Title: Inverse probability weighting to estimate impacts of hypothetical occupational limits on radon exposure to reduce lung cancer

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ABSTRACT
Radon is a known cause of lung cancer. Protective standards for radon exposure are derived largely from studies of working populations that are prone to healthy worker survivor bias. This bias can lead to under-protection of workers and is a key barrier to understanding health effects of many exposures.

We apply inverse probability weighting to study a set of hypothetical exposure limits among 4,137 male, White and American Indian radon-exposed uranium miners in the Colorado Plateau followed from 1950 to 2005. We estimate cumulative risk of lung cancer through age 90 under hypothetical occupational limits.

We estimate that earlier implementation of the current US Mining Safety and Health Administration annual standard of 4 working level months (implemented here as a monthly exposure limit) could have reduced lung cancer mortality from 16/100 workers to 6/100 workers (95% confidence intervals: 3/100, 8/100), in contrast with previous estimates of 10/100 workers. Our estimate is similar to that among contemporaneous occupational cohorts.

Inverse probability weighting is a simple and computationally efficient way address healthy worker survivor bias in order to contrast health effects of exposure limits and estimate the number of excess health outcomes under exposure limits at work.

Study of occupational exposure to human carcinogens is key to a better understanding of public and worker health. However, a key barrier to understanding health effects of occupational exposures is healthy worker survivor bias (1-3). Healthy worker survivor bias is a phenomenon in which healthier workers persist longer in jobs than less healthy workers, thus potentially accruing more exposure (4). Employment status often predicts health outcomes under study, which can bias estimates of association between exposure and health if employment status is not considered in analysis (5, 6). Further, when exposure can influence employment status, for example if latent disease caused by exposure leads to impaired ability to work, this bias is not amenable to control through covariate adjustment in standard regression models of exposure-disease relationships (1).

Healthy worker survivor bias was an initial motivation behind the parametric g-formula, an approach that utilizes regression models within the framework of g-computation to estimate causal effects of occupational exposures under assumptions that allow for control of healthy worker survivor bias (7). The parametric g-formula can be used to directly assess impacts of exposure limits on worker health, which aids in decision making around personal exposure limits in the workplace. Briefly, this approach utilizes multiple regression models (exposure, employment, and outcomes) and a Monte Carlo simulation to estimate cumulative risk under hypothetical interventions. The parametric g-formula has been used to assess impacts of hypothetical exposure limits for a number of occupational hazards such as asbestos, arsenic, diesel exhaust, particulate matter, and radon (8-13). However, estimators of the parametric g-formula are highly modeling and simulation intensive, which creates two practical issues: 1) heavy reliance on modeling assumptions for validity and 2) heavy computational burden (14). G-estimation of structural nested models is another feasible approach, but it is difficult to interpret (15) or may not estimate cumulative risk (16), which is often the target of risk assessment. Inverse probability-of-exposure weighted estimation of marginal structural models has been recommended against because the probability of exposure is zero among those who have left work, violating a key assumption of the approach (17).

To address healthy worker survivor bias and assess impacts of exposure limits on worker health, we propose use of inverse probability of censoring weighting for dynamic regimes (18-20). This approach uses the observed data as a pseudo-trial in which individuals are artificially censored from the observed data when they are observed to be inconsistent with the "treatment arm" (e.g., monthly exposure above an occupational limit), and inverse probability weighting is used to correct for the bias introduced by censoring. Here, we demonstrate this approach in a reanalysis of the Colorado Plateau Uranium Miners (CPUM) cohort (21). We demonstrate strengths of this approach for reducing modeling assumptions while estimating impacts of hypothetical occupational exposure limits.

METHODS

Study population

The CPUM cohort has been described previously (21). Briefly, the cohort comprises 4,137 male underground uranium miners who worked in the Colorado Plateau region in the 1950s and 1960s. Lung cancer was ascertained as the underlying cause of death. These underground miners were occupationally exposed to radon gas and associated short-lived radon decay products (RDP). Nearly all dose to lung tissue is attributable to densely ionizing radiation from radon progeny; therefore, "radon" is commonly quantified as the potential alpha energy concentration from RDP, often expressed in Working Level (WL), where 1 WL = 20.8 $\mu J \cdot m^{-3}$. Estimates of cumulative exposure to radon were obtained for each worker (22) and expressed in the historical unit of working level months (WLM), which is exposure to 1 WL for 170 hours (23). Data on dates of exposure to workers were used to interpolate monthly exposure to workers prior to and including follow-up. Smoking data were available from three surveys among surviving workers, which we collapsed to ever (77%) /never (23%) smoking due to limitations of the survey data (24). Racialization can be thought of as a confounder in this study (25). White and American Indian miners were often segregated by job type (influencing exposure), and also experienced different

health care access and environmental health conditions (influencing the outcome). Therefore, White and American Indian racialized categories were included in the analysis.

Person-time-at-risk began on the date of first medical screening (between July 1950 and July 1960) and ended on the earliest of the date of death, loss to follow-up, or study end (December 31, 2005). We excluded 10 miners with no information on smoking, yielding a final analytic cohort of N=4,127.

Dynamic exposure regimes in occupational cohorts and inverse probability weighting
Causal effect estimation for time-varying exposures involves 2 basic steps 1) defining exposure "regimes" of interest and 2) contrasting the expected health outcomes for a population across 2 or more of those regimes (26). These regimes can be dynamic. Dynamic regimes mean that exposure levels on a specific regime may change as a function of time-varying variables.

Dynamic exposure regimes for occupational settings are motivated by personal exposure limits. For radon exposure in US miners, the current regulatory annual personal exposure limit is 4 WLM (27). We operationalize personal exposure limits as a monthly limit (e.g. 0.33 WLM per month). Personal exposure limits can be considered dynamic treatment regimes such as: "if at work, monthly exposures must be below 0.33 WLM" (28). Annual exposure limits could also be used, but we use monthly limits to improve comparability with prior analysis of this cohort (13). These exposure regimes are dynamic because they depend on time-updated employment status.

The underlying concept of this approach is that the treatment and covariate patterns among participants in the observational data are realizations of a dynamic treatment regime. For example, some workers in the CPUM cohort data do, in fact, have exposure below a 0.33 WLM monthly limit while at work. Though we cannot simply compare those workers with the rest of the cohort (because they differ by important confounders), we can instead apply weights so that the low exposed workers represent the mortality experience of the entire cohort, had it been subject to a monthly exposure limit of 0.33 WLM during follow-up.

Contrasts of weighted populations allow causal inference under the assumptions that (a) we account for a sufficient set of baseline and time-varying confounders (i.e., common causes of mortality and the time-varying probability of exceeding a given exposure limit) (b) correctly specified models for the probability of exceeding a limit and (c) positivity (i.e., every worker has a positive chance to exceed or remain below a given exposure limit) (26) (29-31). Under these assumptions, contrasts of mortality between weighted populations can be conceptualized as comparisons of potential outcomes for the same population under different personal exposure limits. The general approach to estimating effects of a dynamic regime at a given limit with inverse probability weighting has been referred to as a "clone-censor-weight" method (32), which we describe here.

Cloning, censoring. First, one "clones" the study data by making a duplicate copy, and then cloned workers are artificially censored at the time that they have exposures that exceed the exposure limit (33). Here, a worker was considered censored in the first person-month during follow-up when he exceeded the limit (e.g., some workers would be censored in their first observation). For workers who never exceeded a limit during follow-up, all observed person-time was retained. Censoring by loss-to-follow up (0.3% of workers) was assumed ignorable (more substantial loss-to-follow-up could be accommodated by additional sets of weights (18, 34)). Artificial censoring is demonstrated in **Figure 1** for a small sample of workers. We assume that censoring occurs temporally prior to other events (exposure, leaving work, mortality) within a month. Censoring is operationalized in the cloned data with a time-varying censoring indicator, where C_m=0 means a worker has not exceeded the limit before or in month m and $C_m = 1$ otherwise. For example, for a 1 WLM limit, a worker would be censored the first time he had a total

exposure within a month > 1 WLM. Observations were kept in each data copy up to and including the first artificially censored month, M.

Censoring models. Next, within each dataset, we model censoring. We fit separate logistic models for the censoring indicator for $m = 1$ (baseline model) or $m > 1$ (follow-up model). The first model included all workers and modeled the log-odds of C_1, given time-fixed covariates and exposure and employment prior to the first month of follow-up. The second model was fit using employed follow-up data and modeled C_m, given time-fixed covariates and exposure and employment prior to the mth month of follow-up, for all months after the first month. Both of these models can be given in the same generic form as

$$\Pr(C_m = 1|\bar{\boldsymbol{A}}_{\boldsymbol{m-1}}, \bar{\boldsymbol{E}}_{\boldsymbol{m-1}}, \bar{\boldsymbol{L}}_{\boldsymbol{m}}, \boldsymbol{Z}, E_m = 1, C_{m-1} = 0; \boldsymbol{\beta}) = \beta_0 + \boldsymbol{g}(\bar{\boldsymbol{A}}_{\boldsymbol{m-1}})\boldsymbol{\beta_1} + \boldsymbol{g}(\bar{\boldsymbol{E}}_{\boldsymbol{m-1}})\boldsymbol{\beta_2} + \boldsymbol{g}(\bar{\boldsymbol{L}}_{\boldsymbol{m-1}})\boldsymbol{\beta_3} + \boldsymbol{Z}\boldsymbol{\beta_4}$$

Where $\boldsymbol{g}(\bar{\boldsymbol{A}}_{\boldsymbol{m-1}})$ is some function of the history of exposure up to and including time m (e.g. cumulative exposure at month $m-1$ with a cubic spline basis), $\boldsymbol{g}(\bar{\boldsymbol{E}}_{\boldsymbol{m-1}})$ is some function of the history of employment up to and including time $m-1$, $\boldsymbol{g}(\bar{\boldsymbol{L}}_{\boldsymbol{m-1}})$ is some function of other time-varying confounders (e.g. age) up to and including time $m-1$, $\boldsymbol{Z}$ are time-fixed confounders, and the $\boldsymbol{\beta}$ coefficients are vectors of logistic model coefficients. Specific model forms are given below. For both $m = 1$ and $m > 1$ we fit two additional censoring models that included only age, which model $\Pr(C_m = 1|\, \boldsymbol{L_{m-1}}, C_{m-1} = 0; \boldsymbol{\alpha})$ and are used for weight stabilization (35, 36). Here we note that two censoring models were used to accommodate our example of interest, and in other cases, a single model may be sufficient. Probability of censoring was zero after employment ended.

Weight estimation. Let $P^*_{cens,m} = \Pr(C_m = 1|\bar{\boldsymbol{A}}_{\boldsymbol{m-1}}, \bar{\boldsymbol{E}}_{\boldsymbol{m-1}}, \bar{\boldsymbol{L}}_{\boldsymbol{m-1}}, \boldsymbol{Z}, C_{m-1} = 0; \widehat{\boldsymbol{\beta}})$, and $P_{cens,m} = \Pr(C_m = 1|\, \boldsymbol{L_{m-1}}, C_{m-1} = 0; \widehat{\boldsymbol{\alpha}})$ be predictions from the fitted censoring models (with estimated parameters $\widehat{\boldsymbol{\beta}}$ and $\widehat{\boldsymbol{\alpha}}$). For each individual in the study, for each regime, we calculated stabilized weights for every month up to the month of censoring M given by

$$W_m = \prod_{j=1}^{m<M} (1 - P_{cens,j})/(1 - P^*_{cens,j})$$

For denominators of both weight models (which were fit separately for all regimes), logistic models estimated the probability of exceeding the limit as a function of age (restricted, cubic spline), date of birth (restricted, cubic spline), racialized category (White versus American Indian), smoking (ever versus never), cumulative radon exposure in WLM under a lag of 5 years (restricted, cubic spline). Numerator models included only a set of terms for a restricted, cubic spline on age. Intuition about how this approach addresses healthy worker survivor bias is given in **Appendix S1**, which includes a graphical explanation using directed acyclic graphs in **Figure S1.**

We note that the special case of modeling censoring at baseline is equivalent to modeling a point exposure as is often done as an alternative approach to adding terms to a regression model for controlling confounding of point exposures. Thus, we could conceptualize the factors that enter into the model for censoring at baseline as confounders for the "exposure" of having annual radon exposure below a limit at baseline, and the other censoring model addresses selection bias that arises when some of those individuals are selected out of the analytic set (artificially censored) based on their annual radon levels (See **Appendix S2**).

Regimes of interest. Regimes of interest for the current study were monthly exposure limits based on WLM. We selected 35 limits ranging from 0.33 WLM to 75 WLM and also including the "natural

course" (no artificial exposure limit, which here is simply the observed data, all of which is included with weights = 1.0; in data subject to loss-to-follow-up, inverse probability of loss-to-follow-up weights should be used with the observed and artificially censored data). Specific values of regimes were chosen because they have recently been under consideration for personal exposure limits on radon (37) or to yield a regularly spaced grid of values (**Appendix S3**). 75 WLM was chosen as the upper limit because cumulative risk did not increase much beyond this limit. A dataset was created for each regime following the clone-and-censor approach, and weights were created separately for each of these datasets.

Estimating impacts of occupational exposure limits from cloned and censored data. We used two approaches to estimating impacts of exposure limits: (1) contrasting each dynamic regime with a referent regime while ignoring information from other regimes (non-pooled approaches), and (2) using a marginal structural model to pool information across all 35 dynamic regimes (pooled approach).

Non-pooled, non-parametric estimator. For each regime, we first estimated cumulative risk of lung cancer mortality from ages 16 to 90 using a weighted Aalen-Johansen estimator, a non-parametric estimator of cumulative risk under competing risks (38). Under causal assumptions of exchangeability, positivity, and correct weight model specification, this approach estimates the cumulative risk of lung cancer among the CPUM cohort, had a more restrictive personal exposure limit been put in place. Lung cancer mortality is rare after age 90, so risk through age 90 approximates lifetime risk.

Non-pooled, semi-parametric estimator. We also used weighted Cox proportional hazards models to estimate cause-specific hazard ratios contrasting the hazard of lung cancer mortality under the 75 WLM limit (referent) with the hazard under each hypothetical exposure limit. The limits were treated as disjoint indicators in a joint, saturated model for all 35 copies of the data (we could have also fit many separate models). This approach is more restrictive than the Aalen-Johansen estimator because it assumes proportional hazards between the treatment regimes.

Marginal structural modeling (pooled) estimator. We then fit a model to estimate the hazard ratio as a smooth function of the exposure limits. First, data for all 35 regimes other than the natural course were combined into a single dataset. Then, a weighted Cox model was fit in which the value of the exposure limit was used as the continuous independent variable. This approach is more restrictive than the non-pooled Cox model because it assumes a smooth parametric form of the relationship between the hazard and the exposure limit under the regime, but it pools information across regimes thus gaining efficiency if that parametric form is correct. If the parametric form is correct, it allows prediction of the hazard at any personal exposure limit. To avoid stringent parametric assumptions we modeled exposure limit values flexibly using a restricted cubic spline with 8 knots (39).

We repeated this model with non-lung cancer mortality and used baseline hazard estimates from both models to estimate the cumulative risk from ages 16 to 90 at a grid of exposure limits, including an extrapolation to risk under no exposure.

All approaches utilized non-parametric bootstrap (resampling individuals with replacement and carrying out the entire analysis repeatedly) variance estimators (200 samples), which were used to create confidence intervals based on a normality assumption (**Figure S2**). To estimate age-specific cancer risks, we chose age as the time-scale of analysis, which necessitates assuming that late-entry (e.g. workers starting employment after age 16) on the age time scale (the time scale for analysis) is ignorable (40). Illustrative code for the non-pooled approaches in the Julia programming language (41), which was used in analysis, is given in **Appendix S4**.

Sensitivity analyses

We conducted two sensitivity analyses for the censoring models in which we added age-at-hire (restricted, cubic spline), or age-at-hire and cumulative years worked (1 year lag, restricted, cubic spline). We also assessed sensitivity to assumptions about confounding by prior exposure by performing an additional analysis that adjusted for recent exposure (monthly radon exposure, 2-year lag, restricted, cubic spline) and cumulative time employed (1 year lag, restricted, cubic spline). We examined potential sparsity by comparing distributions of potential confounders in censored and uncensored observations.

RESULTS

Worker and person-time characteristics are given in **Table 1**. 15% of the workers had deaths attributed to lung cancer. Workers had high cumulative exposure to radon (median across follow-up = 280 WLM, respectively, 5-year lag). Cumulative employment was 6 years (1 year lag), averaged over all follow-up time.

Estimated weights for a limit of 0.33 WLM yielded a mean, stabilized weight of 1.71, indicating substantial concerns for bias. Thus, we did not use censored data from regimes with limits below 0.75 WLM (35). For other regimes, the mean inverse probability weight was close to 1.0 (**Table 2)**. Most censoring occurred in the first observation, rather than later in follow-up. Sparsity was not apparent in tabular analyses, supporting findings from the weights (**Web Table 1**).

Semi-parametric estimates of the hazard ratio were very similar to estimates from the fitted marginal structural model (**Figure 2, Table 3**). Estimates of cumulative mortality incidence derived under the marginal structural Cox model (along with a similar model for competing risks) yielded cumulative incidence estimates that also tracked well with non-parametric estimates suggesting that the fitted model produced accurate risk estimates (**Figure S3**). Notably, extrapolating from this model to estimate lung cancer cumulative incidence by age 90 at a limit of 0.33 WLM yields an estimate (95% confidence interval [CI]) of 0.06 (0.03, 0.09). Under no exposure, cumulative mortality incidence was negligibly lower (at the levels of rounding we used) than the estimate at 0.33 WLM. Non-parametric cumulative mortality incidence estimates from age 16 to 90 at 1 and 2 WLM are lower, but less precise than prior estimates from the parametric g-formula (**Figure 3**) (13).

Sensitivity analyses suggested that further control for employment or exposure histories did not substantially change our estimates of lung cancer risk under the dynamic regimes we examined down to 0.75 WLM **(Web Tables 1-6)**.

DISCUSSION

Personal exposure limits in the occupational setting have a natural interpretation as dynamic exposure regimes. We estimated that, among 4,127 workers in the CPUM cohort, elimination of exposure would have cut lung cancer risk through age 90 from over 16% to just under 6%, a stark demonstration of the hazardously high exposures experienced by this cohort. Our approach to contrasting exposure limits in worker cohorts reduces strong parametric assumptions of existing approaches. Crucially for using occupational data to assess risk from occupational exposures, our approach can reduce concerns about healthy worker survivor bias.

The CPUM cohort makes a compelling example for this approach. First, this cohort has previously been used to estimate effects of dynamic exposure regimes similar to ones we assessed. Second, this cohort has played a role in determining the personal exposure limits that workers experience today (42). Third, this cohort is highly exposed, which helps to highlight some challenges of assessing risk at low exposure, including the role of model specification. Edwards et al used the parametric g-formula to estimate that, under a dynamic regime that capped all worker exposures at 0.33 WLM, risk through age 90 would have been reduced from 16% to 11% (13). In contrast, we estimated a reduction to 6%. There are subtle differences between the dynamic regimes examined, Edwards et al 'capped' exposures at a limit by

reducing high exposures to exactly the limit, whereas in our analysis the worker exposures followed the empirical distribution of exposures under the limit (20). We estimated a risk of 11% at a limit of 7 WLM, in which the weighted mean monthly exposure at work was 1.9 WLM. Thus, it is not likely the differences in regimes fully explain the different results. Differences between approaches likely also relate to model misspecification at low exposures. The parametric g-formula is known to be sensitive to model specification issues, and most of the cases (and hence information for model fitting) occurs among highly exposed workers (43, 44). With radon, "inverse dose-rate" effects suggest that the exposure-response for cumulative exposure is higher with protracted (lower dose-rate) vs. acute exposure; in the parametric g-formula that phenomenon must be explicitly modeled and thus subject to misspecification, or effects will be underestimated at low exposure limits (45). In contrast, our non-pooled approaches do not utilize a model to pool information about the exposure response between low and high exposures, and our MSM agreed broadly with results from the non-pooled approaches.

Our estimated lung cancer risk through age 90 of nearly 6% is consistent with estimates from other occupational populations from a similar era. In prior analyses of other U.S. based occupational cohorts, we estimated a respiratory mortality risk through age 90 among unexposed workers of 7% among copper smelters with an average birth year of 1912 (12), and a lung cancer mortality risk at age 80 of 6% among a pooled cohort of silica exposed workers with an average birth year of 1926 (unpublished sensitivity analysis among 15,158 US-based workers from (11)). Published smoking prevalence among one of the US-based cohorts was >80% among workers exposed above the median cumulative exposure value (46), which was similar to the prevalence of ever-smoking in our cohort (77%). However, applying estimates of lifetime risk among current, former, and never smokers (14.5%, 7.5%, and 1.5% respectively) from a Swiss population directly to the CPUM, a smoking-prevalence (55%, 32%, 23%) weighted estimate of lifetime lung cancer is approximately 9%, which is closer to the estimate of Edwards et al. Notwithstanding the crudeness of these calculations, we intuit that the true risk through age 90, had workers been unexposed to radon, is likely to be somewhere between our estimate and that of Edwards et al.

A strength of using approaches like our weighting approach or other g-methods like the parametric g-formula and structural nested models is that they allow control of confounding by time-varying factors that are affected by prior exposures (e.g. (47)). Confounding by employment status has been proposed to explain healthy worker survivor bias (1, 2, 7). Cumulative radon exposure has been associated with the subsequent hazard of leaving work among these miners (15). Thus, adjusting for employment status by including it in a regression model for lung cancer is not appropriate for controlling for confounding, though the magnitude and direction of bias from such adjustment is unknown (1, 2, 7). In our approach, confounding control is gained by inverse probability weights that account for employment status by fitting censoring models to actively employed person-time.

Previously, Robins and colleagues cautioned against the use of marginal structural models in occupational studies because the probability of occupational exposure among those off work is zero, which violates the positivity assumption (17). Notably, those authors were referring to an approach to inverse probability weighting in which one directly models the probability density of exposure, which is zero in the stratum of unemployed person-time. We avoided the positivity problem by using an alternative strategy to inverse probability weighting, which was similar to that proposed by Joffe (28). We modeled the probability of having exposure *that is consistent with a specific dynamic exposure regime* via inverse probability of censoring weights.

However, we note that we were still potentially sensitive to practical violations of positivity. Workers exposed in the earliest years of the cohort, when no protections were in place, may have had high enough exposures such that none of them followed the low exposure regimes of interest. While basic tabular analysis did not suggest sparsity was an issue, the mean estimated inverse probability weights deviated

from 1.0 at the lowest exposures, nonetheless suggesting bias (35, 36). Consequently, for dynamic regime limits below 0.75 WLM, we extrapolated risk estimates from the marginal structural model. Because the CPUM is one of the highest exposed miner cohorts, non-parametric estimates of radon's effect in the workplace would benefit from the use of data from lower-exposed cohorts (e.g., (48, 49)). There is substantial heterogenity between effect estimates in cohorts of uranium miners, particularly among the earliest cohorts (50, 51).

Relative to the parametric g-formula, inverse-probability weighting trades fewer parametric assumptions for lower precision, as demonstrated in **Figure S4**. Further, the parametric g-formula can estimate effects of a more diverse range of dynamic regime effects; for example, the 'capped' exposure regime utilized by Edwards et al, (20) would not be possible with inverse probability weighting in our data because it would rely on identifying workers whose exposures exactly match the exposure limit. Similarly, we could not estimate effects of regimes of the type "always exposed exactly at a specific level" unless we observed a sufficient number of participants for whom that was true.To estimate exposure impacts at low doses, the parametric g-formula fits a smooth model to all available data. In contrast, our marginal structural modeling approach relied more explicitly (and transparently) on extrapolation to low exposures. Thus, we view the inverse probability weighting and parametric g-formula methods as complementary, in part because they have different underlying assumptions.

We demonstrated a novel application of weighting methods for dynamic regimes to address several challenges of occupational cohort studies including healthy worker survivor bias and the direct assessment of new personal exposure limits. The relative simplicity of our approach, relative to the parametric g-formula, make this a useful tool in the occupational epidemiologists' toolbox.

REFERENCES

1. Arrighi HM, Hertz-Picciotto I. The evolving concept of the healthy worker survivor effect. *Epidemiology* 1994;5(2):189-96.
2. Buckley JP, Keil AP, McGrath LJ, Edwards JK. Evolving methods for inference in the presence of healthy worker survivor bias. *Epidemiology* 2015;26(2):204-12.
3. Picciotto S, Hertz-Picciotto I. Commentary: healthy worker survivor bias: a still-evolving concept. *Epidemiology* 2015;26(2):213-5.
4. Fox AJ, Collier PF. Low Mortality-Rates in Industrial Cohort Studies Due to Selection for Work and Survival in Industry. *Brit J Prev Soc Med* 1976;30(4):225-30.
5. Steenland K, Deddens J, Salvan A, Stayner L. Negative bias in exposure-response trends in occupational studies: Modeling the healthy worker survivor effect. *Am J Epidemiol* 1996;143(2):202-10.
6. Steenland K, Stayner L. The importance of employment status in occupational cohort mortality studies. *Epidemiology* 1991;2(6):418-23.
7. Robins J. A New Approach to Causal Inference in Mortality Studies with a Sustained Exposure Period - Application to Control of the Healthy Worker Survivor Effect. *Mathematical Modelling* 1986;7(9-12):1393-512.
8. Richardson DB, Keil AP, Cole SR, Dement J. Asbestos standards: Impact of currently uncounted chrysotile asbestos fibers on lifetime lung cancer risk. *Am J Ind Med* 2018;61(5):383-90.
9. Neophytou AM, Costello S, Picciotto S, et al. Accelerated lung function decline in an aluminium manufacturing industry cohort exposed to PM(2.5): an application of the parametric g-formula. *Occup Environ Med* 2019;76(12):888-94.
10. Neophytou AM, Costello S, Picciotto S, et al. Diesel Exhaust, Respirable Dust, and Ischemic Heart Disease: An Application of the Parametric g-formula. *Epidemiology* 2019;30(2):177-85.
11. Keil AP, Richardson DB, Westreich D, Steenland K. Estimating the Impact of Changes to Occupational Standards for Silica Exposure on Lung Cancer Mortality. *Epidemiology* 2018;29(5):658-65.
12. Keil AP, Richardson DB. Reassessing the Link between Airborne Arsenic Exposure among Anaconda Copper Smelter Workers and Multiple Causes of Death Using the Parametric g-Formula. *Environ Health Perspect* 2017;125(4):608-14.
13. Edwards JK, McGrath LJ, Buckley JP, et al. Occupational radon exposure and lung cancer mortality: estimating intervention effects using the parametric g-formula. *Epidemiology* 2014;25(6):829-34.
14. Keil AP, Edwards JK, Richardson DB, et al. The parametric g-formula for time-to-event data: intuition and a worked example. *Epidemiology* 2014;25(6):889-97.
15. Keil AP, Richardson DB, Troester MA. Healthy worker survivor bias in the Colorado Plateau uranium miners cohort. *Am J Epidemiol* 2015;181(10):762-70.
16. Picciotto S, Chevrier J, Balmes J, Eisen EA. Hypothetical Interventions to Limit Metalworking Fluid Exposures and Their Effects on COPD Mortality
-. *Epidemiology* 2014;25(3):436-43.
17. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11(5):550-60.
18. Hernan MA, Lanoy E, Costagliola D, Robins JM. Comparison of dynamic treatment regimes via inverse probability weighting. *Basic Clin Pharmacol Toxicol* 2006;98(3):237-42.
19. Robins JM. Analytic methods for estimating HIV-treatment and cofactor effects. *Methodological issues in AIDS behavioral research* 1993:213-88.
20. Young JG, Logan RW, Robins JM, Hernan MA. Inverse probability weighted estimation of risk under representative interventions in observational studies. *J Am Stat Assoc* 2019;114(526):938-47.
21. Schubauer-Berigan MK, Daniels RD, Pinkerton LE. Radon exposure and mortality among white and American Indian uranium miners: an update of the Colorado Plateau cohort. *Am J Epidemiol* 2009;169(6):718-30.
22. Lundin FE, Wagoner JK, Archer VE. Radon Daughter and Respiratory Cancer, Quantitative and Temporal Aspects. *Springfield, VA: Public Health Service, US Department of Health, Education, and Welfare* 1971.
23. International Commission on Radiological P, Clarke RH. *Protection against radon-222 at home and at work*. Pergamon published for the International Commission on Radiological Protection; 1994.
24. Roscoe RJ. An update of mortality from all causes among white uranium miners from the Colorado Plateau study group. *American Journal of Industrial Medicine* 1997;31(2):211-22.
25. Lewis J, Hoover J, MacKenzie D. Mining and environmental health disparities in Native American communities. Curr Environ Health Rep 4 (2): 130–141, PMID: 28447316. 2017.
26. Hernan MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol* 2016;183(8):758-64.
27. Mining Safety and Health Adminstration CFR. Safety and Health Standards—Underground Metal and Nonmetal Mines. United States; 1985. (https://www.ecfr.gov/current/title-30/chapter-I/subchapter-K/part-57/subpart-D/subject-group-ECFR050f3d2837e2329/section-57.5038). (Accessed May 19, 2023).
28. Joffe MM. Structural nested models, g-estimation, and the healthy worker effect: the promise (mostly unrealized) and the pitfalls. *Epidemiology* 2012;23(2):220-2.

29. van der Laan MJ, Petersen ML. Causal effect models for realistic individualized treatment and intention to treat rules. *Int J Biostat* 2007;3(1):Article 3.
30. Orellana L, Rotnitzky A, Robins JM. Dynamic regime marginal structural mean models for estimation of optimal dynamic treatment regimes, Part I: main content. *Int J Biostat* 2010;6(2):Article 8.
31. Orellana L, Rotnitzky A, Robins JM. Dynamic regime marginal structural mean models for estimation of optimal dynamic treatment regimes, Part II: proofs of results. *Int J Biostat* 2010;6(2):Article 9.
32. Maringe C, Benitez Majano S, Exarchakou A, et al. Reflection on modern methods: trial emulation in the presence of immortal-time bias. Assessing the benefit of major surgery for elderly lung cancer patients using observational data. *Int J Epidemiol* 2020;49(5):1719-29.
33. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol* 2016;183(8):758-64.
34. Cain LE, Cole SR. Inverse probability-of-censoring weights for the correction of time-varying noncompliance in the effect of randomized highly active antiretroviral therapy on incident AIDS or death. *Stat Med* 2009;28(12):1725-38.
35. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168(6):656-64.
36. Hernan MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health* 2006;60(7):578-86.
37. Daniels RD, Schubauer-Berigan MK. Radon in Us Workplaces: A Review. *Radiat Prot Dosimetry* 2017;176(3):278-86.
38. Aalen OO, Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. *Scandinavian Journal of Statistics* 1978:141-50.
39. Devlin TF. Spline functions for logistic regression modelling. Presented at Proceedings of the 11th Annual SAS Users Group International Conference1986.
40. Keil AP, Edwards JK. A review of time scale fundamentals in the g-formula and insidious selection bias. *Curr Epidemiol Rep* 2018;5(3):205-13.
41. Bezanson J, Edelman A, Karpinski S, Shah VB. Julia: A Fresh Approach to Numerical Computing. *Siam Review* 2017;59(1):65-98.
42. National Research C. Health effects of exposure to radon: BEIR VI. 1999.
43. McGrath S, Young JG, Hernan MA. Revisiting the g-null Paradox. *Epidemiology* 2022;33(1):114-20.
44. Robins JM, Wasserman LA. Estimation of effects of sequential treatments by reparameterizing directed acyclic graphs. *arXiv preprint arXiv:13021566* 2013.
45. Lubin JH, Boice JD, Jr., Edling C, et al. Radon-exposed underground miners and inverse dose-rate (protraction enhancement) effects. *Health Phys* 1995;69(4):494-500.
46. Checkoway H, Heyer NJ, Seixas NS, et al. Dose-response associations of silica with nonmalignant respiratory disease and lung cancer mortality in the diatomaceous earth industry. *Am J Epidemiol* 1997;145(8):680-8.
47. Naimi AI, Cole SR, Kennedy EH. An introduction to g methods. *Int J Epidemiol* 2017;46(2):756-62.
48. Rage E, Vacquier B, Blanchardon E, et al. Risk of lung cancer mortality in relation to lung doses among French uranium miners: follow-up 1956-1999. *Radiat Res* 2012;177(3):288-97.
49. Kreuzer M, Grosche B, Schnelzer M, et al. Radon and risk of death from cancer and cardiovascular diseases in the German uranium miners cohort study: follow-up 1946-2003. *Radiat Environ Biophys* 2010;49(2):177-85.
50. Richardson DB, Rage E, Demers PA, et al. Lung Cancer and Radon: Pooled Analysis of Uranium Miners Hired in 1960 or Later. *Environ Health Perspect* 2022;130(5):57010.
51. Kelly-Reif K, Bertke SJ, Rage E, et al. Radon and lung cancer in the pooled uranium miners analysis (PUMA): highly exposed early miners and all miners. *Occup Environ Med* 2023;80(7):385-91.

TABLES

Table 1: Characteristics at baseline and across follow-up of 4,127 White and American Indian miners from the Colorado Plateau Uranium Miners cohort, 1951-2005

	N (%)	Mean (S.D.)	Median (IQR)
At baseline			
Ever smoker	962 (23%)		
American Indian racialization	769 (19%)		
Age		35 (11)	33 (26, 43)
Year of birth		1922 (12)	1923 (1913, 1931)
Calendar year		1957 (3)	1957 (1954, 1958)
Year of hire		1953 (6)	1954 (1951, 1957)
Cumulative years employed (1 year lag)		3 (5)	1 (0, 3)
Cumulative exposure (WLM, 5 year lag)		130 (423)	0 (0, 0)
Over follow-up: cohort			
Lung cancer deaths	613 (15%)		
Deaths from other causes	2445 (59%)		
Age		52 (15)	52 (41, 63)
Calendar year		1976 (13)	1974 (1965, 1986)
Cumulative years employed (1 year lag)		7 (6)	6 (2, 11)
Cumulative exposure (WLM, 5 year lag)		594 (922)	280 (72, 755)
Over follow-up: lung cancer cases			
Age		50 (13)	49 (40, 59)
Calendar year		1973 (12)	1971 (1963, 1981)
Cumulative years employed (1 year lag)		10 (7)	9 (5, 14)
Cumulative exposure (WLM, 5 year lag)		989 (1167)	627 (202, 1412)

IQR: interquartile range

[a] Includes 3 African-American miners and 2 Asian-American miners

Table 2: Characteristics of observed data and data under a set of 8 representative copies of the observed data with artificial censoring, along with inverse probability of censoring weight distributions across person time in each copy of the data, 4,127 White and American Indian miners from the Colorado Plateau Uranium Miners cohort.

	Lung cancer deaths	Artificially censored		Person-years of follow-up (X1000)	Cumulative exposure during follow-up (WLM)	Inverse probability weights
Limit[a,b]	N (%)	At baseline N (%)	During follow-up N (%)		Weighted median (95th percentile)	Mean (min, max)
None	613 (100%)	0 (0%)	0 (0%)	134.6	264 (1845)	1.00 (1.00, 1.00)
75 WLM	566 (92%)	78 (2%)	160 (4%)	127.6	239 (1350)	1.00 (0.88, 2.22)
50 WLM	541 (88%)	150 (4%)	220 (5%)	123.8	227 (1255)	1.00 (0.83, 2.32)
20 WLM	383 (62%)	705 (17%)	489 (12%)	98.5	158 (831)	1.01 (0.61, 4.26)
10 WLM	249 (41%)	1327 (32%)	617 (15%)	74.6	110 (529)	1.02 (0.48, 8.59)
5 WLM	124 (20%)	2133 (52%)	607 (15%)	48.8	67 (311)	1.01 (0.39, 4.59)
2 WLM	36 (6%)	3117 (76%)	379 (9%)	22.4	36 (150)	0.99 (0.27, 3.99)
1 WLM	17 (3%)	3549 (86%)	193 (5%)	13.2	6 (124)	0.98 (0.10, 5.09)
0.75 WLM	13 (2%)	3641 (88%)	149 (4%)	11.5	2 (122)	1.03 (0.07, 4.60)

[a] Monthly personal exposure limits expressed in units of working level months (WLM)
[b] A monthly limit of 0.33 WLM corresponding to the current Mining Safety and Health Administration annual limit of 4 WLM was omitted because of poor weight diagnostics (see text for details)

Table 3: Cause specific risk of lung cancer through age 90, risk differences and hazard ratios contrasting multiple dynamic regimes using non-pooled and pooled marginal structural model estimators for 8 representative dynamic regimes among 4,127 White and American Indian miners from the Colorado Plateau Uranium Miners cohort.

	Non-pooled			Marginal Structural model		
Limit[a]	**Age-90 risk (95% CI[b])**	**Age-90 risk difference (95% CI)**	**Hazard ratio (95% CI)**	**Age-90 risk (95% CI)**	**Age-90 risk difference (95% CI)**	**Hazard ratio (95% CI)**
None	0.16 (0.15, 0.18)	0.01 (0.00, 0.01)	1.05 (1.03,1.07)			
75 WLM	0.16 (0.14, 0.17)	Ref[c]	Ref[c]	0.16 (0.15, 0.18)	Ref[c]	Ref[c]
50 WLM	0.16 (0.14, 0.17)	0.00 (0.00, 0.00)	0.98 (0.96, 1.00)	0.16 (0.15, 0.17)	0.00 (-0.01, 0.00)	0.98 (0.96, 1.00)
20 WLM	0.14 (0.12, 0.15)	-0.02 (-0.03, -0.01)	0.84 (0.79, 0.89)	0.14 (0.13, 0.16)	-0.02 (-0.03, -0.01)	0.84 (0.80, 0.89)
10 WLM	0.12 (0.10, 0.13)	-0.04 (-0.05, -0.03)	0.68 (0.62, 0.75)	0.12 (0.11, 0.14)	-0.04 (-0.05, -0.03)	0.70 (0.63, 0.77)
5 WLM	0.10 (0.08, 0.11)	-0.06 (-0.08, -0.04)	0.52 (0.45, 0.61)	0.10 (0.08, 0.11)	-0.07 (-0.08, -0.05)	0.53 (0.46, 0.61)
2 WLM	0.07 (0.05, 0.09)	-0.09 (-0.11, -0.06)	0.39 (0.28, 0.54)	0.07 (0.05, 0.09)	-0.09 (-0.11, -0.07)	0.38 (0.28, 0.52)
1 WLM	0.07 (0.03, 0.10)	-0.09 (-0.13, -0.06)	0.36 (0.21, 0.62)	0.06 (0.04, 0.09)	-0.10 (-0.13, -0.07)	0.34 (0.22, 0.51)
0.75 WLM	0.05 (0.02, 0.08)	-0.10 (-0.14, -0.07)	0.30 (0.15, 0.61)	0.06 (0.03, 0.09)	-0.10 (-0.13, -0.07)	0.33 (0.21, 0.51)
0.33 WLM				0.06 (0.03, 0.09)	-0.10 (-0.13, -0.08)	0.31 (0.19, 0.51)
No exposure[d]				0.06 (0.03, 0.08)	-0.11 (-0.14, -0.08)	0.30 (0.18, 0.51)

Empty cells imply that a given method did not supply an estimate for the given regime or contrast

[a] Expressed in units of working level months per month (WLM), which are defined in the text

[b] Confidence intervals from estimate $\pm 1.96 * \hat{\sigma}_b$, where $\hat{\sigma}_b$ is the standard deviation of estimates from 200 bootstrap samples.

[c] The referent limit of 75 WLM was used because the marginal structural model approach does not accommodate inclusion of a "none" group when considering exposure limits and because it is sufficiently high to approximate the hazard or risk under no intervention. "No exposure" is also not a valid common reference groups because non-parametric approaches could not accommodate it.

[d] Derived from projections of the marginal structural model down to a monthly exposure limit of 0 WLM

FIGURE LEGENDS

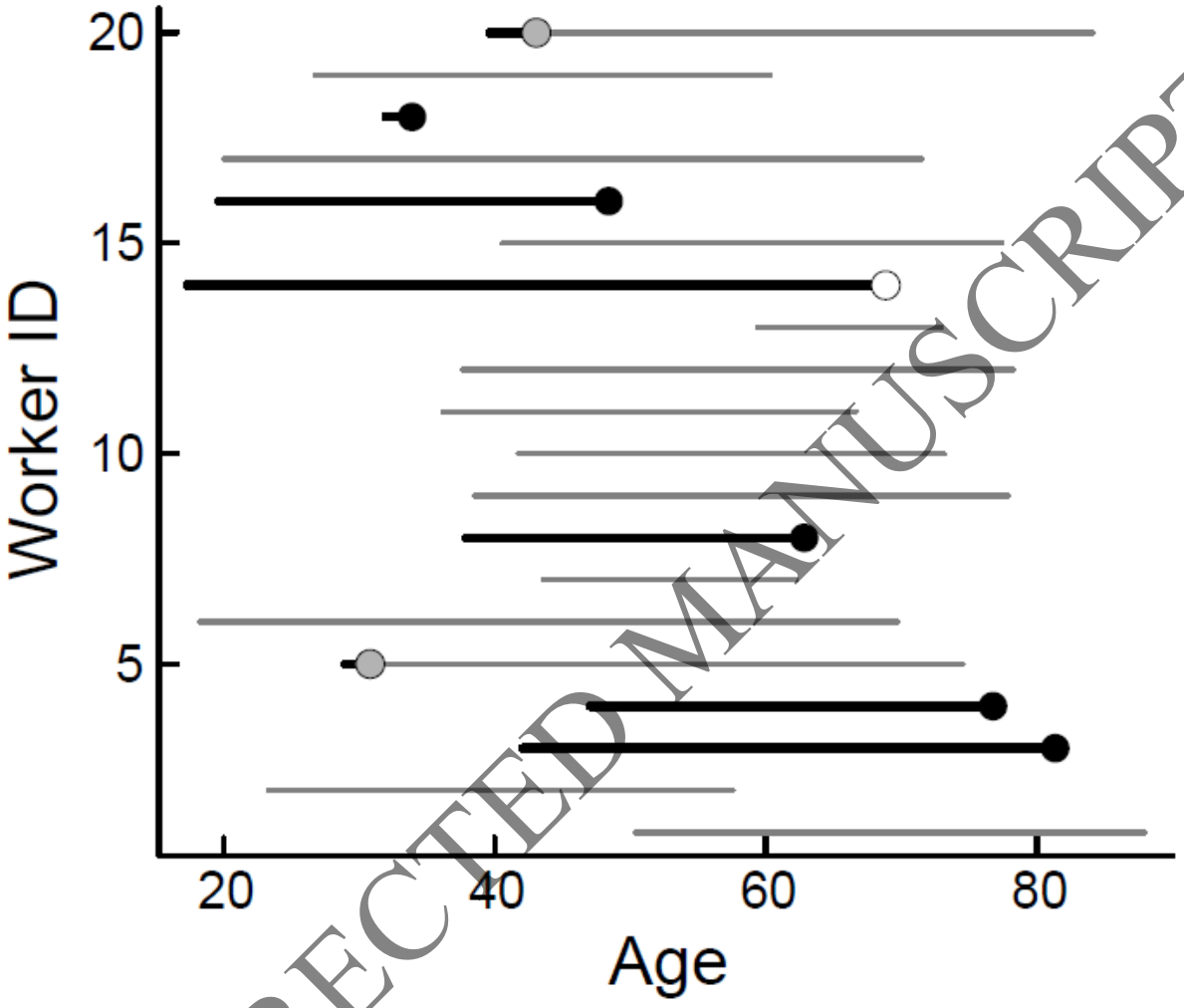

Figure 1: Person-time diagram demonstrating how artificial censoring occurred for a sample of 20 miners with a dynamic exposure regime that sets a monthly personal exposure limit of 5 WLM (Colorado Plateau Uranium Miners cohort). Person-time for a given miner is represented by each line. Gray lines represent all observed person-time, whereas black lines represent only observed person-time for which a miner had exposure < 5 WLM (thus, if no black line overlaps a gray line, then that miner exceeded 5 WLM in his first month of follow-up and had no observations in the copy of the data representing the dynamic regime "if at work, monthly exposures must be < 5WLM." Events (censoring, mortality) are represented by circles where black circles represent deaths, white circles represent censoring by the end of follow-up, and gray circles represent artificial censoring when exposure exceeded 5 WLM during follow-up.

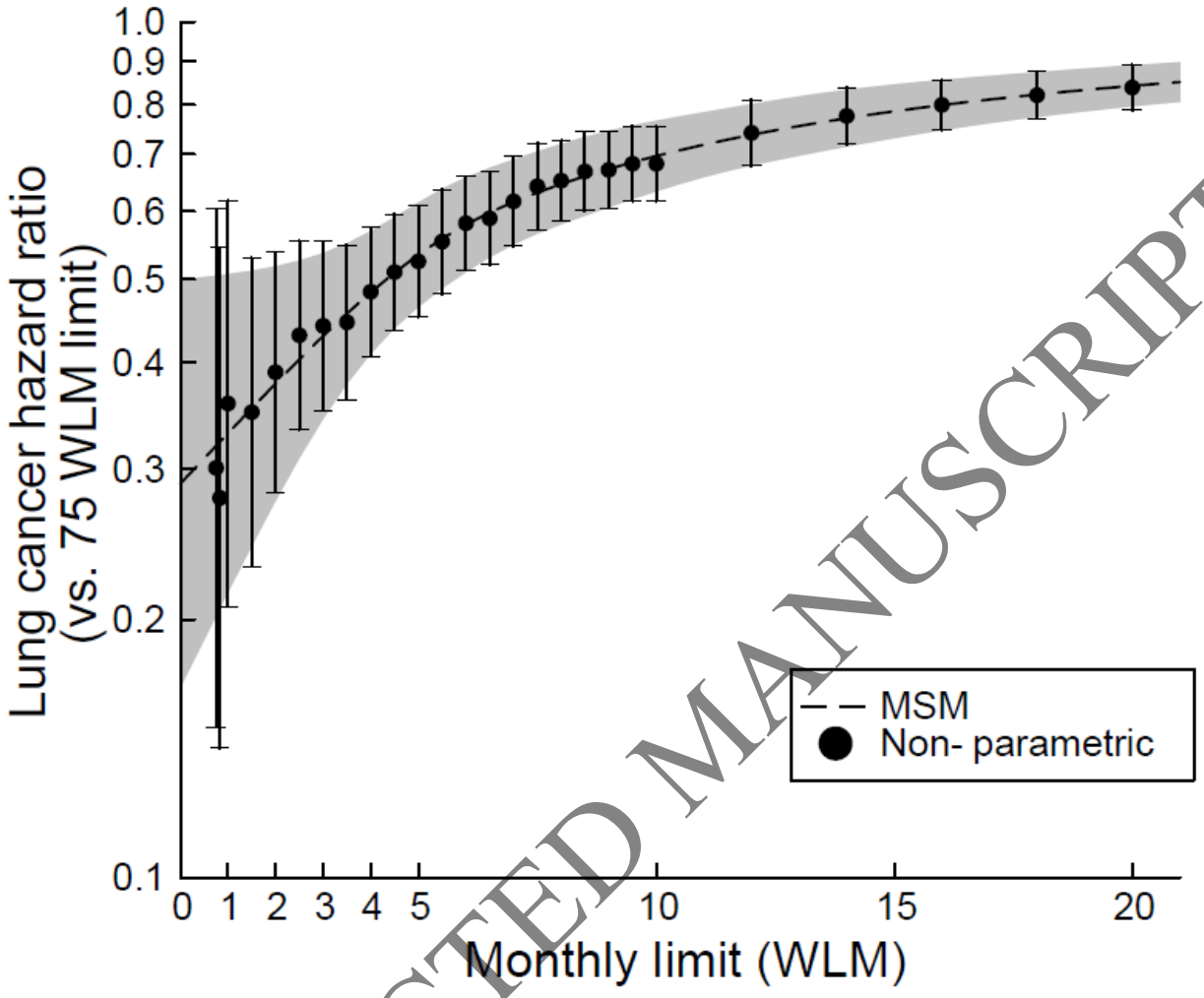

Figure 2: Inverse probability weighted hazard ratios for lung cancer among 4,127 White and American Indian miners from the Colorado Plateau Uranium Miners cohort. The hazard ratios represent contrasts among a series of dynamic regimes expressed as "if at work, exposure must be less than X WLM." The points represent non-parametric estimates of the hazard ratio comparing the hazard of lung cancer at the limit "< 75 WLM" to the hazard of lung cancer at 34 different limits described in the text, and the whiskers represent 95% confidence intervals. The dashed line and grey band represent the hazard ratio and 95% pointwise bootstrap confidence interval from a marginal structural model for the hazard of lung cancer by exposure limit, the fitting of which is described in the main text. The horizontal axis is truncated at 20 WLM for clarity.

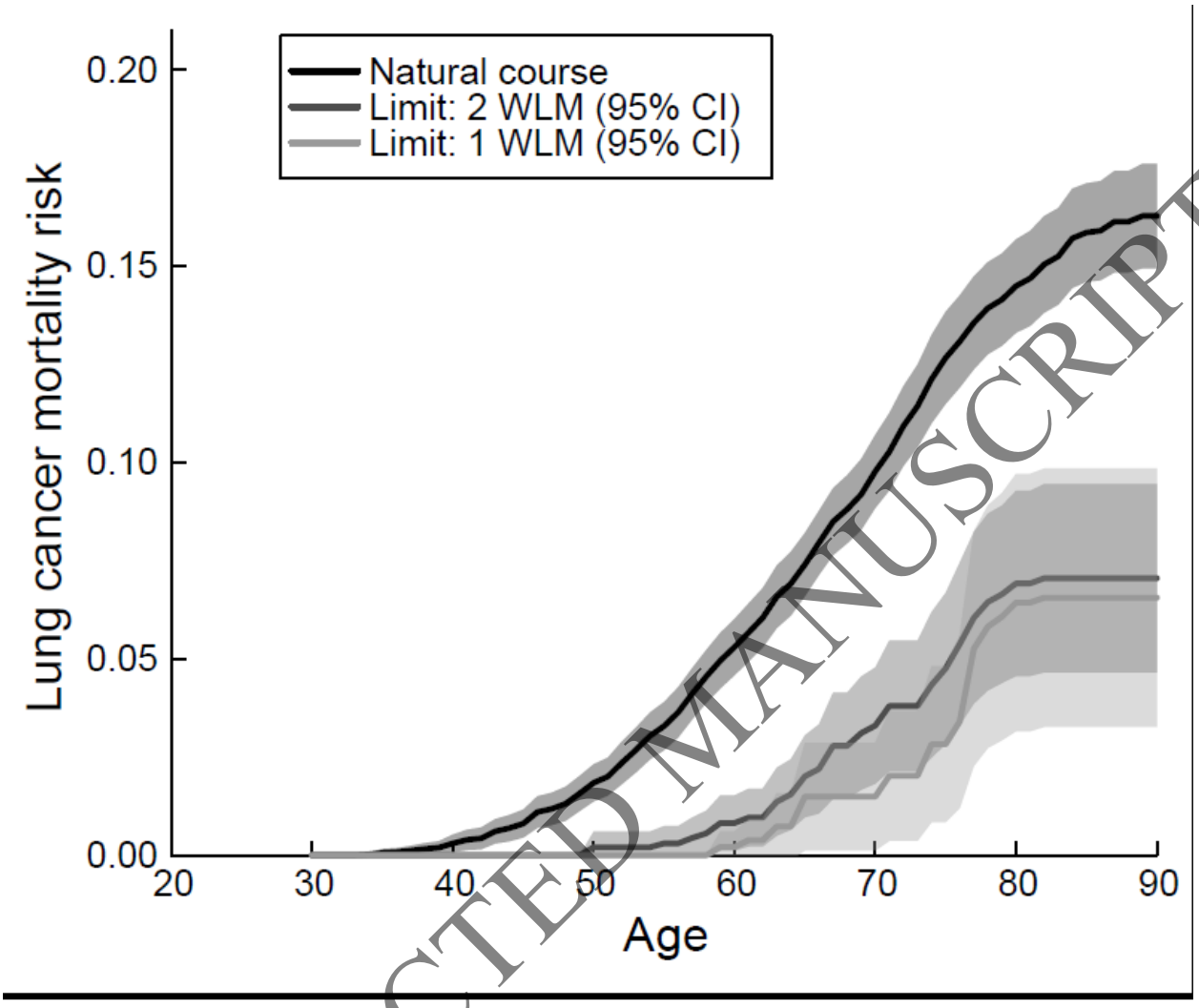

Figure 3: Cumulative lung cancer mortality risk estimates (lines) and 95% pointwise bootstrap confidence intervals (bands) from ages 16 to 90 among 4,127 White and American Indian miners from the Colorado Plateau Uranium Miners cohort. The estimate under "no intervention" is the non-parametric estimate in the observed data, while both estimates for both exposure limits are inverse probability weighted non-parametric estimates.