometimes accounting for multiple types and sources of radiation exposure. Since most MPS cohorts are occupational, it is common that personal dosimeter records are available. Although this is a robust way to monitor radiation exposure, there are multiple sources of uncertainty that could be modeled for these workers. Personal dosimeters, like most measurement devices, have a limited precision. The uncertainty related to the dosimeter precision is a form of random error. Random errors are unpredictable and likely to differ in magnitude and direction for each individual in the cohort. A second source of uncertainty is systematic error, which biases all measurements in the same direction. For personal dosimetry, systematic error can result from inaccurate dosimeter calibration. Assuming that all individuals in a cohort wear the same type of dosimeter, calibrated by the same standards, this uncertainty would be shared across the cohort.

Approaches have been developed to account for dose uncertainty in radiation epidemiology, many of which are covered in NCRP Commentary 34 ([NCRP, 2023](#)). The commentary describes how uncertainties can be either classical or Berkson, depending on the statistical relationship between the true dose and estimated dose. Classical error pertains to error in the measurement of dose that is additive and independent of the true value. Notably, classical error can attenuate the slope of the dose-response curve. For Berkson error, the true exposure varies around the assigned exposure, and often occurs when group exposure estimates are assigned as individual dose values. Most dosimetry systems have complex uncertainty, comprised of both classical and Berkson components. Commentary 34 reviewed seven statistical methods with potential to correct for dosimetric uncertainty. Each have distinct strengths and weaknesses. Some thrive in specific uncertainty scenarios, while others can be more generally applied. It was recommended that software repositories be developed

for some of these methods. Methods most appropriate for radiation epidemiology must be determined so that this important source of uncertainty can be properly represented in risk models.

Epidemiology can reveal important relationships between population characteristics and disease risk, potentially leading to population-specific disease prevention efforts. It is known that factors such as sex and age can affect human radiosensitivity ([Little et al., 2022](#); [Narendran et al., 2019](#)). Radiation epidemiology is particularly well-suited to study these factors simultaneously, as opposed to biological studies, in which a single variable is often isolated. Personalized, or precision, medicine could be greatly improved through understanding of human genetic variability. Genetic variation is often characterized by single nucleotide polymorphisms (SNPs), which are single nucleotide (A, T, C, or G) changes at specific locations in a DNA sequence and the simplest form of DNA variation among individuals ([Shastry, 2009](#)). The National Institute of Health (NIH) maintains the Single Nucleotide Polymorphism Database (dbSNP), which consists of 1.2 billion unique reference SNPs ([NCBI, 2025](#)). One study found that a typical genome differs from a reference human genome at 4.1 to 5.0 million sites ([1000 Genomes Project, 2015](#)). Specific genetic features can be tied to radiosensitivity through molecular epidemiology, an expanding field that investigates how molecular and genetic factors influence disease risk ([Honardoost et al., 2018](#)). A major challenge for molecular radiation epidemiology is obtaining genetic data on exposed individuals. The greatest potential in studies would be realized by obtaining voluntary biological samples from living members of actively-followed cohorts.

As methods in radiation epidemiology are refined to overcome limitations and enhance quality of results, continued follow-up increases statistical power. Pooled cohort studies are now large enough to detect statistically-significant ERRs as small as 0.05 at a 100 mGy exposure level for some frequently-observed outcomes ([Boice, 2024](#)). With unprecedented precision, results from these studies have great potential to inform radiation protection guidelines. Thus, it is crucially important that reported radiation risks are maximally accurate and fully considerate of flaws and limitations.

1.3 Objectives

As MPS cohorts are pooled, it is important that pooled results maintain the quality of results presented for each individual cohort. This becomes challenging when highly heterogeneous cohorts are pooled. The focus of the present study is on the pooling of the MPS Nuclear Power Plant (NPP), Industrial Radiographer (IR), and Medical Radiation Worker (MW) cohorts. Conveniently, the NPP and IR cohorts have been maintained using similar methods and involve similar workplace exposures. The MW cohort is relatively dissimilar, but can be feasibly pooled with the others. These cohorts were selected as components for one of the first MPS cohort pooling efforts primarily due to their large sizes. It is additionally advantageous that the MW cohort contains a relatively large proportion of females. This study investigates the impact of a data-transformation method used in an analysis of pooled-cohort lung cancer mortality risk. This method may have biased resulting risk estimates. Further background is necessary to properly contextualize the method in question and societal significance of the results.

1.3.1 Sex Differences in Radiation-Associated Lung Cancer

Not all cancers—and certainly not all health outcomes—appear to have an association with radiation exposure. In a cohort study, the distribution of doses among those who experience a specific outcome heavily influences the ability to detect an excess risk of obtaining that outcome. An association is easiest to detect when dose values are large, creating stark contrast between exposed and unexposed populations. Cohorts in the present study contain relatively low-dose exposures. To observe statistically significant radiation-associated risks in this case, cohorts must be large, providing a sufficient dose contrast and number of events.

In MPS cohorts, lung cancer is usually among the most frequently occurring outcomes. Still, only for select cohorts (IR and MW) are lung cancer excess risks significantly greater than zero. The third cohort analyzed here (NPP) actually exhibits a non-significant negative excess relative risk for lung cancer mortality, as shown in Table 1.2. Interestingly, the upper 95% confidence interval bound for the NPP estimate matches the lower bounds of the IR

and MW cohort estimates.

Table 1.2: *Lung cancer risks among MPS cohorts. Adapted from (Boice et al., 2022b).*

Cohort	Number of workers	ERR at 100 mGy ^a (95% CI)
Nuclear power plant (NPP)	135,193	−0.04 (−0.11, 0.02)
Industrial radiographers (IR)	123,556	0.13 (0.02, 0.23)
Medical radiation workers (MW)	109,019	0.15 (0.02, 0.27)
NPP + IR + MW	367,727 ^b	0.02 (−0.03, 0.07)
Atomic veterans	114,270	0.04 (−0.11, 0.19)
Mound	4,954	0.00 (−0.03, 0.04) ^c
Mallinckrodt	2,514	−0.02 (−0.18, 0.06) ^c
Rocketdyne	5,801	−0.02 (−0.18, 0.17) ^c
Los Alamos Nat’l Lab	26,328	0.01 (−0.10, 0.11) ^c
Tenn. Eastman Corp.	26,650	−0.08 (−0.17, 0.02) ^c
Rocky Flats	9,535	0.01 (−0.10, 0.11) ^c

^a Doses are at 100 mGy for Mallinckrodt, Los Alamos National Laboratory, Tennessee Eastman Corporation and Rocky Flats where a dose weighting factor of 1 was used for uranium and plutonium dose.

^b 46 workers were in two cohorts and are counted only once in this pooled analysis.

^c Taken as the Hazards Ratio minus 1 at 100 mSv; a dose weighting factor was not applied.

Given that almost all MPS cohorts are overwhelmingly male, it is unlikely to obtain meaningful sex-dependent risks. However, the three-cohort pooling may be the most powerful attempt to date, considering the number of females in the MW cohort and the large number of total lung cancer deaths. Sex-specific lung cancer risks have recently been a popular topic in radiation epidemiology research. NCRP Commentary 32 was released in 2022, covering existing evidence for a sex-specific difference in lung cancer risk and recommendations for improving risk projection (NCRP, 2022). The commentary’s special focus on space activities was prompted by NASA’s concern about elevated mortality risk for female astronauts, based on evidence that female atomic bomb survivors have higher lung cancer mortality risks than males (Cahoon et al., 2017). Ultimately, the commentary suggested that more work must be done in epidemiology, biology, and astronaut risk modeling, as current evidence does not support a definitive sex difference for radiogenic lung cancer.

Conclusions surrounding sex-specific differences in radiogenic lung cancer risks cannot currently be drawn from epidemiology due to inconsistent results and lack of statistical

power. Generally, in nonsmoker or smoking-adjusted cohorts, risk of lung cancer incidence is greater for females, while lung cancer mortality is equivalent or greater for males. To better understand these risks, the NCRP has made suggestions for future epidemiological studies. A glaring issue in lung cancer studies is proper adjustment for smoking. Currently, many MPS cohorts make indirect adjustments for smoking (e.g., socioeconomic status (SES) and year of birth (YOB)). With direct smoking histories, this important confounder can be considered with greater confidence. The MPS is currently making linkages with Centers for Medicare and Medicaid Services data, expecting to obtain information on tobacco use for over 600,000 workers ([Boice et al., 2022b](#)). With data on smoking histories, nonsmoker subgroups could be compared to assess lung cancer risks free of the influence of smoking.

Identified in Commentary 32, Section 4, are multiple plausible biological mechanisms that may explain a greater risk of lung cancer for females. The stated goal of the section is to address *radiogenic* lung cancers. However, most of the mechanistic evidence presented does not involve radiation exposure. So, for these mechanisms to support a radiation-related sex-specific difference, one must assume that radiation exposure influences lung cancer risk in a way that parallels baseline susceptibility. A popular explanation for the sex-specific difference is estrogen’s ability to promote lung cancer cell proliferation. Experiments on both mice and lung cancer cell lines have demonstrated this effect ([Hammoud et al., 2008](#); [Stabile et al., 2005](#)). Clinically, estrogen replacement therapy has been associated with increased lung cancer risks ([Chlebowski et al., 2009](#); [Ganti et al., 2006](#)). Still, some studies have found non-significant or opposite estrogen-related effects ([Meinhold et al., 2011](#); [Pesatori et al., 2013](#)).

Females may have a greater susceptibility to adenocarcinomas ([Barta and McMahon, 2019](#)). This is related to frequent mutations in the female Epidermal Growth Factor Receptor (EGFR), causing abnormal cell growth ([Collisson et al., 2014](#)). A possible relevant factor is biological differences between the male and female lungs. About 60 genes are expressed differentially in the lung between males and females ([Gershoni and Pietrokovski, 2017](#)). However, it is unknown whether these differences have an impact on lung cancer risk. A final point raised in Commentary 32 is that the male and female immune systems exhibit

differences, which lead to higher female rates for autoimmune diseases and other noncancer outcomes. It is concluded in the commentary that evidence from biological and animal studies is not sufficient to make a determination on whether females are at a greater risk for lung cancer, or precisely why this difference may exist.

NASA radiation risk models are derived from LSS atomic bomb survivor data. As discussed in Section 1.2, assumptions must be made to transport risks to NASA’s target population, usually astronauts. Commentary 32 suggests that NASA’s risk of exposure-induced cancer (REIC) and risk of exposure-induced death (REID) overestimate risks because the NASA EAR model was derived from a population that included smokers. NASA was encouraged to incorporate information from several radiation epidemiology studies in its risk projections. Utilizing multiple study results, optimally-informed lung cancer risk projections can be obtained.

The present study investigates a risk estimate within Section 3.2.2.7 of NCRP Commentary 32. A sex-averaged lung cancer mortality ERR at 100 mGy of 0.02 (95% CI: -0.03, 0.07) is reported, as shown in Table 1.2. The resulting risk estimate, also reported in (Boice et al., 2022b), indicates no significant radiation-associated excess lung cancer risk for the population. This result comes from the pooled NPP+IR+MW cohort with about 6,400 lung cancer deaths among 367,722 total workers. Females comprise more than 19% of the cohort, making it especially well-suited for assessing sex-specific lung cancer differences. However, since the individual IR and MW cohort risk estimates are much larger and significantly positive (0.13, 0.15, respectively), the validity of the pooled estimate has been questioned.

1.3.2 Person-Year Grouping

When the NPP, IR, and MW cohorts were pooled, the resulting dataset was too large to perform Cox proportional hazards regression in the 32-bit version of epidemiology software Epicure (Preston et al., 1993). To work around this issue, analysts grouped every two person-years, or rows, in the dataset, nearly halving its size. All explanatory variables in the dataset were preserved, but represented in two-year, rather than one-year, intervals. It was assumed

that the loss in granularity would not substantially impact risk estimation.

Now, enhanced epidemiology software capabilities have been developed ([Giunta et al., 2025](#)), enabling analysis of the full pooled dataset. Thus, the full dataset can be rapidly grouped and reanalyzed in an effort to characterize bias introduced by the person-year grouping method. In the following chapters, three unique grouping methods are applied to individual and pooled cohorts. For mortality from lung cancer, Parkinson’s disease, leukemia except for chronic lymphocytic leukemia (CLL), and ischemic heart disease, risk estimates for each individual cohort and a summary estimate from a meta-analysis are presented. The selected outcomes are common among previous MPS analyses and conveniently provide a variety of number of events and risk estimate magnitudes. The effect of person-year grouping is characterized for each estimate, and a simulation study is performed to provide context to the observed effect. Finally, the pooled cohort risk estimate is compared to the previously published value. Implications of the observed bias are explained and recommendations are given for future analyses.

Chapter 2

Methods & Materials

2.1 Statistical Methods

2.1.1 Survival Analysis Basics

Survival analysis is a branch of statistics for which the outcome variable of interest is the expected time until an event, or failure, occurs. In its simplest form, with no additional explanatory variables, a survival model will depend only on the times at which the events of interest occur. The probability that a subject survives after some time t is represented by the survival function,

$$S(t) = P(T > t) = 1 - F(t) = \int_t^{\infty} f(x)dx, \quad (2.1)$$

where T is a random variable denoting the failure time with cumulative distribution function (CDF) $F(t)$ and probability distribution function (PDF) $f(t)$. These three related functions are represented in Figure 2.1, with dotted lines marking values at $t = 4$. Following Eq. 2.1, it is evident that 37% of the survival time distribution is greater than $T = 4$. This can be interpreted as 37% of the study population surviving past $t = 4$.

Traditionally, once a subject experiences an event, they are no longer considered at risk (i.e., subject exits the “risk set”). During the study period, when a subject enters or

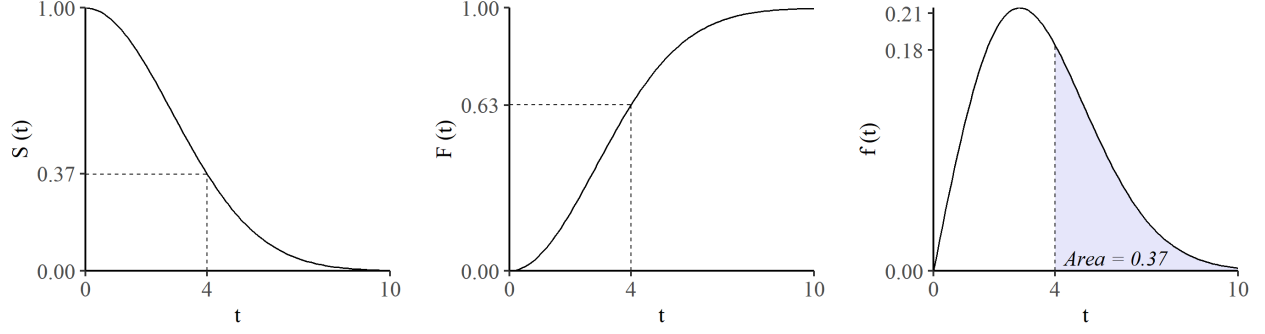


Figure 2.1: Representative survival function $S(t)$ generated from a Weibull model with shape parameter $\gamma = 2$ and scale parameter $\lambda = 5$. Dotted lines are placed at $t = 4$, demonstrating the relationship between the three functions.

exits the risk set before experiencing the event of interest, this is considered censoring—an important concept in survival analysis. In a cohort study, censoring can occur if the subject experiences an alternative event (e.g., death), the study period ends, or the subject drops out—often labeled as “loss to follow-up.” A key assumption in most survival analysis models is that censoring is non-informative, meaning that it does not provide information on the individual’s likelihood of experiencing the event. This assumption is violated in some cases, such as when an individual drops out of the study due to poor health. Statistical methods have been developed to incorporate information from censoring when appropriate ([Jin and Fang, 2024](#); [Turkson et al., 2021](#)). Censoring is categorized as right, left, or interval. Loss to follow-up is a case of right censoring, where the true survival time is only known to be greater than the censoring time. Left censoring occurs when a subject enters the risk set after the study period begins. For non-fatal events, it is possible that a left-censored subject experienced the event of interest before joining the study. Interval censoring is when a subject is both left and right censored. The three forms of censoring are illustrated in [Figure 2.2](#).

An alternative way to express survival is by the hazard function, $\lambda(t)$, defined as the instantaneous risk of event occurrence at time t , conditional on survival up to that time, formally defined in [Eq. 2.2](#). The hazard at time t is more conveniently expressed as the ratio of the probability density at time t to the probability of surviving beyond time t , [Eq. 2.3](#). Also relevant to risk assessment in survival analysis is the cumulative hazard function $\Lambda(t)$,

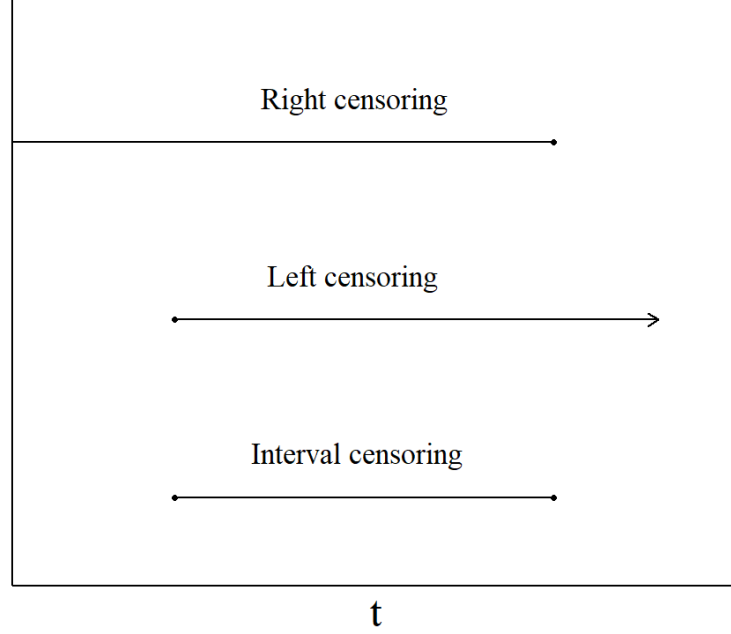


Figure 2.2: *Illustration of censoring types with dots representing censoring. X-axis represents the ongoing study period beginning at $t = 0$.*

which can be interpreted as the accumulated risk up to time t , expressed in Eq. 2.4. When expressing risk in survival models, $\lambda(t)$ is usually preferable to $\Lambda(t)$ and $S(t)$.

$$\lambda(t) = \lim_{\Delta t \rightarrow 0} \frac{P(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t} \quad (2.2)$$

$$\lambda(t) = \frac{f(t)}{S(t)} \quad (2.3)$$

$$\Lambda(t) = \int_0^t \lambda(x) dx \quad (2.4)$$

An array of survival- and risk-related questions can be addressed through the use of existing survival models. Kaplan-Meier estimation is a foundational non-parametric method for generating survival curves (Kaplan and Meier, 1958). Survival is updated every time an event occurs, factoring in any censored observations between event times. This concept is best demonstrated through an example. Consider 10 asthmatic individuals administered a new medication and instructed to maintain usual activity levels, followed until an asthma attack occurs. Shortly after the study begins, a first individual experiences an asthma at-

tack. Survival is updated to $9/10$, or 0.9 , creating a new time interval (2) with a smaller survival probability. Next, an individual drops out of the study, citing nausea after taking the medication. The individual is censored and survival remains at 0.9 , as no new event occurred and censoring is assumed non-informative to the risk of experiencing an asthma attack. Then, a second individual experiences an asthma attack. Because one has already experienced the event and another has been censored, the total number at risk at the event time is 8. The probability of surviving through this second interval is $7/8$, or 0.875 . Now, the cumulative survival (through intervals 1 and 2) is 0.9×0.875 , creating a new interval with $S(3) = 0.7875$. This progression is shown in Figure 2.3. Survival of multiple groups can be compared by overlaying Kaplan-Meier curves on the same graph. Figure 2.4 depicts realistic survival curves stratified by sex with shaded confidence intervals and vertical ticks representing censoring. This type of comparison is also commonly made with curves representing different treatments in an interventional study.

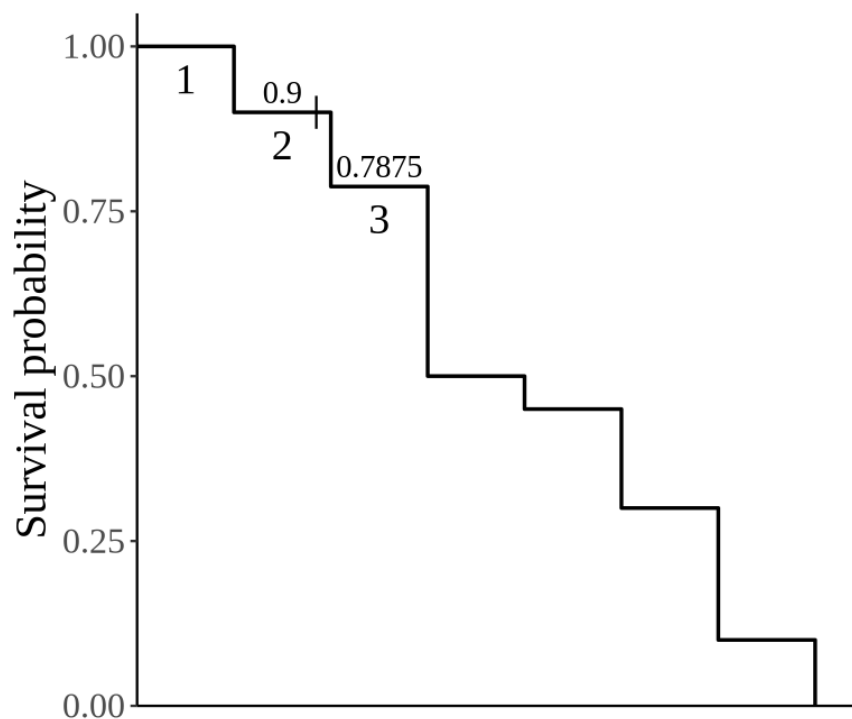


Figure 2.3: *Kaplan-Meier survival curve corresponding to the given Kaplan-Meier example calculations. The vertical tick in interval 2 represents the described censoring.*

Parametric survival models rely on underlying distributions to characterize expected

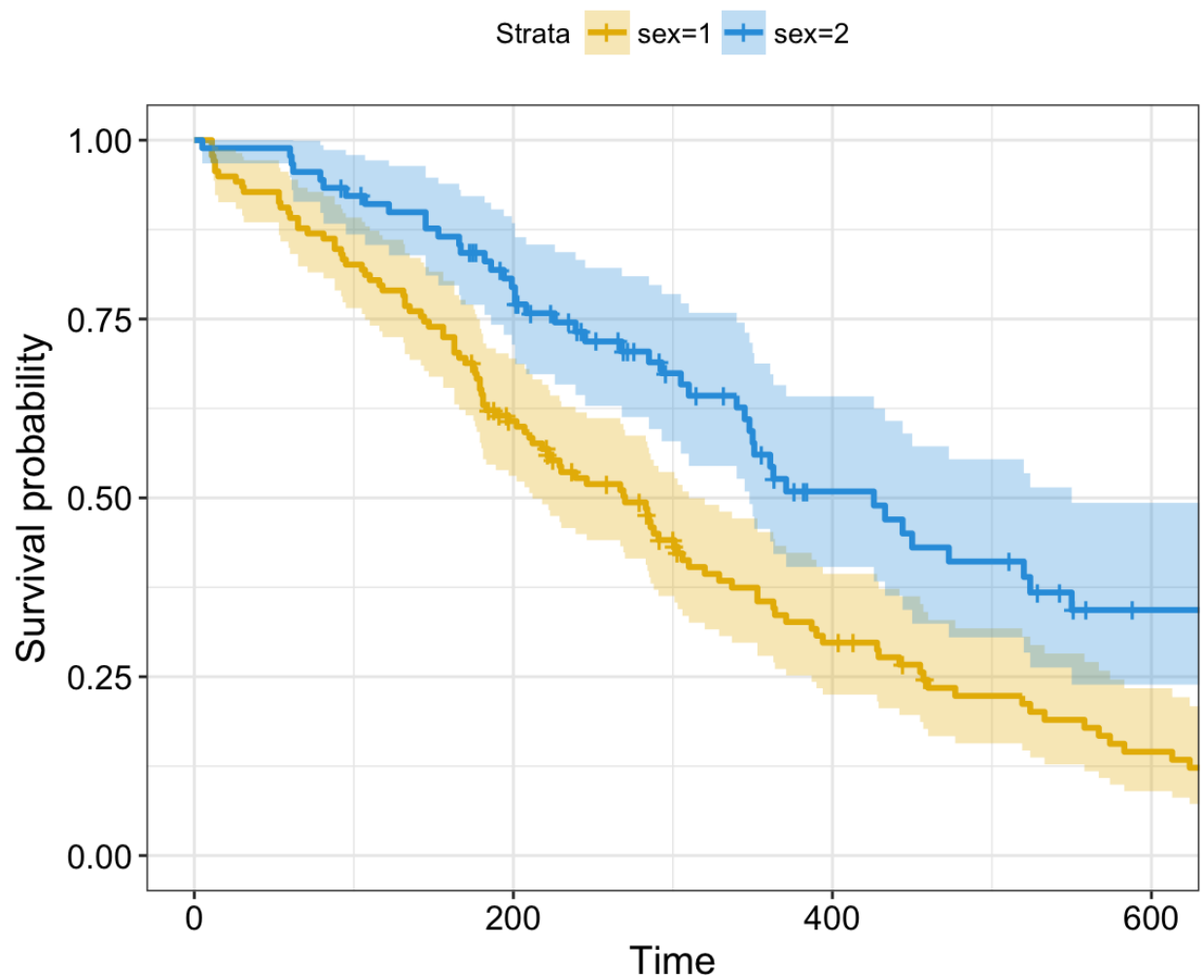


Figure 2.4: *Realistic sex-stratified Kaplan-Meier survival curves with shaded confidence intervals and vertical ticks representing censoring. Reproduced from <https://www.sthda.com/english/wiki/survival-analysis-basics>.*

survival times. The simplest example of this is the exponential model, which assumes a constant hazard rate λ with survival decreasing exponentially over time (Eqs. 2.5, 2.6). Because risks usually change over time, the exponential model is unrealistic for most real-world applications.

$$h(t) = \lambda \quad (2.5)$$

$$S(t) = \exp(-\lambda t) \quad (2.6)$$

A more realistic model is the Weibull model, in which the hazard monotonically increases or decreases, depending on the shape parameter γ (Eqs. 2.7, 2.8) (Weibull, 1951). Over time, the hazard increases if $\gamma > 1$, decreases if $\gamma < 1$, and reduces to the exponential model when $\gamma = 1$.

$$h(t) = \lambda \gamma t^{\gamma-1} \quad (2.7)$$

$$S(t) = \exp(-\lambda t^\gamma) \quad (2.8)$$

A third model often used to represent biological aging is the Gompertz model, in which the hazard increases or decreases exponentially over time (Eqs. 2.9, 2.10) (Gompertz, 1825). Similar to the Weibull model, a parameter γ influences the shape of the hazard.

$$h(t) = \lambda \exp(\gamma t) \quad (2.9)$$

$$S(t) = \exp\left(-\frac{\lambda}{\gamma}(\exp(\gamma t) - 1)\right) \quad (2.10)$$

While these models can be used to describe hazard and survival functions directly, they are best utilized when embedded into regression frameworks that relate covariates to survival time. Accelerated Failure Time (AFT) models assume covariates accelerate or decelerate the passage of time to an event, rather than directly manipulating the hazard (Wei, 1992). The AFT model is a linear model of the log survival time,

$$\log(T) = \mu + \beta^\top X + \sigma \epsilon, \quad (2.11)$$

with intercept μ , regression coefficients β , covariate vector X , and error term ϵ , which is scaled by σ and follows a specified distribution (e.g., Weibull, Gompertz). Instead of risk, a covariate change indicates a relative change (increase or decrease) in expected survival time. The AFT model is best utilized when survival times are well-represented by a parametric distribution and interpretable covariate effects on survival time are desirable. Accordingly, AFT models are often used in reliability engineering testing and simulation. For analyzing health outcomes, it may be more natural to use models focused on translatable risks, described in the following sections.

2.1.2 Cox Proportional Hazards Regression

Researchers are often interested in quantifying risk rather than survival. A popular model for assessing the influence of external factors on risk is the Cox proportional hazards model. Proposed by Sir David Cox in 1972, proportional hazards regression enables estimation of a hazard ratio (HR) based on specified predictor variables, without direct specification of the baseline hazard function (Cox, 1972). Avoiding assumptions about the shape of the baseline hazard, the Cox model provides a convenient way to assess comparative risks. It is considered a semi-parametric model because covariate effects ($\vec{\beta}$) are parametric while the baseline hazard $h_0(t)$ is nonparametric. The Cox model relies on the assumption of proportional hazards, meaning that the hazard ratio remains constant over time. Consequently, all regression parameters ($\vec{\beta}$) must not change with time. This is violated when a covariate effect is heavily time-dependent, such as heightened sensitivity to risk factors immediately following a surgical procedure.

In a standard Cox model, covariate values must be fixed (e.g., sex, year of birth). When assessing radiation risks, it is necessary that dose accumulates over time, requiring a time-varying covariate $X(t)$. The Andersen-Gill (AG) formulation of the model was designed to handle time-varying covariates by use of a counting process framework (Andersen and Gill, 1982). For the standard Cox model, a compatible dataset includes one row per subject. In the AG counting process framework, the survival dataset contains multiple rows for each subject

(often by year) in which explanatory variables can vary. Each interval at risk contains an event indicator, interval start and stop times, and up-to-date covariate values (e.g., current cumulative dose). A basic formulation of the Cox model with time-varying covariates is

$$h(t) = h_0(t) \exp(\beta^\top X(t)). \quad (2.12)$$

Rearranging, the ratio of the covariate-influenced hazard to the baseline hazard (HR) can be directly estimated by

$$\frac{h(t)}{h_0(t)} = \exp(\beta^\top X(t)). \quad (2.13)$$

In the case of rare events (e.g., radiation epidemiology), the HR is a valid approximation of relative risk (RR) ([Greenland, 1987](#)).

The AG formulation of the Cox proportional hazards model is well suited for estimating excess, radiation-associated risks in large cohort studies. With exposure data and a corresponding fitted regression coefficient $\hat{\beta}_D$, the relative risk for a population exposed to a dose of say, 100 mGy, can be calculated as

$$RR \simeq \exp(\hat{\beta}_D \times 100 \text{ mGy}). \quad (2.14)$$

$$ERR = RR - 1 \quad (2.1)$$

This relative risk can be interpreted as the risk for a population exposed to a 100 mGy dose relative to the risk for an unexposed population. In practice, $\hat{\beta}_D$ would be one parameter in a fitted model containing additional $\hat{\beta}_i$ terms adjusting for known confounding and modifying effects. The relative risk for any isolated $\hat{\beta}_i$ variable can be calculated as described in [Eq. 2.14](#). Uncertainty surrounding the relative risk will be characterized by variance associated with the fitted regression parameter $\hat{\beta}_i$.

2.1.3 Poisson Regression

Another popular way to model radiation risks is by Poisson regression ([McCullagh and Nelder, 1989](#); [Poisson, 1837](#)). Although not typically considered a survival analysis model, its properties are well-suited for estimating event risks. In this framework, the response variable is typically a “count,” assumed to follow a Poisson distribution. The model estimates the expected number of events μ as a function of explanatory variables X . An offset term $\ln(t)$ is then included to account for differing person-time contributions across observations. The model can be reformulated to estimate the counts per unit time, or event rate $\lambda = \frac{\mu}{t}$. To ensure that counts and count rates are restricted to positive values, an exponential link function is applied to the model’s response variable, leading to the following model formulation:

$$\ln(\mu) = \beta^T X + \ln(t) \quad (2.15)$$

$$\ln\left(\frac{\mu}{t}\right) = \ln(\lambda) = \beta^T X \quad (2.16)$$

Poisson regression assumes a constant event rate over time within each covariate stratum. So, convenient comparisons of stratified event rates can be made using this fully parametric framework. Unlike the Cox proportional hazards model, a baseline model must be specified to generate comparisons (e.g., relative risks). When assessing radiation exposure effects, obtaining a realistic baseline model is challenging when the cohort lacks unexposed individuals. External event rates, such as U.S. mortality statistics, can be used as a baseline but are unlikely to accurately represent the study population ([Li and Sung, 1999](#)). For example, occupational cohorts are subject to the healthy worker effect—the concept that employed populations are typically healthier than the general population. Possible solutions include using an unexposed, working external population or defining a dose range (e.g., < 5 mGy) as an internal comparison group. Although convenient for making comparisons, the constant event rate assumption can be unrealistic. For example, many disease rates are strongly dependent on age. Including age as a model covariate may accommodate for this effect. In some cases, follow-up time is used in the model to further soften the constant event rate

assumption.

Just as Cox model hazard ratios approximate relative risks, Poisson model risk ratios are reported as relative risks in radiation epidemiology. Members of the MPS have demonstrated that Cox and Poisson models will yield similar radiation risk estimates, given that appropriately narrow age categories were utilized to control the confounding of age in Poisson models ([Golden et al., 2024](#)). This underscores the importance of making appropriate time-related adjustments when applying Poisson regression to epidemiological data. It was concluded that Cox and Poisson regression are equally viable for this purpose. Although unified methodology may be desirable to some, the diverse model choices among radiation epidemiologists will only strengthen confidence in converging results. Still, continued discourse and formal study of methodological choices in radiation epidemiology would be beneficial to the field.

2.2 Software Tools

2.2.1 R

Statistical analysis and data manipulation were performed using R, a free and open source software language and environment for statistical computing and graphics ([R Core Team, 2025](#)). R was developed to be easily extended via packages, many of which are hosted on the Comprehensive R Archive Network (CRAN) family of websites covering a wide range of modern statistical approaches. A few important R packages crucial to the present study are described in the following subsections.

2.2.1.1 Colossus

Colossus is an R package that provides an open source means of performing survival analysis on big data with complex risk formulas ([Giunta et al., 2025](#)). Although developed for radiation epidemiology, Colossus is a powerful tool capable of performing large-scale survival analysis in any field. Cox proportional hazards, Poisson, and Fine-Grey competing

risk models can be flexibly defined as sums or products of linear and/or non-linear terms. Notably, Colossus can handle datasets with over 50 million rows, enabling regression on large pooled cohorts in radiation epidemiology. The computational efficiency of Colossus is enabled through backend C++ integration, in which large matrix regression can be performed. Additionally, calculations in Colossus can be parallelized, significantly reducing computational time and further enabling intensive regressions.

Colossus is used in the present study to perform Cox proportional hazards regression and for light data manipulation with the `factorize()` function, which creates leveled indicator variables from categorical data in preparation for regression. Simple log-linear Cox models are fit to datasets exceeding 10 million rows in size—a burdensome task without the Colossus package.

2.2.1.2 data.table

`data.table` is an R package that provides an enhanced version of the base R `data.frame` object type ([Barrett et al., 2025](#)). The `data.table` format enables data management and transformation capabilities that greatly exceed those of base R. Importantly, iterative modifications to dataset features process quickly due to in-place object modification, efficient memory use, and other low-level functional optimizations.

Detailed in [Section 2.4](#), rows of data are grouped using combinations of multiple group sizes, methods, and outcomes, requiring hundreds of grouping procedures applied to datasets containing millions of person-years. Fast versions of data querying, if-else, and write/read functions make rapid person-year grouping possible. Operations using `data.table` were followed by Colossus regressions. By reducing computational time, these packages together enabled more expansive analyses within the present study.

2.2.1.3 ggplot2

`ggplot2` is a renowned data visualization package in R with impressive flexibility and control over visual output ([Wickham, 2016](#)). Uniquely, `ggplot2` follows a conceptual framework called

The Grammar of Graphics ([Wilkinson, 2005](#)), which allows you to create graphs based on composable elements, instead of being limited to a predefined set of charts. Most of the graphical figures in the present study were generated using ggplot2.

2.2.2 Python

Some figures were produced using the matplotlib.pyplot library in the Python programming language ([Hunter, 2007](#); [Python Software Foundation, 2025](#)). Among data scientists, Python is a popular choice for its machine learning libraries. This work, however, involves no machine learning approaches.

2.3 Data

The data used in this study are from three of the largest single cohorts in the MPS. Upon pooling the three cohorts, risks for a variety of outcomes can be estimated with greater precision than in past MPS studies. Datasets were acquired from multiple sources and each have unique features related to dosimetry, outcomes, and covariate distributions. A de-identified version of the Nuclear Power Plant Workers cohort is available to U.S. researchers through the Oak Ridge Institute of Science and Education (ORISE) Comprehensive Epidemiology Data Resource (CEDR) platform ([ORISE, 2025](#)). All data in this study from NPP, IR, and MW cohorts were supplied by the MPS, including NPP data that may be updated beyond what is available on CEDR. Institutional review board (IRB) exemptions from Kansas State University and Vanderbilt University were obtained to ensure safe and lawful access of the de-identified data used in this investigation. The following cohort descriptions reflect information presented in the major publications associated with each cohort. Relevant summary statistics for the individual and pooled cohorts are shown in Table [2.1](#).

2.3.1 Nuclear Power Plant Workers

Over one million U.S. nuclear power plant workers employed from 1957 through 2011 were available for study ([Boice et al., 2022a](#)). Most of the cohort exists within the NRC-maintained Radiation Exposure Information Reporting System (REIRS) ([Anzenberg et al., 2010](#)). About 16% of the final cohort overlapped with the Landauer, Inc. dosimetry database, while less than 1% of individuals were drawn only from Landauer ([Yoder et al., 2021](#)). Workers were excluded if their date of first monitoring was after 1984. Workers employed after 1984 were less likely to have received moderate to high cumulative doses, and they were younger and less likely to have died, so the final cohort was selected from those first monitored before 1985 on the basis of cost and information value. The 1980-1985 period was strategically included to capture increased worker exposures due to reactor modifications following the 1979 Three Mile Island reactor accident. Of more than 300,000 workers with cumulative doses less than 10 mSv, a 10% sample was selected. This was done to save costs while maintaining strong statistical power for dose-response analyses. Short-term workers (< 30 days) and duplicate or invalid identifier records were removed. The final study population is 135,193 workers, just over 3% of which were female. Measures of SES were determined based on census block mean education levels ([Cohen et al., 2022](#)).

Vital status was determined through 2011 using the Social Security Administration (SSA) Service for Epidemiological Researchers for alive status ([U.S. SSA, 2025](#)) and the Center for Disease Control and Prevention (CDC) National Death Index (NDI) for death notifications ([CDC, 2025](#)). A matching algorithm was used to confirm the fact of death ([Campbell et al., 2008](#)). Information from the NDI, state mortality data files, and death certificates from state health departments identified underlying and contributing causes of death. For follow-up through 2011, 106,069 were confirmed or assumed alive and 29,124 workers were found to have died. Causes of death were coded based on the International Classification of Diseases (ICD) revision in effect at the time of death. Special care was taken to classify forms of leukemia into CLL and non-CLL categories, since CLL has a relatively slow progression and generally affects older populations ([Rozman and Montserrat, 1995](#)).

Dosimetry for all three cohorts closely follows the recommendations of NCRP Report No. 178 (NCRP, 2018a). Radiation exposures received by nuclear power plant workers were mostly from external gamma radiation, with negligible contributions from neutrons or internal exposures (Bouville et al., 2015). Personal dose equivalents, $H_p(10)$, were available from both REIRS and Landauer files. The study roster was linked to the U.S. DOE-maintained Radiation Exposure Monitoring System (REMS) to account for past exposures including DOE employment and military service dosimetry databases. All available doses were combined to create annual dose estimates following methods previously described (Boice et al., 2018). Mean cumulative personal dose equivalents were 19.5 mSv for all eligible workers and 52.6 mSv for the study population. Information on exposure circumstances was derived from a workshop held with former NPP workers, dosimetrists, and health physicists (EPRI, 2017). Most exposures were from high-energy low-LET photons, predominantly from Co-58, Co-60, and Cs-137 during maintenance, modification, and repair work. Exposure fields were generally anterior to posterior (AP) with degraded energy through piping, valves, or tank steel. Personal dose equivalents were converted to organ doses by way of a conversion coefficient accounting for exposure geometry and incident gamma radiation following methods in ICRP 116 (ICRP, 2010).

2.3.2 Industrial Radiographers

The industrial radiographers cohort consists of workers followed from 1969 through 2019 using methods very similar to those of the NPP cohort (Dauer et al., 2024; Mumma et al., 2023). A study population of 123,401 was drawn from the NRC REIRS and Landauer databases, without cumulative dose and year of first employment exclusion criteria. Individuals in the IR cohort were considered eligible if they had at least 30 days of radiation monitoring and if Social Security Number or name and date of birth were available. SES was again assigned by average education levels from census block data.

Vital status was determined from the mortality databases specified for the NPP cohort. Individuals were linked to REMS records to include any other career radiation exposures. No

internal radiation exposures were considered as there were minimal intakes of radionuclides among industrial radiographers. Primary exposures sources in this population were Ir-192 and less commonly Co-60. NCRP 178 methods were used for dose conversion, as described for the NPP cohort. Workers primarily serviced nuclear power plants and U.S. naval shipyards, so typical exposure scenarios were similar to those experienced by NPP cohort members. Due to their comparable occupational settings and experiences, minimal heterogeneity is expected between the IR and NPP study populations.

2.3.3 Medical Radiation Workers

Millions of workers in hospitals, clinics, and private medical practices have been monitored by Landauer since 1977 (Boice et al., 2024; Yoder et al., 2022). Over 1.7 million medical workers first monitored between 1965 and 1994 were determined to be study eligible. Cost-benefit analysis led to exclusion of individuals with less than 10 mSv cumulative badge dose, less than 2 years monitored, or presence in another MPS study, leading to a study population of 109,019 workers. Notably, this population is nearly 50% female. The cohort contains a wide variety of occupations within medical settings, categorized into general radiology, interventional radiology, nuclear medicine and radiation oncology, or other. No direct measure of SES was assessed.

Vital status was determined as for the NPP and IR cohorts. Through 2016 follow-up, nearly 90% of the workers were still either alive or assumed alive. Following NCRP 178, $H_p(10)$ doses were adjusted to represent organ absorbed doses, accounting for conditions of the exposures. Unique to this cohort, some workers wore lead aprons when conducting radiation-involved procedures. Most of the time, dosimeters would be worn over the lead apron, leading to an average 20-fold overestimation of dose to organs in the torso area (NCRP, 2018a). Careful dose reconstruction was performed to accurately represent doses to organs shielded and unshielded by lead aprons. Because high energy photons are not easily shielded by a lead apron, individuals were categorized into three exposure groups: exposure to low energy photons without a protective apron, exposure to low energy photons

with a protective apron, and exposure to higher energy photons (NCRP, 2018a).

Although there are differences among the three cohorts, fundamental methodological choices align the cohorts in important areas such as selection, dosimetry, and outcome determination. Modeling choices for the pooled analysis described in Section 2.8 are made with careful consideration of the similarities and differences among these cohorts.

Table 2.1: *Characteristics of pooled and individual cohorts assessed in the present study, including average lung dose and total lung cancer deaths.*

Cohort	Size	% Alive	% Female	Follow-Up	Person-Years	Mean Lung Dose (mGy)	LC ^b Deaths
NPP	135,193	78.5%	3.3%	1957–2011	4,079,404	40.4	3,382
IR	123,401	80.5%	10.5%	1969–2019	3,415,656	15.0	2,772
MW	109,019	89.5%	49.4%	1965–2016	2,779,613	11.2	850
Pooled ^a	362,542	83.6%	19.6%	1957–2019	10,116,807	22.6	6,868

^a 5,071 workers were in both NPP and IR cohorts, but only counted once in the pooled analysis.

^b Lung Cancer

2.4 Person-Year Grouping Methods

As described in Section 1.3.2, a published pooled lung cancer risk estimate was potentially biased by grouping of person-year records (NCRP, 2022). Person-year grouping was performed to condense data to a size suitable for Cox proportional hazards regression in the 32-bit version of the Epicure risk modeling software (Preston et al., 1993). To properly assess the impact of person-year grouping, the process must be well-defined.

The grouping process can be described through a generic exposure-outcome study with annual follow-up, cumulative dose as the exposure variable, and age as the underlying time scale. To satisfy the counting process format required by the Andersen-Gill Cox model formulation, each row represents a follow-up year with age at entry and age at exit values. Columns for the exposure variable—cumulative dose—and a binary outcome indicator are also used. Other covariates may be included, but it is assumed they are time-invariant and thus unaffected by grouping.

A decision must be made on how time-varying variables are represented in grouped records. For the case of cumulative dose (a cumulative and continuous metric), the most

accurate representation in a two year interval is the cumulative dose at the end of the interval. Figure 2.5A shows a standard grouping process in which the most recent (maximum) cumulative dose is used for the resulting grouped rows. Figure 2.5B illustrates the new cumulative dose representation. With potential for bias in mind, two additional grouping methods are tested. First, the average—rather than maximum—cumulative dose in the grouped interval is used as the resulting cumulative dose value. This is the standard way of grouping with the DATAB module of Epicure, often employed when grouping records for Poisson analysis. Figure 2.6A and 2.6B demonstrate this method.

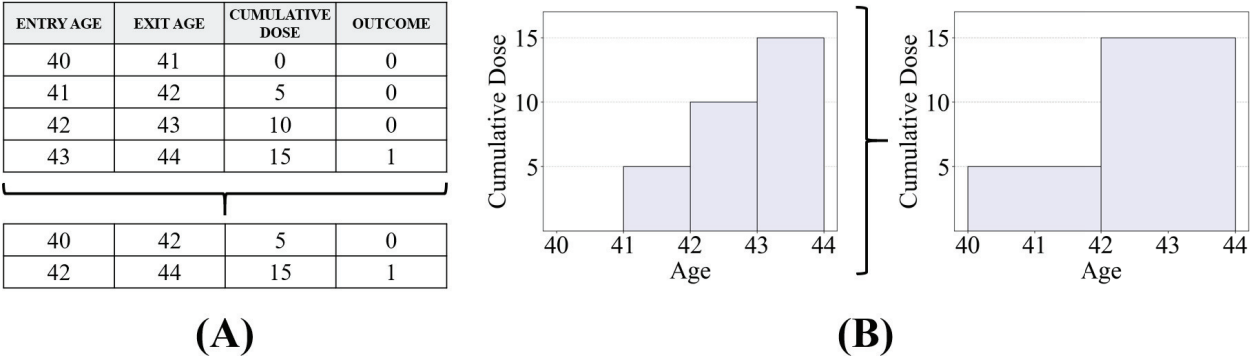


Figure 2.5: Representations of the maximum cumulative dose grouping method, shown as a hypothetical data snippet (A) and an illustration of annual cumulative dose values (B).

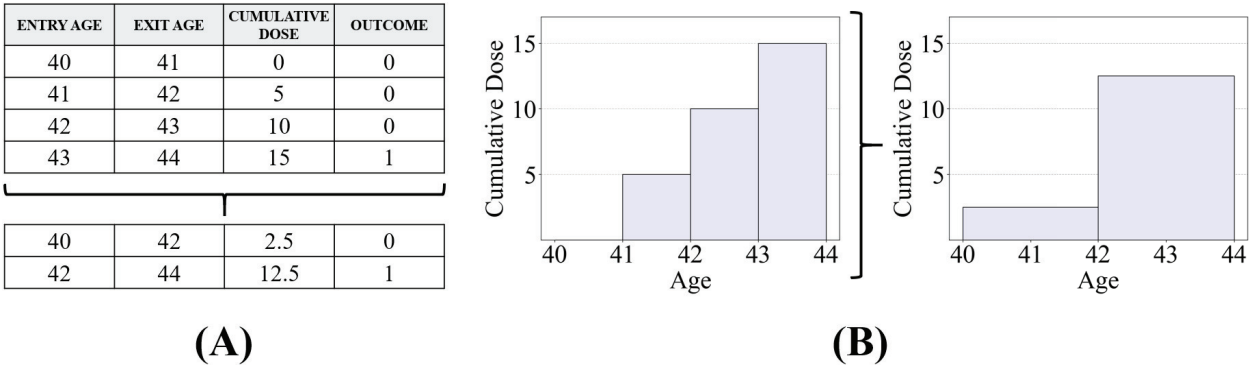


Figure 2.6: Representations of the average cumulative dose grouping method, shown as a hypothetical data snippet (A) and an illustration of annual cumulative dose values (B).

The binary outcome indicator, which changes only for those who obtain the outcome of interest, is another time-varying variable necessarily present in a Cox analysis. As a final grouping method, event rows are excluded from the grouping process in an effort to avoid

misclassifying the event time. This method substantially affects regression results only when grouping with the average cumulative dose method. The three grouping methods are applied with group sizes of up to six rows for each outcome of interest in individual cohort, pooled, and simulated datasets.

Custom algorithms for grouping are developed within R, utilizing the `data.table` package’s optimized data handling capabilities. Algorithm runtime is reduced immensely over the course of development, which is necessary for the eventual multi-method, multi-outcome grouping of the pooled dataset. In early versions, minimal use of `data.table` functionalities and inappropriate use of nested while-loops resulted in day-long, single-method grouping of 4-million-row NPP lung cancer data. Vast improvements are made by taking advantage of the `data.table` object’s ability to split datasets into ordinal vectors. In the final algorithms, datasets are grouped by study ID, records within IDs are tagged (categorized) based on desired group size, and then grouped according to the desired grouping method. Final grouping functions process the pooled dataset in under five minutes for the most strenuous grouping cases. Scripts for individual cohort, pooled, and simulated person-year grouping functions can be accessed at <https://github.com/deckerberg/pyg-thesis/blob/main/group-header.R>.

2.5 Individual Cohort Analysis

For the NPP, IR, and MW cohorts, risk estimates are generated for a variety of outcomes and person-year grouping methods using the Andersen-Gill formulation of the Cox proportional hazards regression ([Andersen and Gill, 1982](#); [Cox, 1972](#)). Model choices reflect methods in the MPS analyses, but regressions for ERR estimates are instead performed using the Colossus R package ([Giunta et al., 2025](#)). Each cohort’s Cox model uses age as the underlying time scale and cumulative radiation dose as the exposure of interest. A categorical year of birth (YOB) covariate is included to adjust for potential health and behavioral trends. The NPP and IR cohorts have six YOB categories with four 10-year intervals between “<1920” and “≥1960” categories. The MW cohort has six categories between “<1910” and “≥1970.” SES for the

NPP and IR cohorts is based on census block data (Cohen et al., 2022), split into three categories—low, medium, and high. For MWs, census block data is not available. However, it was demonstrated that occupational category has a credible correlation to SES (Boice et al., 2024). Adjusting for SES is viewed as crucially important to account for various lifestyle factors, particularly as an indirect adjustment for smoking (Cohen et al., 2022). Thus, all occupational category levels are included in the model. Finally, biological sex is included as a model covariate to adjust for any sex-specific differences in risk.

In the resulting Cox proportional hazards model, all variables are log-linear such as covariates X in the simplified model,

$$\lambda(t) = \lambda_0(t) \exp(\beta X). \quad (2.17)$$

Risk estimates are presented as ERR at 100 mGy with variance represented by Wald-type 95% confidence intervals. Each of the three grouping methods described in Section 2.4 are applied with up to six-record group sizes for the outcomes of mortality attributed to non-CLL leukemia, lung cancer, Parkinson’s disease, and ischemic heart disease. Contributing cause of death cases are included only for non-CLL leukemia, following previous MPS analyses (Boice et al., 2022a, 2024, 2022b). Risk estimates are presented for 60 combinations of grouping method, group size, and outcome for each of the three cohorts. Full-dataset (ungrouped) risk estimates serve as baselines to which grouped estimates can be compared.

2.6 Simulation Study

Observation of person-year grouping-related bias in MPS cohorts is limited by the fact that the underlying true risk estimate is unknown. Thus, it would go unnoticed if a grouping process led to a more accurate risk estimate. To explore this possibility, person-year grouping is applied to simulated survival datasets, in which the underlying risk estimate is known.

Datasets are designed to approximate MPS cohort data. Individual exposures are simulated based on the NPP cohort, in which about 28% of annual records contain a positive

dose value. For 150,000 simulated individuals, each annual record has a 28% chance of being assigned a positive dose value. Of those positive dose records, a dose value is sampled from a log-normal distribution with a mean of 1.188 and a standard deviation of 1. This distribution closely resembles the distribution of doses among positive annual dose records in the NPP cohort. The resulting annual dose data is converted to cumulative dose for regression.

Events for the arbitrary outcome of interest are simulated based on the survival function's cumulative distribution function, which represents the accumulated risk up to time t ,

$$F(t) = 1 - S(t) = 1 - \exp \left(- \lambda_0 \exp (\beta_D X(t)) \right), \quad (2.18)$$

with baseline hazard λ_0 , cumulative dose data X , and a cumulative dose regression parameter β_D . A baseline hazard value of 0.001 and a dose regression parameter of $\ln(1.001)$ resulted in about 7,500 events in each simulated dataset, resembling lung cancer mortality event prevalence in the NPP cohort. The chosen dose regression parameter translates to an ERR at 100 mGy of 0.1, which is expected to reach statistical significance given the simulated cohort size and event prevalence. Also influencing the number of events are follow-up duration and censoring. Each simulated individual has a maximum of 50 follow-up records. No other forms of censoring are implemented, since censoring is already assumed non-informative and is not particularly relevant to the effect under investigation. Thus, all censoring is administrative censoring, occurring due to study cessation before experiencing an event.

A total of 50 datasets are simulated, Cox proportional hazards regressions are performed, and mean risk estimates are reported for each grouping method and group size, and additionally for the ungrouped dataset.

2.7 Meta-Analysis

Fixed- and random-effects meta-analyses are conducted to produce summary risk estimates for each outcome, combining the statistical power of the three studies. The fixed-effects

model (Borenstein et al., 2010) computes the inverse-variance weighted mean parameter,

$$\hat{\beta}_{FE} = \frac{\sum w_i \hat{\beta}_i}{\sum w_i}, \quad (2.19)$$

in which the component parameter estimates $\hat{\beta}_i$ for each of i studies are weighted by

$$w_i = \frac{1}{\text{Var}(\hat{\beta}_i)}. \quad (2.20)$$

Variance for the fixed-effects model summary estimate can be computed as

$$\text{Var}(\hat{\beta}_{FE}) = \frac{1}{\sum w_i}. \quad (2.21)$$

The random-effects model accounts for between-study variation using the DerSimonian-Laird method (DerSimonian and Laird, 1986). Heterogeneity among studies can be quantified by the Cochran Q statistic,

$$Q = \sum w_i (\hat{\beta}_i - \hat{\beta}_{FE})^2, \quad (2.22)$$

which is the weighted sum of the squared differences between each individual study's estimate $\hat{\beta}_i$ and the overall pooled estimate $\hat{\beta}_{FE}$ (Cochran, 1954). Q follows a chi-squared distribution with degrees of freedom equal to one less than the number of studies k . It is commonly assessed by way of a p -value with the null hypothesis that all studies are homogeneous. In the DerSimonian-Laird random-effects model, the weighting term

$$w_i^* = \frac{1}{\text{Var}(\hat{\beta}_i) + \tau^2} \quad (2.23)$$

is modified by

$$\tau^2 = \max \left\{ 0, \frac{Q - (k - 1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}} \right\}, \quad (2.24)$$

which includes the fixed-effects weighting term w_i , Cochran's Q , and its degrees of freedom,

$k - 1$. Using the modified weighting term w_i^* , the resulting random-effects model is

$$\hat{\beta}_{RE} = \frac{\sum w_i^* \hat{\beta}_i}{\sum w_i^*} \quad (2.25)$$

with variance,

$$\text{Var}(\hat{\beta}_{RE}) = \frac{1}{\sum w_i^*}. \quad (2.26)$$

The I^2 index—a function of Q and k —indicates the percentage of the observed variation across estimates due to genuine differences between the studies rather than chance ([Higgins and Thompson, 2002](#)).

$$I^2 = \max \left\{ 0, \frac{Q - (k - 1)}{Q} \right\} \times 100\% \quad (2.27)$$

If I^2 is large, it is unlikely that all studies within the meta-analysis are estimating the same effect. By inspection of τ^2 (Eq. 2.23) and I^2 (Eq. 2.26), it is clear that with low evidence of heterogeneity (small Q), the random-effects model converges to the fixed-effects model. Depending on the presence (Q) and degree (I^2) of heterogeneity, either the fixed- or random-effects model may be preferable.

2.8 Pooled Analysis

A major objective of the MPS is to combine large radiation-exposed populations for unprecedented statistical power among radiation epidemiology studies ([Boice, 2012](#)). Now, with rigorous analyses of some of the largest MPS cohorts completed, it is feasible to begin pooling. Initial results have been published for pooled NPP+IR and NPP+IR+MW cohorts ([Boice et al., 2022b](#); [Dauer et al., 2024](#)). In the present study, the NPP+IR+MW cohort is repooled and analyzed, to assess the effects of person-year grouping. In combining the three component cohorts, special consideration must be given to accommodate the unique features of each cohort. As described in Section 2.3, the NPP and IR cohorts share important features and therefore can be combined with relative ease. However, there is overlap between the two study populations. Confirming a prior study ([Mumma et al., 2023](#)),

5,071 overlapping study IDs were observed. Since each cohort includes exposures from other careers, the overlapping records should not be combined. In the pooled cohort, these individuals are represented by their IR cohort records, which contain more recent follow-up than NPP data.

As noted in Section 2.5, the MW cohort contains two more YOB categories than the NPP and IR cohorts include. Upon consultation with analysts involved in the original three-cohort pooling and observed Akaike Information Criterion (AIC) trends indicating best model fit, the six-level YOB categorization used in NPP and IR studies is adopted in the pooled model (Akaike, 1974; Walsh, 2025). The MW cohort also utilized an entirely different, indirect measure of SES. Again, following past analyses and AIC trends, a three-category, education-based SES classification is constructed. Levels 1-3 of the new classification approximate low, medium, and high education, respectively. For the MW cohort, all workers in the “other” occupational category are assigned to the new SES category 2, with the remaining workers assigned to category 3. NPP and IR “low” and “medium” SES workers are assigned to the new category 1, while “high” SES workers are in category 2 on the new scale. The new classification resulted in the best model fit for a combined SES measure; it also appears realistic as medical workers are likely to have comparatively high education levels. SES classifications for each individual cohort and the pooled cohort are shown in Figure 2.7. With unified measures of YOB and SES, Cox regression is performed using a model form identical to that of each individual cohort.

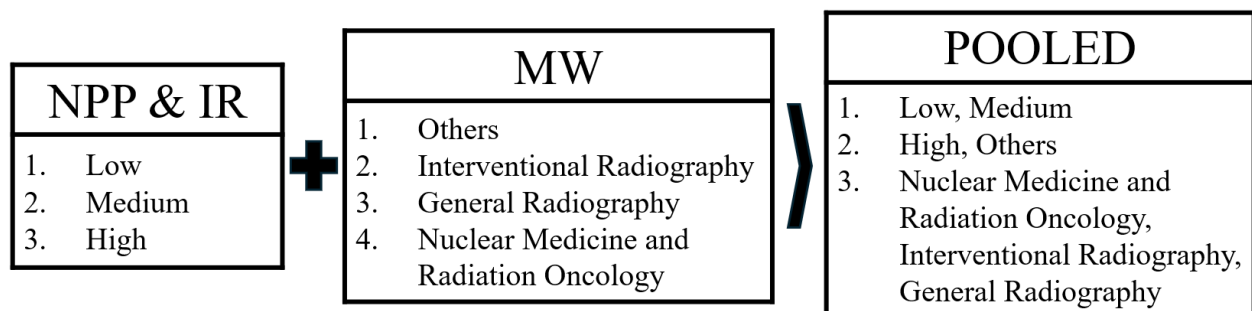


Figure 2.7: Pooled cohort highest education categories as an indirect measure of SES. NPP and IR cohort measures are based on mean highest education levels from census block data (Cohen *et al.*, 2022). Occupational categories from the MW cohort are used as an approximate measure of highest education. Pooled cohort categories are based on best model fit, and match those of the NCRP Commentary 32 pooled analysis (NCRP, 2022). Categories are listed from lowest to highest SES.

Chapter 3

Results

3.1 Individual Cohort Analyses

Across all cohorts and outcomes, similar trends were observed for each method as group size increased, typically resulting in negatively biased risk estimates. Grouping using maximum cumulative dose produced the most pronounced bias, with risk estimates deviating by up to 404% from ungrouped values. Grouping by average cumulative dose typically yielded less bias. Notably, grouping only non-event rows while using average cumulative dose successfully attenuated bias in most cases. Bias trends for key outcomes—lung cancer, Parkinson’s disease, non-CLL leukemia, and ischemic heart disease mortality—are illustrated in Figures [3.2-3.4](#) with 95% confidence intervals in inset plots. Risk estimates, 95% confidence intervals, and relative bias (as a percentage compared to ungrouped estimates) are presented in Tables [3.3-3.5](#).

3.2 Simulation Study

The observed impact of each grouping method closely resembles trends observed in MPS cohort data. Bias magnitude for both average and maximum cumulative dose methods is substantially larger than observed in the real data, with relative bias reaching 563%.

Resulting mean risk estimates are presented in Table 3.1, and trends are illustrated in Figure 3.1.

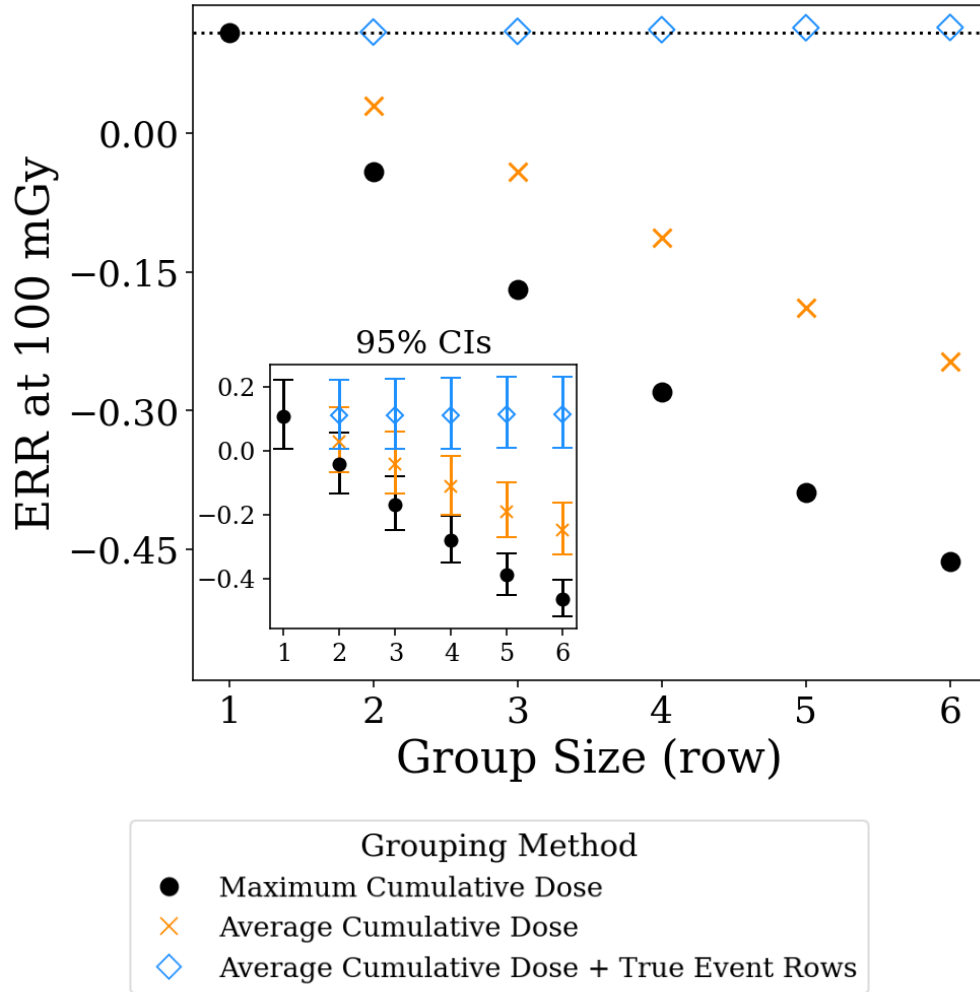


Figure 3.1: Changes in mean risk estimates as group size increases for each grouping method, based on 50 simulated survival datasets. Horizontal dashed line represents the mean risk estimate among ungrouped datasets. Each method of grouping uniquely biases the risk estimates. 95% confidence intervals for grouped and ungrouped estimates are shown in inset plots.

3.3 Meta-Analysis

Fixed- and random-effect meta analyses were conducted for all four key outcomes, combining ERR at 100 mGy estimates from the ungrouped NPP, IR, and MW cohorts. Presence

Table 3.1: Mean estimated ERR at 100 mGy and relative bias across methods and group sizes based on 50 simulated datasets. Risk estimates are accompanied by 95% confidence intervals. Bias is calculated relative to the ungrouped risk estimate shown. Between-estimate standard errors for risk estimates from the 50 datasets are between 0.04 and 0.07.

Method	Simulated Data											
	Ungrouped Mean ERR at 100 mGy = 0.108 (Mean 95% CI: 0.005; 0.221)											
	Group Size				Group Size				Group Size			
	2			3			4			5		
	Mean ERR at 100 mGy	Bias		Mean ERR at 100 mGy	Bias		Mean ERR at 100 mGy	Bias		Mean ERR at 100 mGy	Bias	
Max. Cumulative Dose	-0.042 (-0.132; 0.058)	-142%		-0.169 (-0.249; -0.081)	-269%		-0.280 (-0.350; -0.202)	-380%		-0.389 (-0.449; -0.322)	-489%	
Avg. Cumulative Dose	0.029 (-0.068; 0.137)	-71%		-0.042 (-0.134; 0.060)	-142%		-0.113 (-0.199; -0.016)	-213%		-0.189 (-0.270; -0.099)	-289%	
Avg. + Ungrouped Event Rows	0.109 (0.006; 0.223)	+9%		0.110 (0.006; 0.224)	+10%		0.112 (0.007; 0.227)	+12%		0.114 (0.009; 0.230)	+14%	
										0.114 (0.009; 0.231)	+14%	
										0.247 (-0.323; -0.162)	-347%	
										0.463 (-0.517; -0.403)	-563%	

of heterogeneity between cohort estimates is quantified by the Cochran Q statistic and corresponding p-value, while the I^2 index quantifies degree of heterogeneity. Q and I^2 metrics indicate substantial heterogeneity among lung cancer mortality risk estimates. There is no evidence for heterogeneity among risk estimates for the other outcomes. Meta-analysis results are presented in Table 3.2.

Table 3.2: *Fixed- and random-effect meta analysis results for key outcomes in NPP, IR, and MW cohorts. Q and I^2 values reflect heterogeneity between component risk estimates.*

Outcome	Fixed Effects Estimate ^a	Random Effects Estimate ^a	Q (p-value)	I^2
Lung	0.041 (0.001;0.082)	0.051 (-0.047;0.160)	12.3 (0.002)	83.7%
PD	0.221 (0.044;0.429)	0.221 (0.044;0.429)	0.31 (0.856)	0%
non-CLL	0.174 (0.043;0.320)	0.174 (0.043;0.320)	0.11 (0.948)	0%
IHD	-0.030 (-0.067;0.009)	-0.030 (-0.067;0.009)	0.96 (0.620)	0%

^a ERR at 100 mGy (95% CI) summary estimate

3.4 Pooled Analysis

NPP, IR, and MW cohorts were pooled and person-years were grouped using the same methods and group sizes applied to individual cohorts. Grouping led to similar negative biases, with the true event row and average cumulative dose method exhibiting the greatest stability in risk estimates. Person-year grouping effects for the pooled cohort are quantified in Table 3.6 and illustrated in Figure 3.5. For each key outcome, a forest plot comparing individual cohort, meta-analysis, and pooled risk estimates is presented in Figures 3.6-3.9.

Table 3.3: *Estimated ERR at 100 mGy and relative bias across methods and group sizes for four selected outcomes in the NPP cohort. Risk estimates are accompanied by 95% confidence intervals. Bias is calculated relative to the ungrouped risk estimate reported below each outcome label.*

Lung Cancer												
Ungrouped ERR at 100 mGy = -0.045 (95% CI: -0.105; 0.018)												
Group Size												
4												
5												
6												
Method	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	-0.058 (-0.117-0.004)	-28%	-0.073 (-0.132-0.011)	-61%	-0.086 (-0.145-0.024)	-90%	-0.089 (-0.147-0.027)	-95%	-0.109 (-0.167-0.047)	-140%	-0.109 (-0.167-0.047)	-140%
Avg. Cumulative Dose	-0.055 (-0.115-0.008)	-22%	-0.065 (-0.124-0.002)	-43%	-0.073 (-0.132-0.009)	-60%	-0.076 (-0.136-0.012)	-68%	-0.089 (-0.149-0.025)	-96%	-0.089 (-0.149-0.025)	-96%
Avg. + Ungrouped Event Rows	-0.045 (-0.104-0.018)	+1%	-0.042 (-0.101-0.021)	+7%	-0.042 (-0.102-0.021)	+7%	-0.036 (-0.095-0.027)	+21%	-0.039 (-0.099-0.025)	+15%	-0.039 (-0.099-0.025)	+15%
Parkinson's Disease												
Ungrouped ERR at 100 mGy = 0.291 (95% CI: -0.004; 0.673)												
4												
5												
6												
Method	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	0.288 (-0.007-0.669)	-1%	0.285 (-0.010-0.666)	-2%	0.282 (-0.012-0.664)	-3%	0.281 (-0.013-0.663)	-3%	0.278 (-0.016-0.660)	-4%	0.278 (-0.016-0.660)	-4%
Avg. Cumulative Dose	0.289 (-0.005-0.672)	0%	0.290 (-0.005-0.672)	0%	0.291 (-0.004-0.673)	0%	0.293 (-0.003-0.675)	+1%	0.285 (-0.011-0.670)	-2%	0.285 (-0.011-0.670)	-2%
Avg. + Ungrouped Event Rows	0.291 (-0.003-0.673)	0%	0.293 (-0.002-0.674)	+1%	0.294 (-0.001-0.676)	+1%	0.296 (0.001-0.678)	+2%	0.298 (0.002-0.680)	+2%	0.298 (0.002-0.680)	+2%
Non-CLL Leukemia												
Ungrouped ERR at 100 mGy = 0.164 (95% CI: -0.030; 0.398)												
4												
5												
6												
Method	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	0.157 (-0.037-0.390)	-5%	0.147 (-0.046-0.381)	-10%	0.140 (-0.054-0.373)	-15%	0.133 (-0.061-0.366)	-19%	0.126 (-0.067-0.359)	-23%	0.126 (-0.067-0.359)	-23%
Avg. Cumulative Dose	0.162 (-0.032-0.396)	-1%	0.158 (-0.037-0.392)	-4%	0.159 (-0.036-0.393)	-3%	0.157 (-0.038-0.392)	-4%	0.149 (-0.046-0.385)	-9%	0.149 (-0.046-0.385)	-9%
Avg. + Ungrouped Event Rows	0.165 (-0.030-0.398)	0%	0.164 (-0.030-0.398)	0%	0.166 (-0.029-0.399)	+1%	0.168 (-0.027-0.402)	+2%	0.170 (-0.025-0.405)	+4%	0.170 (-0.025-0.405)	+4%
Ischemic Heart Disease												
Ungrouped ERR at 100 mGy = -0.017 (95% CI: -0.064; 0.033)												
4												
5												
6												
Method	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	-0.030 (-0.077-0.019)	-79%	-0.046 (-0.092-0.003)	-173%	-0.060 (-0.107-0.011)	-257%	-0.062 (-0.109-0.014)	-271%	-0.085 (-0.131-0.036)	-405%	-0.085 (-0.131-0.036)	-405%
Avg. Cumulative Dose	-0.026 (-0.073-0.023)	-57%	-0.035 (-0.082-0.015)	-109%	-0.044 (-0.092-0.006)	-165%	-0.046 (-0.094-0.004)	-176%	-0.057 (-0.105-0.007)	-243%	-0.057 (-0.105-0.007)	-243%
Avg. + Ungrouped Event Rows	-0.016 (-0.063-0.033)	+3%	-0.014 (-0.061-0.036)	+18%	-0.014 (-0.061-0.035)	+15%	-0.008 (-0.055-0.042)	+52%	-0.012 (-0.059-0.038)	+29%	-0.012 (-0.059-0.038)	+29%

Table 3.4: *Estimated ERR at 100 mGy and relative bias across methods and group sizes for four selected outcomes in the IR cohort. Risk estimates are accompanied by 95% confidence intervals. Bias is calculated relative to the ungrouped risk estimate reported below each outcome label.*

Lung Cancer										
Ungrouped ERR at 100 mGy = 0.087 (95% CI: 0.031; 0.147)										
Method	Group Size									
	2	3	4	5	6					
	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	0.082 (0.026-0.142)	-6%	0.078 (0.021-0.137)	-11%	0.073 (0.017-0.132)	-16%	0.069 (0.013-0.129)	-20%	0.066 (0.009-0.125)	-25%
Avg. Cumulative Dose	0.084 (0.028-0.144)	-3%	0.082 (0.025-0.142)	-6%	0.079 (0.022-0.139)	-10%	0.079 (0.022-0.139)	-10%	0.076 (0.018-0.136)	-13%
Avg. + Ungrouped Event Rows	0.087 (0.031-0.147)	0%	0.088 (0.032-0.147)	+1%	0.088 (0.032-0.148)	+2%	0.090 (0.034-0.150)	+4%	0.091 (0.035-0.151)	+5%
Parkinson's Disease										
Ungrouped ERR at 100 mGy = 0.178 (95% CI: -0.052; 0.465)										
	2	3	4	5	6					
	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	0.178 (-0.053-0.464)	0%	0.177 (-0.053-0.463)	-1%	0.177 (-0.054-0.463)	-1%	0.176 (-0.054-0.462)	-1%	0.176 (-0.054-0.462)	-1%
Avg. Cumulative Dose	0.178 (-0.052-0.465)	0%	0.178 (-0.052-0.465)	0%	0.179 (-0.052-0.465)	0%	0.179 (-0.052-0.466)	0%	0.180 (-0.051-0.466)	+1%
Avg. + Ungrouped Event Rows	0.178 (-0.052-0.465)	0%	0.179 (-0.052-0.465)	0%	0.179 (-0.052-0.465)	0%	0.179 (-0.051-0.466)	+1%	0.180 (-0.051-0.466)	+1%
Non-CLL Leukemia										
Ungrouped ERR at 100 mGy = 0.189 (95% CI: 0.004; 0.408)										
	2	3	4	5	6					
	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	0.186 (0.001-0.405)	-1%	0.183 (-0.002-0.403)	-3%	0.180 (-0.005-0.400)	-4%	0.177 (-0.008-0.398)	-6%	0.175 (-0.010-0.395)	-7%
Avg. Cumulative Dose	0.185 (-0.000-0.405)	-2%	0.181 (-0.005-0.403)	-4%	0.178 (-0.009-0.400)	-6%	0.175 (-0.013-0.398)	-7%	0.177 (-0.010-0.400)	-6%
Avg. + Ungrouped Event Rows	0.189 (0.004-0.408)	0%	0.189 (0.004-0.408)	0%	0.189 (0.004-0.408)	0%	0.189 (0.004-0.409)	0%	0.190 (0.005-0.410)	+1%
Ischemic Heart Disease										
Ungrouped ERR at 100 mGy = -0.026 (95% CI: -0.066; 0.017)										
	2	3	4	5	6					
	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	-0.031 (-0.071-0.011)	-20%	-0.036 (-0.076-0.007)	-38%	-0.041 (-0.081-0.001)	-59%	-0.044 (-0.084-0.002)	-72%	-0.048 (-0.089-0.006)	-89%
Avg. Cumulative Dose	-0.029 (-0.070-0.013)	-13%	-0.032 (-0.073-0.011)	-24%	-0.035 (-0.075-0.008)	-35%	-0.037 (-0.078-0.006)	-45%	-0.041 (-0.083-0.002)	-62%
Avg. + Ungrouped Event Rows	-0.026 (-0.066-0.017)	+1%	-0.025 (-0.066-0.017)	+2%	-0.025 (-0.066-0.017)	+3%	-0.023 (-0.064-0.019)	+9%	-0.023 (-0.064-0.019)	+10%

Table 3.6: *Estimated ERR at 100 mGy and relative bias across methods and group sizes for four selected outcomes in the pooled NPP+IR+MW cohort. Risk estimates are accompanied by 95% confidence intervals. Bias is calculated relative to the ungrouped risk estimate reported below each outcome label.*

Lung Cancer										
Ungrouped ERR at 100 mGy = 0.053 (95% CI: 0.012; 0.095)										
Method	Group Size									
	2	3	4	5	6					
	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	0.044 (0.003–0.086)	-17%	0.034 (-0.006–0.077)	-34%	0.026 (-0.015–0.068)	-51%	0.022 (-0.019–0.064)	-58%	0.011 (-0.030–0.053)	-80%
Avg. Cumulative Dose	0.046 (0.005–0.089)	-11%	0.041 (-0.000–0.084)	-22%	0.036 (-0.005–0.079)	-31%	0.035 (-0.007–0.078)	-33%	0.028 (-0.014–0.072)	-47%
Avg. + Ungrouped Event Rows	0.053 (0.012–0.095)	+1%	0.054 (0.014–0.097)	+4%	0.055 (0.014–0.097)	+5%	0.059 (0.018–0.101)	+12%	0.058 (0.017–0.101)	+11%
Parkinson's Disease										
Ungrouped ERR at 100 mGy = 0.158 (95% CI: -0.012; 0.358)										
	2	3	4	5	6					
	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	0.156 (-0.014–0.356)	-1%	0.154 (-0.016–0.354)	-2%	0.153 (-0.018–0.353)	-3%	0.152 (-0.019–0.352)	-4%	0.150 (-0.020–0.351)	-5%
Avg. Cumulative Dose	0.158 (-0.013–0.357)	0%	0.157 (-0.013–0.357)	0%	0.158 (-0.013–0.358)	0%	0.158 (-0.013–0.358)	0%	0.155 (-0.016–0.356)	-2%
Avg. + Ungrouped Event Rows	0.158 (-0.012–0.358)	0%	0.159 (-0.012–0.359)	+1%	0.160 (-0.011–0.359)	+1%	0.161 (-0.009–0.361)	+2%	0.162 (-0.008–0.362)	+3%
Non-CLL Leukemia										
Ungrouped ERR at 100 mGy = 0.187 (95% CI: 0.057; 0.332)										
	2	3	4	5	6					
	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	0.182 (0.052–0.327)	-3%	0.176 (0.046–0.322)	-6%	0.170 (0.040–0.317)	-9%	0.166 (0.035–0.312)	-11%	0.161 (0.031–0.308)	-14%
Avg. Cumulative Dose	0.184 (0.054–0.330)	-1%	0.180 (0.050–0.326)	-4%	0.179 (0.048–0.325)	-4%	0.176 (0.045–0.323)	-6%	0.173 (0.042–0.321)	-7%
Avg. + Ungrouped Event Rows	0.187 (0.057–0.332)	0%	0.187 (0.057–0.332)	0%	0.187 (0.058–0.333)	0%	0.188 (0.059–0.334)	+1%	0.190 (0.060–0.335)	+2%
Ischemic Heart Disease										
Ungrouped ERR at 100 mGy = -0.024 (95% CI: -0.054; 0.007)										
	2	3	4	5	6					
	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias	ERR at 100 mGy	Bias
Max. Cumulative Dose	-0.032 (-0.063–0.001)	-36%	-0.042 (-0.072–0.011)	-76%	-0.051 (-0.081–0.020)	-115%	-0.054 (-0.084–0.023)	-128%	-0.067 (-0.097–0.036)	-181%
Avg. Cumulative Dose	-0.030 (-0.060–0.002)	-24%	-0.035 (-0.066–0.004)	-48%	-0.040 (-0.071–0.009)	-70%	-0.043 (-0.074–0.011)	-81%	-0.050 (-0.081–0.018)	-112%
Avg. + Ungrouped Event Rows	-0.023 (-0.054–0.008)	+1%	-0.022 (-0.052–0.009)	+7%	-0.022 (-0.053–0.009)	+6%	-0.019 (-0.049–0.012)	+20%	-0.020 (-0.051–0.011)	+14%

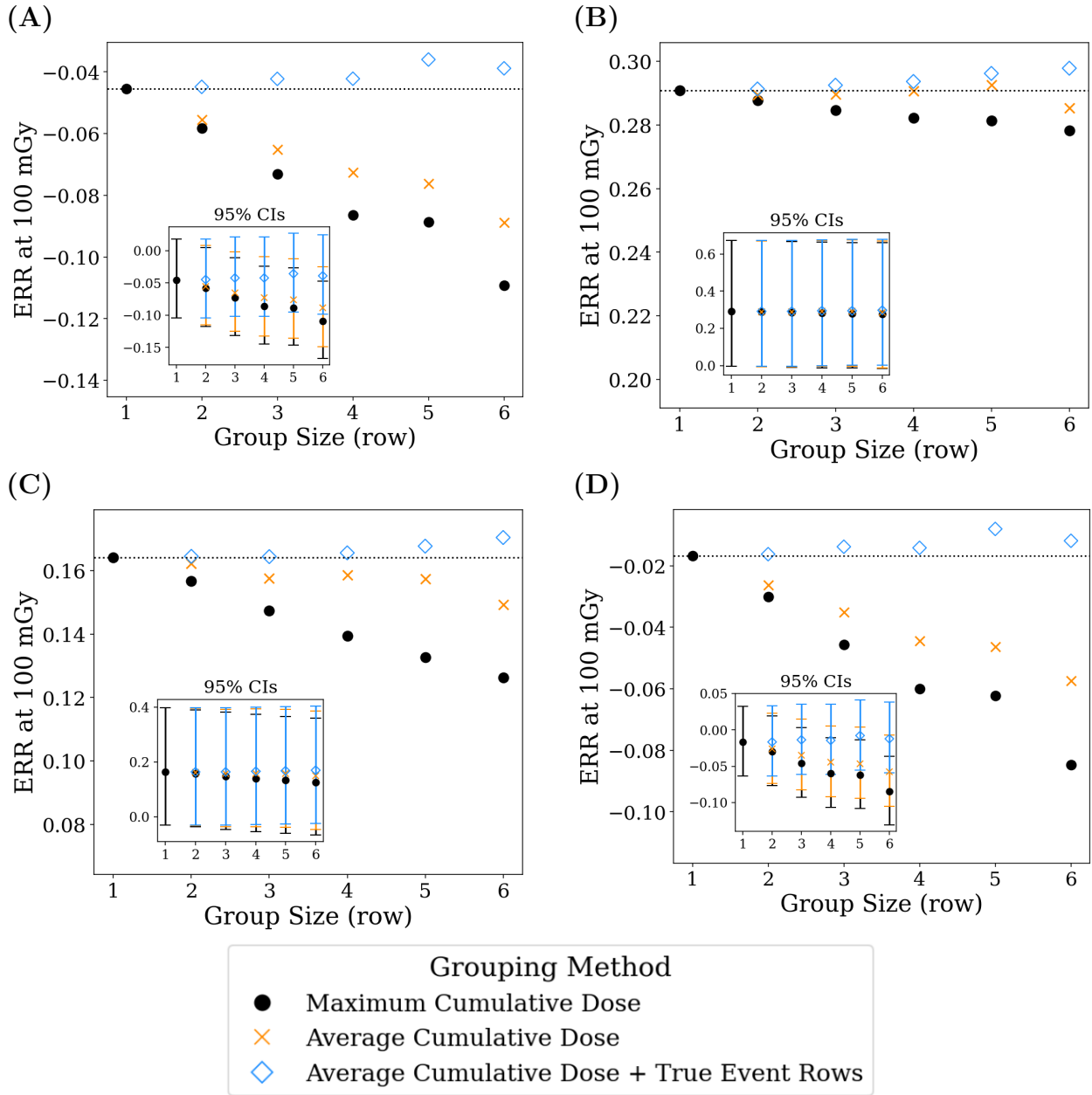


Figure 3.2: Changes in risk estimates as group size increases for selected outcomes in the Nuclear Power Plant Workers cohort. Displayed are (A) lung cancer, (B) Parkinson's disease, (C) non-CLL leukemia, and (D) ischemic heart disease. Horizontal dashed lines represent the risk estimate for each outcome resulting from the ungrouped, full-size dataset. Each method of grouping uniquely biases the risk estimates. 95% confidence intervals for grouped and ungrouped estimates are shown in inset plots.

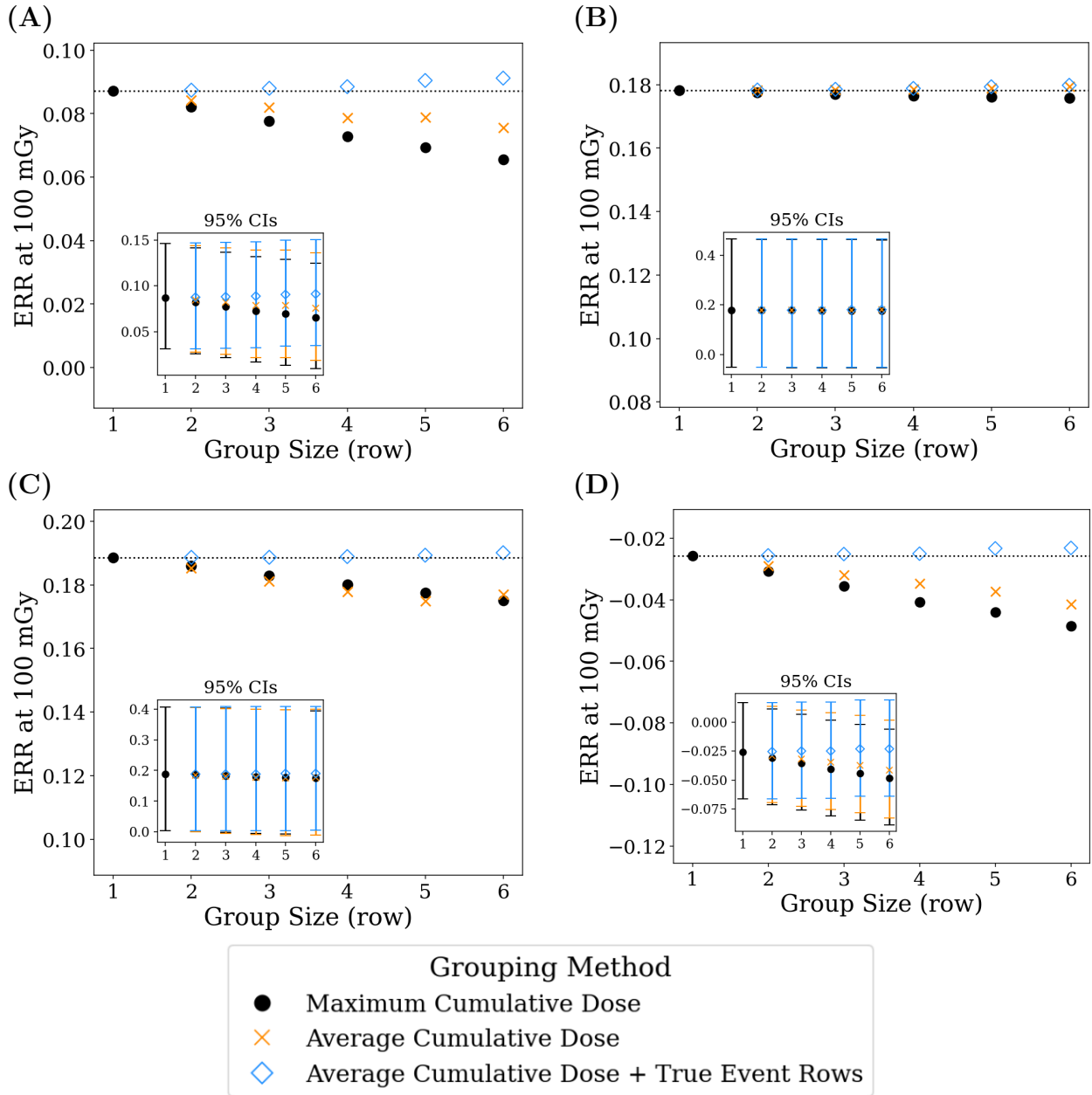


Figure 3.3: Changes in risk estimates as group size increases for selected outcomes in the Industrial Radiographers cohort. Displayed are (A) lung cancer, (B) Parkinson's disease, (C) non-CLL leukemia, and (D) ischemic heart disease. Horizontal dashed lines represent the risk estimate for each outcome resulting from the ungrouped, full-size dataset. Each method of grouping uniquely biases the risk estimates. 95% confidence intervals for grouped and ungrouped estimates are shown in inset plots.

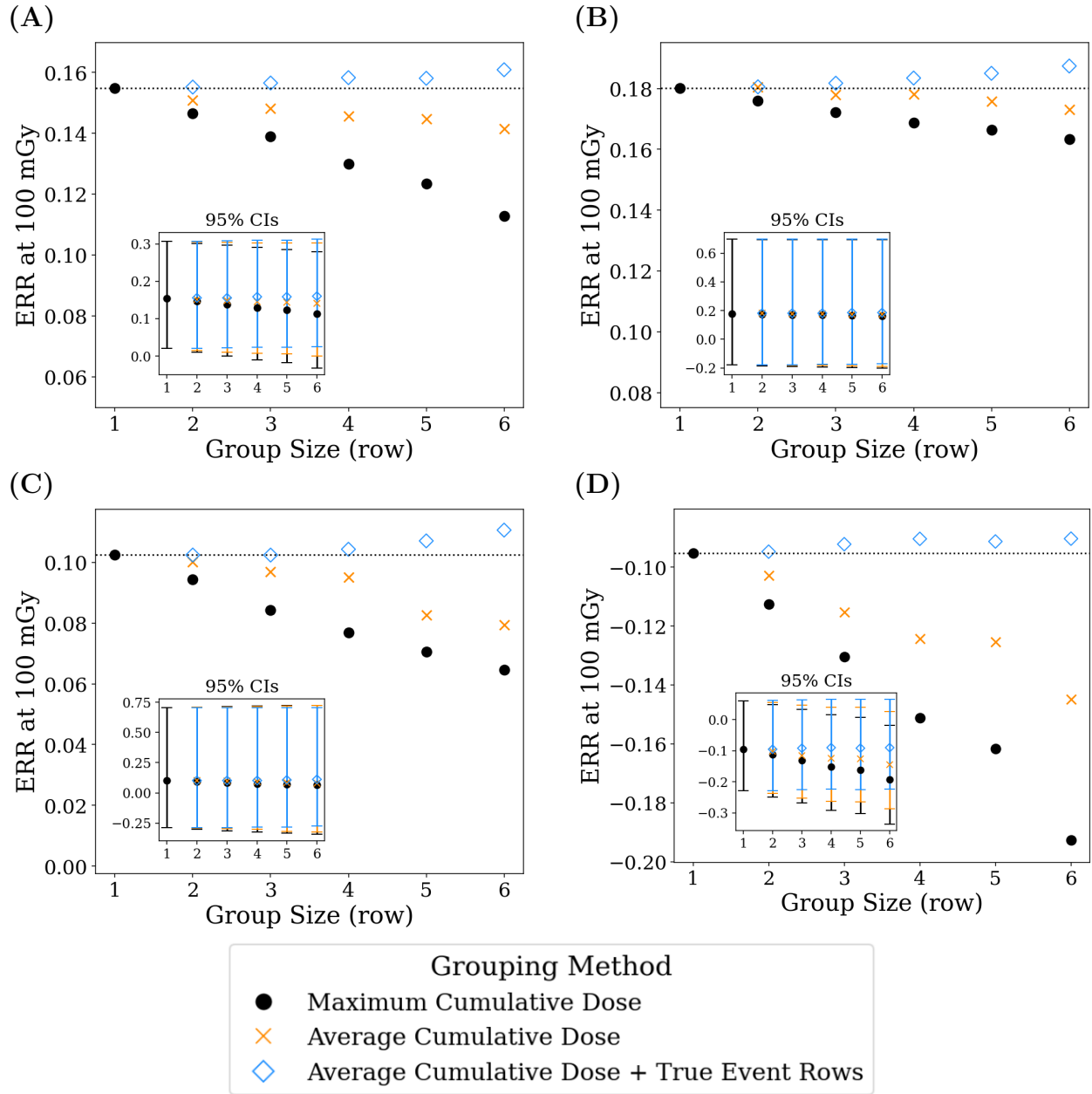


Figure 3.4: Changes in risk estimates as group size increases for selected outcomes in the Medical Radiation Workers cohort. Displayed are (A) lung cancer, (B) Parkinson's disease, (C) non-CLL leukemia, and (D) ischemic heart disease. Horizontal dashed lines represent the risk estimate for each outcome resulting from the ungrouped, full-size dataset. Each method of grouping uniquely biases the risk estimates. 95% confidence intervals for grouped and ungrouped estimates are shown in inset plots.

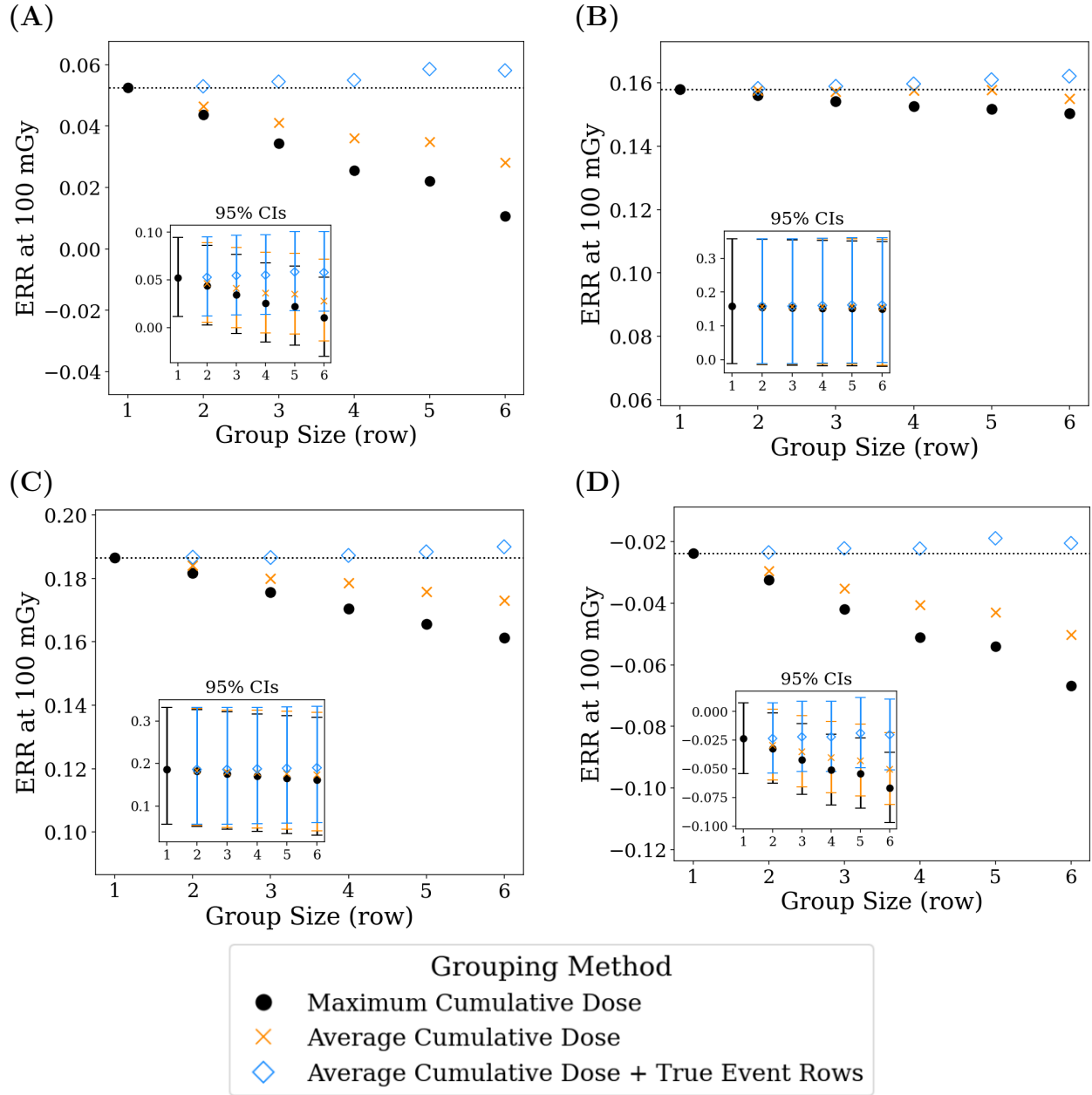


Figure 3.5: Changes in risk estimates as group size increases for selected outcomes in the pooled NPP+IR+MW cohort. Displayed are (A) lung cancer, (B) Parkinson's disease, (C) non-CLL leukemia, and (D) ischemic heart disease. Horizontal dashed lines represent the risk estimate for each outcome resulting from the ungrouped, full-size dataset. Each method of grouping uniquely biases the risk estimates. 95% confidence intervals for grouped and ungrouped estimates are shown in inset plots.

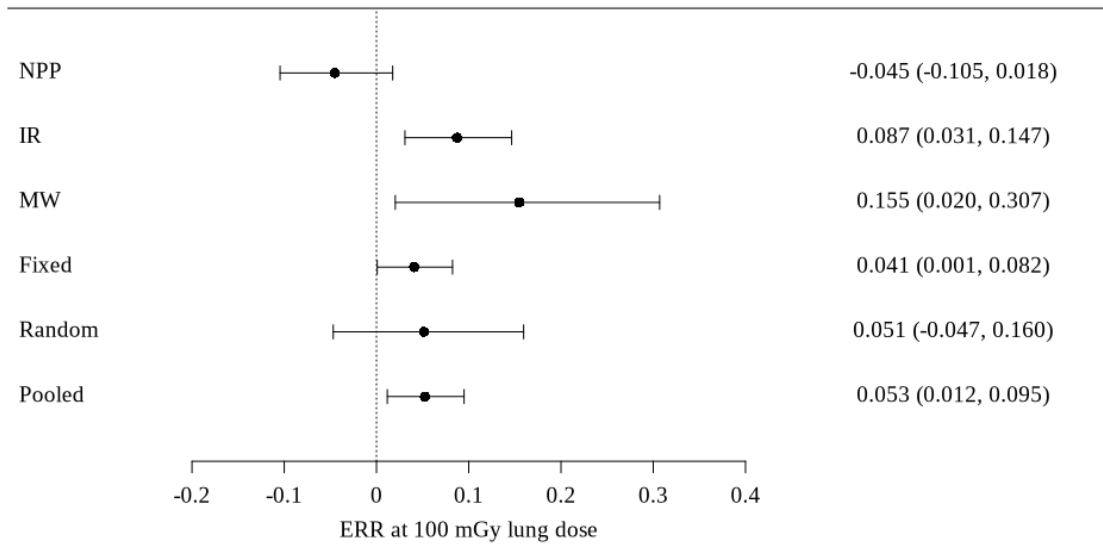


Figure 3.6: Forest plot for lung cancer mortality risk estimates from individual cohorts, fixed- and random-effects meta analyses, and the three-cohort pooled dataset. ERR at 100 mGy point estimates are accompanied by 95% confidence intervals.

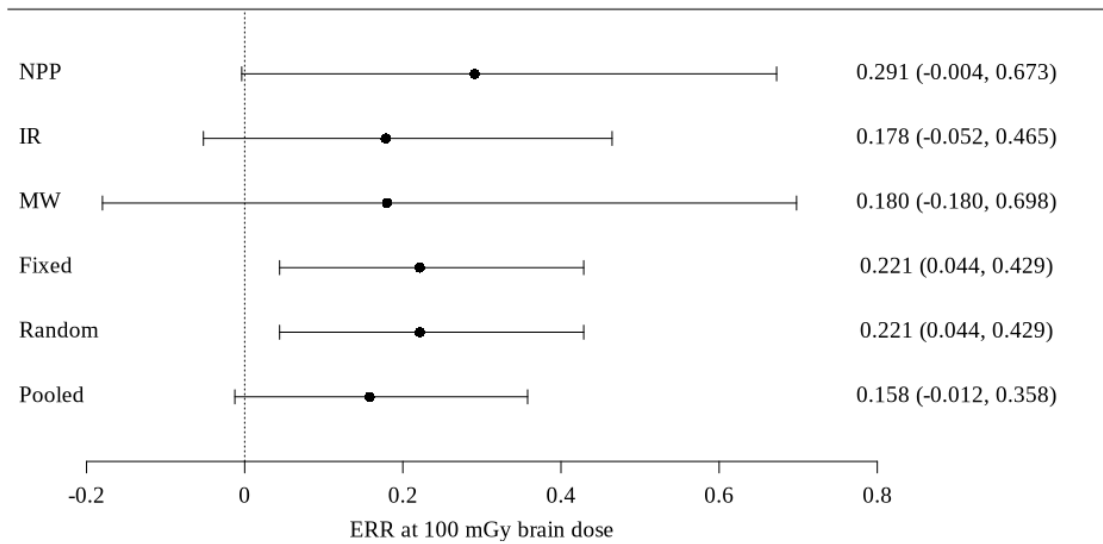


Figure 3.7: Forest plot for Parkinson's disease mortality risk estimates from individual cohorts, fixed- and random-effects meta analyses, and the three-cohort pooled dataset. ERR at 100 mGy point estimates are accompanied by 95% confidence intervals.

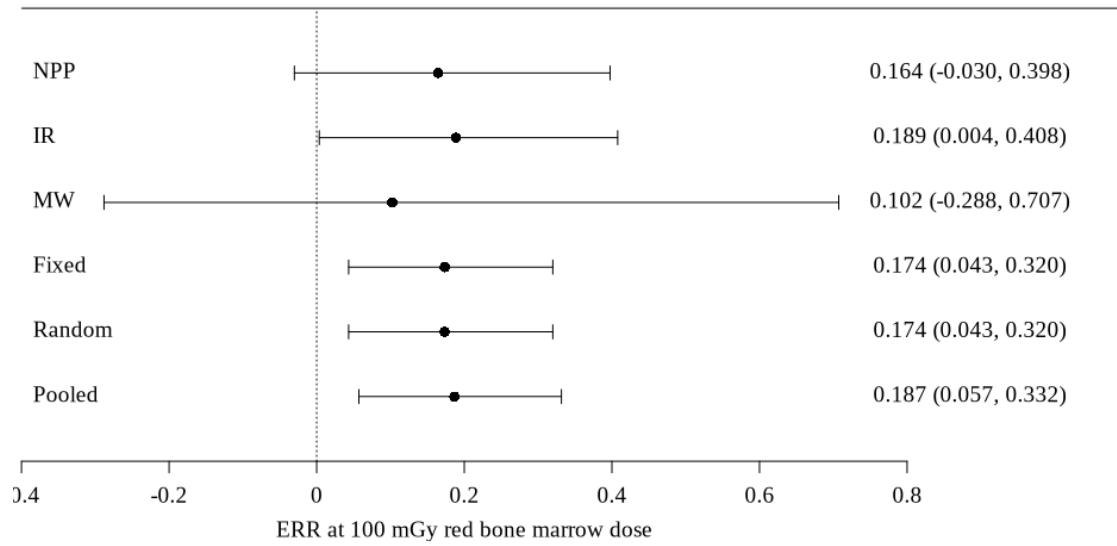


Figure 3.8: Forest plot for non-CLL leukemia mortality risk estimates from individual cohorts, fixed- and random-effects meta analyses, and the three-cohort pooled dataset. ERR at 100 mGy point estimates are accompanied by 95% confidence intervals.

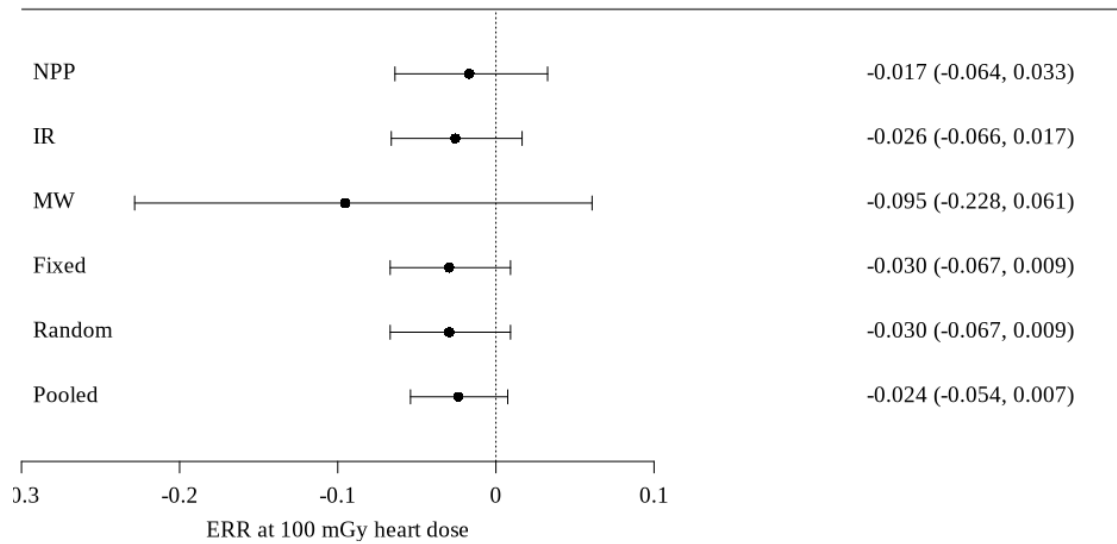


Figure 3.9: Forest plot for ischemic heart disease mortality risk estimates from individual cohorts, fixed- and random-effects meta analyses, and the three-cohort pooled dataset. ERR at 100 mGy point estimates are accompanied by 95% confidence intervals.

Chapter 4

Discussion

4.1 Person-Year Grouping Effects

Grouping follow-up records into larger time intervals can introduce observable bias to risk estimates generated from Cox proportional hazards regression. Three methods of grouping person-year records were applied to MPS NPP, IR, and MW cohorts, and a pooled dataset comprised of all three cohorts. To elucidate the biases observed for each grouping method, this post-hoc analysis examines how each method alters the original, full-scale dataset.

First, the maximum cumulative dose method—which typically introduced strong negative bias—will overestimate the dose toward the beginning of the grouped interval, unless the cumulative dose is constant among component intervals. Grouping this way misrepresents the exposure for follow-up records with cumulative dose less than that of the final record in the grouped interval. In the case of rare events, non-event records dominate each individual’s survival time. Thus, dose is overestimated primarily in non-event rows. This artificially weakens the relationship between exposure and outcome, biasing risk estimates in the negative direction.

If using average cumulative dose in grouped records, the cumulative dose may be under- or overestimated at different points in the new interval. Here, exposure is overestimated in the first and underestimated in the second half of the grouped interval, reducing the

deviation of the grouped exposure value from the component ungrouped values. Thus, it is reasonable that grouping using average cumulative dose would result in less bias than the maximum cumulative dose method, as was observed in this study.

If event and non-event rows are grouped, the event time incorrectly encompasses the non-event row's component interval. With events binned in larger intervals, the incidence rate (events per person-time)—and consequently the risk estimates—are diluted. To remove this misrepresentation, event rows can be excluded from the grouping process. The preservation of singular event rows, in the presence of average cumulative dose grouping, substantially reduced bias. As group size increased beyond 3 or 4 rows using this method, risk estimates began to bias in the positive direction. A potential explanation for this effect is that as doses are averaged in increasingly large non-event row intervals, an artificially larger contrast is created between the dose values of non-event rows and preserved event rows.

Each grouping method results in a reduced-size dataset approximating the full-scale data, at the cost of temporal granularity. It was expected that risk estimate variance would increase with group size. Although this was generally the case, variance increases were not particularly large (generally <5%, maximum 20%). This suggests that the magnitude of likelihood functions underlying the regressions are robust to the loss in temporal granularity and supported primarily by dose values and event occurrences, which are well-preserved in person-year grouping.

Although variance is generally robust to person-year grouping, the process often biased risk point estimates. A consistent negative bias was present in the maximum and average dose grouping methods. Observed bias was typically largest in outcomes with the greatest number of events. However, the magnitude of bias for a given outcome varies across cohorts, as the exposure profiles among individuals with that outcome can differ substantially between cohorts. As a result, greatest grouping-related bias was observed for lung cancer and ischemic heart disease mortality risk estimates. Substantial bias in lung cancer risk estimates may explain the unexpectedly-low pooled lung cancer risk estimate published in NCRP Commentary 32, which was generated from two-year grouped data. Comparisons to the Commentary 32 estimate are presented in Section [4.3](#).

4.2 Simulation Study

Risk estimates were biased as expected for each grouping method applied to simulated data. Maximum cumulative dose grouping created the largest bias and preserving true event rows attenuated bias. The magnitude of observed bias was larger than that of the individual and pooled cohort analyses. It is plausible that the many covariates in the MPS cohort risk models would attenuate bias induced by grouping the cumulative dose variable. So, additional covariates with various distributions and effect sizes were initially added to the simulated data. However, the multi-variate model resulted in a negligible difference in bias magnitude compared to the single-predictor model. Thus, only cumulative dose is simulated and modeled.

Results indicate that confidence interval size decreases as risk estimates are biased negatively. This is an artifact of the exponential form of the Cox proportional hazards model. For average and maximum cumulative dose grouping methods, as group size increases and risk estimates decrease, variance about the cumulative dose parameter estimate increases slightly. This behavior reflects what was observed in individual and pooled variance analysis, but is especially evident in the simulation study results due to large negative bias.

Further insight could be derived from simulated survival data with different features. For example, implementing other forms of censoring or testing various numbers of events could provide better understanding of the observed bias. In the present study, however, simulated data are designed to reflect average, or typical, MPS survival data. Overall, the simulation study results support the grouping-related bias observed in the MPS cohorts.

4.3 Meta-Analysis and Pooled Cohort Results

Findings from individual cohorts were combined in a meta-analysis, resulting in significant positive summary ERR estimates for both Parkinson’s disease and non-CLL leukemia mortality. The summary 95% confidence interval for ischemic heart disease mortality risk encompasses zero, which aligns with past MPS findings (Boice, 2024). Cochran Q statistics

indicate no evidence of heterogeneity among individual cohort Parkinson’s disease, non-CLL leukemia, and ischemic heart disease findings. Among lung cancer findings, however, the Q statistic indicates significant evidence of heterogeneity ($p = 0.002$). Thus, there is a statistically significant departure from random variation among the findings of the three individual cohorts. This is expected, as the lung cancer mortality risk point estimate from the NPP cohort is significantly different from that of the IR and MW cohorts, at the 5% significance level (see Figure 3.6).

Such a result indicates that a component estimate in the meta-analysis may be due to model misspecification. Considering lung cancer mortality risk estimates from other large radiation epidemiology studies (Table 1.1), it is most likely that the NPP cohort estimate is misrepresenting the true risk. Other than the lack of a direct adjustment for smoking (which similarly limits the IR and MW studies), there is no obvious reason for such a different NPP risk estimate. Considering the random-effects lung cancer meta-analysis ERR at 100 mGy result of 0.051 (95% CI: -0.047; 0.160), which accounts for study heterogeneity, there is a low probability of observing the NPP lung cancer mortality data. Thus, it is unlikely that existing NPP cohort lung cancer mortality ERR models are accurate. Further investigation into differences among the three MPS cohorts studied here would be beneficial. Inclusion of other large MPS cohorts such as Atomic Veterans and eventually Nuclear Submariners will inform the validity of each cohort’s risk estimates.

Risk estimates from the pooled cohort analysis tend to align with meta-analysis results. Interestingly, the pooled Parkinson’s disease risk estimate—considering only underlying-cause deaths—does not reach statistical significance. Pooled-cohort confidence intervals are smaller than those of fixed-effects meta-analyses, except for lung cancer mortality. This reflects the large variation in lung cancer risks among cohorts, which becomes a between-subject variation once cohorts are pooled. The heterogeneity between cohorts comprising the pooled lung cancer data raises concern of whether the pooled lung cancer risk estimate can be trusted. Regardless, the pooled estimate for lung cancer mortality ERR reaches statistical significance.

The potential that the person-year grouping method biased the pooled NPP+IR+MW

cohort risk estimate reported in NCRP Commentary 32 motivated this study. The value reported in the commentary is an ERR at 100 mGy of 0.02 (95% CI: -0.03; 0.07), derived from a condensed version of the pooled dataset in which every two person-year records were grouped using the average cumulative dose method. For this case, the estimate in the present study is 0.046 (95% CI: 0.005; 0.089)—just 0.007 less than the ungrouped point estimate. Evidently, bias related to the person-year grouping method, although present, is unlikely to have produced the risk estimate reported in NCRP Commentary 32.

Considering that these estimates were derived from the same datasets, it is likely that the difference is due to modeling choices. Cohort pooling and risk modeling choices in the present study were made to reflect the methods applied to individual cohorts. Although fixed- and random-effects meta-analysis estimates are closer to the pooled estimate in the present study, heterogeneity among the three component cohort leads to great uncertainty about the true risk estimate. It is ultimately imperative that differences among prior and present pooled-cohort risk estimation approaches are understood and reconciled.

Chapter 5

Conclusions and Future Work

The goal of this study was to determine whether grouping follow-up records in survival data introduces bias in Cox proportional hazards regression. This method was previously applied to analyze a pooled cohort consisting of three MPS populations, generating an unexpectedly low lung cancer mortality risk estimate which was published in NCRP Commentary 32 ([NCRP, 2022](#)). Today, grouping follow-up records is generally unnecessary in radiation epidemiology, as enhanced software capabilities have enabled fast regression upon survival data with over 50 million rows ([Giunta et al., 2025](#)). Thus, in addition to the effect of grouping follow-up records, the full-scale pooled NPP+IR+MW cohort was analyzed. A thorough analysis was conducted, with three grouping methods and five grouped interval sizes applied to individual NPP, IR, and MW cohorts, the pooled cohort, and simulated survival data. Risk estimates are generated for outcomes of mortality from lung cancer, Parkinson’s disease, non-CLL leukemia, and ischemic heart disease. A meta-analysis was conducted to produce summary risk estimates and assess heterogeneity among the three individual cohorts.

The three grouping methods were selected based on how the time-varying exposure variable is grouped, and how event rows are handled. The maximum cumulative dose method with two-row group size was used to produce the NCRP Commentary 32 pooled lung cancer mortality risk estimate. This method uses the final (therefore, maximum) cumulative dose

value among the grouped interval's component rows. The average cumulative dose method uses the arithmetic mean between the first and last dose values in a grouped interval as the resulting dose. The last method involves grouping only non-event rows, preserving the temporal specificity of the events of interest. Maximum and average cumulative dose grouping resulted in negatively biased risk estimates, with greater bias as group size increased. Using the maximum cumulative dose usually led to the greatest bias. When event-rows were preserved, grouping bias was substantially attenuated and often exhibited bias in the positive direction as group size increased past three or four rows. The three methods behaved similarly when applied to each individual cohort, the pooled cohort, and simulated data.

The lung cancer mortality ERR at 100 mGy risk estimate from the ungrouped pooled dataset was 0.05 (95% CI: 0.01; 0.10), which differs substantially from the 0.02 (95% CI: -0.03; 0.07) estimate presented in NCRP Commentary 32. Although the grouped estimate is biased in the negative direction, the observed bias is not strong enough to produce the Commentary 32 estimate. Thus, other differences between past and present pooled lung cancer mortality risk estimation must exist.

Bias observed in the present study indicates that grouping follow-up records in survival data should be avoided in the presence of time-varying variables. It is especially advisable to avoid grouping event rows, which results in misclassification of the outcome time. These findings highlight the importance of ensuring minimal bias is present in epidemiological and statistical methods.

Results of this study are from analyses of MPS cohorts and simulated data made to closely resemble these cohorts. It is likely that results would change given survival data with different follow-up times, event rates, and covariate distributions. Additionally, the impact of grouping the radiation exposure variable may differ from that of other time-varying variables. Thus, the ability to generalize these results beyond low-dose radiation epidemiology is limited.

Risk estimates reported in this study are not intended to precisely match past MPS analyses. Some modeling decisions can lead to substantial changes in risk estimates. For example, different methods of combining overlapping records in the pooled cohort often

produced different risk estimates. Still, the chosen methods were selected with the intent to estimate risks accurately, and in a way that reflects past MPS studies.

Future work includes expanding MPS risk analysis to larger pooled cohorts. This can be done only once differences in pooled cohort risk modeling methods are reconciled among MPS analysts. Additionally, further investigation into temporal effects in the radiation dose-response are of interest. Advancements in this area could be made by regressing on annual, rather than cumulative, dose. This pursuit can be aided by machine learning approaches, which are rarely implemented in large-scale epidemiological cohort studies. Innovation in these areas will further strengthen confidence in the practice of radiation risk modeling.

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