Estimating survival in left filtered data

Kevin Chen

Stat 256: Causal Inference (Fall 2021)

Introduction

The United Auto Workers-General Motors (UAW-GM) Cohort Study is a longitudinal occupational cohort study established in the early 1980s to study the health effects of metalworking fluids (Eisen et al. 1992, 2001). Metalworking fluids (MWF) are complex mixtures of fluids used in industrial metalworking operations to lubricate and cool machinery and parts. The three major classes of MWF are straight, soluble, and synthetic metalworking fluids (Byers 2006). Possible routes of human exposure include absorption through skin, inhalation of aerosols, and ingestion of droplets.

A central concern in the analysis of longitudinal occupational cohort data is the potential for bias due to the healthy worker survivor effect (HWSE), the phenomenon by which healthy individuals remain at work, while less healthy individuals leave work – possibly in response to exposure-related health decline. In the presence of the HWSE, those with the highest cumulative occupational exposures are also those who are less at risk of disease (more likely to have potential outcome no disease under both exposure and no exposure scenarios). Thus, standard measures of association would show an inverse relationship between occupational exposure and poor health outcomes (Arrighi and Hertz-Picciotto 1994). The HWSE is an example of time-varying confounding affected by past exposure. Previous studies have attempted to assess the presence of the HWSE in observed data by assessing so-called path-specific associations using Cox proportional hazards modeling (Naimi et al. 2013; Garcia et al. 2017). However, in those studies, the estimates were themselves subject to the confounding structures they sought to characterize.

If conditional sequential ignorability of exposure and censoring status at each point in follow-up and positivity (overlap) can be attained given covariate history, then longitudinal causal methods can be applied to account for the HWSE. Past studies have applied causal methods capable of accounting for time-varying confounding affected by past exposure to the study of MWF exposures and cancer mortality outcomes in the UAW-GM Cohort Study (Garcia et al. 2018; Izano et al. 2019). However, the study of cancer incidence outcomes is further problematized by the incomplete observation of cancer incidence outcomes at every point of follow-up over the study period. Nonetheless, we wish to make inferences about the carcinogenicity of MWF exposure over an individual's lifetime starting upon entry into the workforce. The UAW-GM Cohort included those hired roughly between 1938

and 1985. However, cancer incidence reporting did not begin until 1973. Hence, our observed cohort data exhibits *left filtering*: cancer incidence is the outcome of interest, but before 1985, both cancer incidence status and time of cancer incidence are unknown. Observation of the complete cancer incidence outcome vector over the study period was conditional on an individual surviving to 1985 cancer-free.

In the presence of the HWSE, left filtering implies outcome misclassification that is informative of true cancer status. As part of her dissertation research, Izano (2017) conducted a quantitative bias analysis for the estimation of survival curves using left filtered data in the presence of HWSE. She simulated data compatible with the HWSE and estimated cancer-free survival curves using an inverse probability of treatment and censoring weighted Kaplan-Meier (WKM) estimator and the WKM with an Aalen filter for left-filtering (AWKM) (Andersen et al. 1993; Xie and Liu 2005). Data were simulated under five different scenarios. The survival curves under the following interventions were computed or estimated in 250 replicates: (1) always exposed at work with no censoring due to death and (2) never exposed at work with no censoring due to death. For each intervention, three survival curves were produced: (1) the true survival curve, (2) the WKM survival curve, and (3) AWKM survival curve. Estimator bias was evaluated by comparing the average of 250 estimates of to the average difference in cancer-free survival under the two rules to the true average difference in survival when exposure and censoring were controlled deterministically.

The present project replicates the simulation and bias analyses presented in Chapter 3 of Izano (2017), embeds the problem in the non-parametric structural causal approach of (**Pearl_1995?**), and applies the WKM and AWKM estimators to the estimation of digestive-system cancer-free survival under exposure and no censoring rules in the UAW-GM Cohort. The `stremr` package was used to estimate the WKM and AWKM survival curves in both the simulation and the applied analyses (Sofrygin, van der Laan, and Neugebauer 2021). All code necessary for replicating the analyses presented here may be found on GitHub/kvntchn/gm-delayed-entry. Note that running the script for the applied analyses will require additional permissions.

Methods

Causal model

The UAW-GM Cohort data included person-year level exposure, outcome, and covariate data starting at hire. To emulate the shape of the data for this longitudinal cohort, we considered 20 years of data over time indexed by years since hire. Notation representing the variables of interest are presented in Table 1. The causal model represents hypothetical relationships between variables over time compatible with the theory underlying the HWSE in longitudinal occupational cohort studies. At each time point, the effect of cumulative exposure $\bar{A}(t)$ on cancer incidence $Y^*(t)$ is confounded by the path through employment status $N(t)$ and underlying health $H(t)$ as well as the path through past exposure $\bar{A}(t-1)$ and vital status $D(t)$. These paths follow straightforward

Table 1: Descriptions of variables.

Variable	Description
R	Time until start of registry
W	Baseline covariates
S	Susceptibility to effects of metalworking fluid exposure
$H(t)$	Adverse health status at time t
$N(t)$	Employment status at time t
$A(t)$	Metalworking fluid exposure at time t
$D(t)$	Mortality status at time t
$Y^*(t)$	Cancer status at time t
$Y(t)$	Observed Cancer status at time t
$t = \{1, 2, ..., 20\}$	Time, indexed in years after hire

logic: occupational exposure depends upon employment status and past exposure; mortality status is affected by past exposure and cancer history. Confounding by baseline covariates W is assumed throughout.

Assume we have $n = 50\,000$ iid units in X with

$$X_i(t) = \left(R_i = 0, W_i, S_i, \bar{H}_i(t), \bar{N}_i(t), \bar{A}_i(t), \bar{a}_i(t), \bar{Y}_i^*(t) = \bar{Y}_i(t)\right).$$

In general, we use bar notation to indicate variable history as follows $\bar{X}_i(t) = (X_i(k))_{k=1}^t$. Note that true cancer status $Y^*(t)$ is not observed until $t \geq R$, after the start of the registry. Call X the full data, where we have $R = 0$ for all. In the observed data X^{obs}, we cannot assume $R = 0$ for all. Additionally, susceptibility S and underlying health status H are not known:

$$X_i^{\text{obs}}(t) = \left(R_i, W_i, \bar{N}_i(t), \bar{A}_i(t), \bar{a}_i(t), \bar{Y}_i(t)\right).$$

Under the causal model, we assume the following non-parametric structural equations:

$$\begin{aligned}
R &= f_R\left(U_R\right) \\
W &= f_W\left(U_W\right) \\
S &= f_S\left(U_S\right) \\
H(t) &= f_{H(t)}\left(H(t-1), U_{H(t)}\right) \\
N(t) &= f_{N(t)}\left(W, N(t-1), H(t), A(t-1), U_{N(t)}\right) \\
A(t) &= f_{A(t)}\left(W, \bar{A}(t-1), N(t), U_{A(t)}\right) \\
D(t) &= f_{D(t)}\left(W, \bar{A}(t-1), D(t-1), Y^*(t-1), U_{D(t)}\right) \\
Y^*(t) &= f_{Y^*(t)}\left(W, S, H(t), \bar{A}(t), D(t), Y^*(t-1), U_{Y^*(t)}\right) \\
Y(t) &= Y^*(t) \times \mathbb{1}\left[Y^*(\lfloor R \rfloor) = 0\right] \times \mathbb{1}\left[D(t) = 0\right] \ .
\end{aligned}$$

The exogenous variables (errors) $U = \left(U_R, U_W, U_S, U_{H(t)}, U_{N(t)}, U_{A(t)}, U_{D(t)}, U_{Y^*(t)}\right)_{t=1}^{T}$ are mutually independent. Exposure status is a time-varying indicator, and exposure history is summarized as $\bar{A}(t) = \mathbb{1}\left[\sum_{k=1}^{t} \mathbb{1}\left[A(k) = 1\right] > 0\right]$. The outcome of interest is a survival outcome, so $Y^*(t-1) = 1 \Rightarrow Y^*(t) = 1$. The observed outcome $Y(t)$ at time t is a function of true outcome status, time of left censoring, and time of right censoring. An abbreviated directed acyclic graph (DAG) representing the causal relationships encoded in the equations above is presented in Figure 1.

Figure 1: Directed acyclic graph representing the causal relationships encoded in the non-parametric structural equation model at time t.

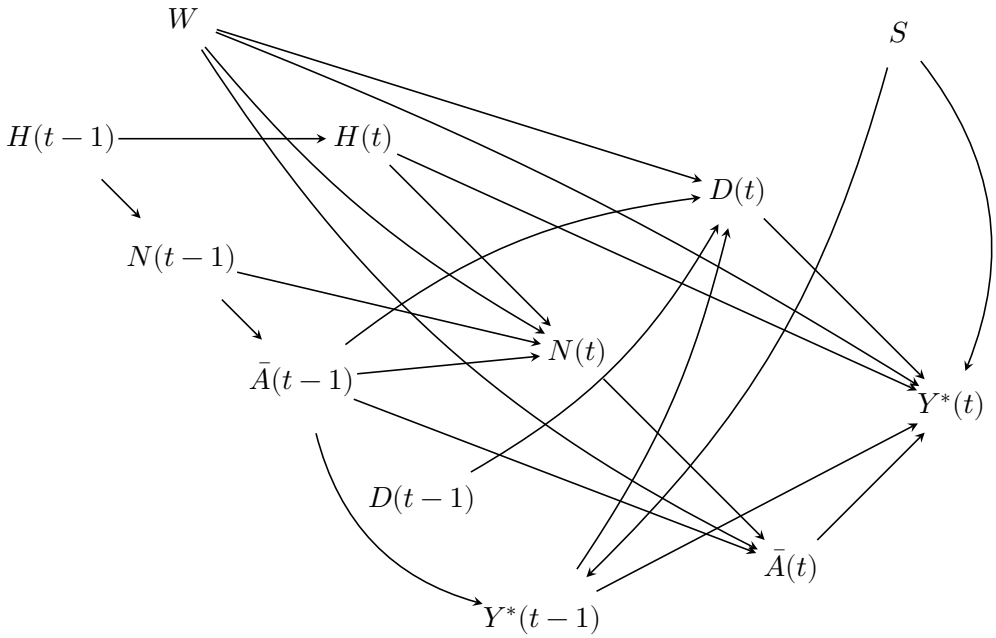


Figure 1 clarifies our conceptualization of the HWSE. At each time point t, the cumulative effect of exposure $\bar{A}(t)$ on cancer incidence $Y^*(t)$ is confounded by employment status $N(t)$ through the backdoor path $\bar{A}(t) \leftarrow N(t) \leftarrow H(t) \rightarrow Y^*(t)$. In the absence of observed data on health status $H(t)$, an analyst may be tempted to conduct an analysis by simply "blocking" or conditioning on employment status $N(t)$, but doing so would introduce collider bias while blocking the causal path between past exposure $\bar{A}(t-1)$ and cancer $Y^*(t)$. Furthermore, an analysis starting at an arbitrary time point after the time origin (hire) would be tantamount to conditioning on those still alive at that time, which would result in both collider bias and the conditioning on nodes on the causal path between the exposure and the outcome of interest.

Simulation

To generate data compatible with our structural causal model, we imposed parametric relationships between the variables. For the $n = 50\,000$ units over $T = 20$ years, we have:

- $U_j \overset{\text{iid}}{\sim} \text{uniform}\,[0,1]$ for all j
- In full data $R = 0$ otherwise $R \sim \text{uniform}\,[0,30]$
- $W = \mathbb{1}\left[U_W \leq p_W\right] \sim \text{Bernoulli}\,(p_W)$
- $S = \mathbb{1}\left[U_S \leq p_S\right] \sim \text{Bernoulli}\,(p_S)$
- If $H(t-1) = 1$, then $H(t) = 1$ otherwise $H(t) = \mathbb{1}\left[U_{H(t)} \leq p_H\right] \sim \text{Bernoulli}\,(p_H)$
- if $N(t-1) = 0$ then $N(t) = 0$ otherwise

$$N(t) \sim \text{Bernoulli}\left\{\text{logit}\,\left(\beta_0^N + \beta_W^N W + \beta_H^N H(t) + \beta_A^N A(t-1) \times \mathbb{1}\left[t > 1\right] + U_{N(t)}\right)\right\}$$

- If $N(t) = 0$ then $A(t) = 0$ otherwise

$$A(t) \sim \text{Bernoulli}\left\{\text{logit}\,\left(\left(\beta_0^A + \beta_W^A W\right) \times \mathbb{1}\left[t = 1\right] + \beta_A^A A(t-1) \times \mathbb{1}\left[t > 1\right] + U_{A(t)}\right)\right\}$$

- If $D(t-1) = 1$ then $D(t) = 1$ otherwise

$$D(t) \sim \text{Bernoulli}\left\{\text{logit}\,\left(\begin{array}{r}\beta_0^D + \beta_W^D W + \beta_{\bar{A}}^D \bar{A}(t-1) \times \mathbb{1}\left[t > 1\right] \\ +\beta_{\bar{Y}}^D \sum_{k=1}^{t-1} Y^*(k) \times \mathbb{1}\left[t > 1\right] + U_{D(t)}\end{array}\right)\right\}$$

- If $Y^*(t-1) = 1$ then $Y^*(t) = 1$ otherwise

$$Y^*(t) \sim \text{Bernoulli}\left\{\text{logit}\,\left(\begin{array}{r}\beta_0^Y + \beta_W^Y W + \beta_A^Y A(t) + \beta_{\bar{A}}^Y \bar{A}(t-1) \times \mathbb{1}\left[t > 1\right] \\ +\beta_S^Y S \times \bar{A}(t) + \beta_H^Y H(t) + U_{Y^*(t)}\end{array}\right)\right\}$$

- If $t < R$ then $Y(t) = 0$
- If $t \geq R$ then $Y(t) = Y^*(t) \times \mathbb{1}\left[Y^*(\lfloor R \rfloor) = 0\right] \times \mathbb{1}\left[D(t) = 0\right]$.

Five sets of data were generated using these equations, but with different parameters, to represent

five scenarios. Scenario 1 represents the base case where 10% of workers are susceptible to exposure-related effects, the odds ratio of mortality each additional year following cancer diagnosis is about 1.6, and there is moderate time-varying confounding by health status. In scenario 2, we have greater cancer-related mortality by increasing $\beta_{\bar{Y}}^{D}$. In scenario 3, we increase p_S, the proportion of the study population susceptible to the carcinogenic effects of MWF exposure. In scenario 4, we consider greater time-varying confounding by health status by increasing β_H^N and β_H^Y. In the last scenario, we have greater background cancer incidence by increasing β_0^Y. The sets of parameters used in the five scenarios are presented in Table 2.

Table 2: Simulation parameters.

Parameter	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
p_S	0.10	0.10	**0.20**	0.10	0.10
p_W	0.20	0.20	0.20	0.20	0.20
p_H	0.30	0.30	0.30	0.30	0.30
β_0^N	3.00	3.00	3.00	3.00	3.00
β_W^N	-0.10	-0.10	-0.10	-0.10	-0.10
β_H^N	-0.50	-0.50	-0.50	**-1.50**	-0.50
β_A^N	-1.50	-1.50	-1.50	-1.50	-1.50
β_0^A	-1.50	-1.50	-1.50	-1.50	-1.50
β_W^A	-0.50	-0.50	-0.50	-0.50	-0.50
β_A^A	2.50	2.50	2.50	2.50	2.50
β_0^D	-5.50	-5.50	-5.50	-5.50	-5.50
β_W^D	1.00	1.00	1.00	1.00	1.00
$\beta_{\bar{A}}^D$	0.50	0.50	0.50	0.50	0.50
$\beta_{\bar{Y}}^D$	0.50	**2.00**	0.50	0.50	0.50
β_0^Y	-7.00	-7.00	-7.00	-7.00	**-6.00**
β_W^Y	2.00	2.00	2.00	2.00	2.00
β_A^Y	0.25	0.25	0.25	0.25	0.25
$\beta_{\bar{A}}^Y$	0.20	0.20	0.20	0.20	0.20
β_H^Y	0.70	0.70	0.70	**1.70**	0.70
β_S^Y	0.30	0.30	0.30	0.30	0.30

Interventions, potential outcomes, target parameters, and estimation

The substantive question of interest was the causal effect of occupational exposure to MWF on cancer incidence risk. Since occupational MWF exposure occurs only when individuals are at work, we defined dynamic exposure regimes that depend on employment status. Under rule a_0, set $D(t) = 0$, and set $A(t) = 0$ while $N(t) = 1$. Under rule a_1, set $D(t) = 0$, and set $A(t) = 1$ while $N(t) = 1$. Under both rules, we prevented censoring by death as if it were intervenable. The causal effect was defined by contrasting the survival functions $S_{a_1}(t) = 1 - \mathbb{E}\left[Y_{a_1}(t)\right]$ under rule a_1 to $S_{a_0}(t) = 1 - \mathbb{E}\left[Y_{a_0}(t)\right]$ that under rule a_0. Note that this causal estimand was defined over *a priori*

counterfactuals not observable in the real world (**Frangakis_2002?**). This approach is standard in epidemiologic studies.

The survival function expresses the probability that a person following rule a is cancer-free at the end of time point t. The expected time until cancer under rule a is $\mu_a = \sum_0^K S_a(t)\,dt$. The parameter used in the estimation of bias was the summary measure $\psi = \mu_{a_1} - \mu_{a_0}$, the difference in expected time until event under two different interventions over 20 years of follow-up under five different data generating scenarios. Bias was evaluated by comparing estimates of ψ to its true value in 250 simulations per scenario (the original analysis performed 500). The true value was calculated by simulating the full data for 500 000 individuals (the original analysis used one million) with rules a_0 and a_1 applied deterministically. Estimates of ψ were obtained by estimating the survival curves $S_a(t)$ using two estimators: the inverse probability weighted Kaplan-Meier estimator (WKM) and the Aalen-filtered WKM (AWKM). These survival estimators are detailed in the following section.

Kaplan-Meier estimator and extensions

To estimate survival, we applied extensions of the widely-known Kaplan-Meier (KM) estimator for survival (Kaplan and Meier 1958). First, we review the estimator of Xie and Liu (2005), an extension of the KM estimator where units are weighted by the inverse probability of treatment. The standard KM estimator requires counting up the number of cases $c_a^0(t)$ that occurred in interval $(t-1, t]$ and the number of units at risk $r_a^0(t)$ in that interval at all event times t. Assuming cancer status was assessed at the end of regular intervals $t = 1, \ldots, K$, we have:

$$c_a^0(t) = \sum_i^n \mathbb{1}\left[Y_i(t) = 1\right] \times \mathbb{1}\left[Y_i(t-1) = 0\right] \times \mathbb{1}\left[\bar{A}_i(t) = \bar{a}(t)\right]$$
$$r_a^0(t) = \sum_i^n \mathbb{1}\left[Y_i(t-1) = 0\right] \times \mathbb{1}\left[\bar{A}_i(t) = \bar{a}(t)\right].$$

The standard survival estimator is

$$\hat{S}_a^0(t) = \begin{cases} 1 & \text{if } t < t_1 \\ \prod_{j \le t} \left(1 - \frac{c_a^0(j)}{r_a^0(j)}\right) & \text{if } t \ge t_1 \end{cases}$$

where t_1 is the first event time.

In observational studies, survival contrasts estimated using the standard KM estimator are biased for the true causal survival contrast. However, if conditional ignorability and positivity are attained, the inverse probability weighted KM (WKM) estimator of Xie and Liu (2005) yields unbiased estimates of the true causal survival curve. The WKM estimator augments the standard KM estimator by

weighting units at time t by $w_{i,a}(t)$ the inverse probability of treatment:

$$c_a^w(t) = \sum_i^n w_{i,a}(t) \times \mathbb{1}\left[Y_i(t) = 1\right] \times \mathbb{1}\left[Y_i(t-1) = 0\right] \times \mathbb{1}\left[\bar{A}_i(t) = \bar{a}(t)\right]$$
$$r_a^w(t) = \sum_i^n w_{i,a}(t) \times \mathbb{1}\left[Y_i(t-1) = 0\right] \times \mathbb{1}\left[\bar{A}_i(t) = \bar{a}(t)\right]$$

The WKM survival estimator for rule a is

$$\widehat{S}_a^w(t) = \begin{cases} 1 & \text{if } t < t_1 \\ \prod_{j \le t} \left(1 - \frac{c_a^w(j)}{R_a^w(j)}\right) & \text{if } t \ge t_1 \end{cases}$$

where t_1 is the first event time.

Finally, to account for (uninformative) left filtering, we applied the Aalen filter, which considers only the units at time t for which the outcome is observed:

$$c_a(t) = \sum_i^n w_{i,a}(t) \times \mathbb{1}\left[Y_i(t) = 1\right] \times \mathbb{1}\left[Y_i(t-1) = 0\right] \times \mathbb{1}\left[\bar{A}_i(t) = \bar{a}(t)\right] \times \mathbb{1}\left[t \ge R_i\right]$$
$$r_a(t) = \sum_i^n w_{i,a}(t) \times \mathbb{1}\left[Y_i(t-1) = 0\right] \times \mathbb{1}\left[\bar{A}_i(t) = \bar{a}(t)\right] \times \mathbb{1}\left[t \ge R_i\right]$$

The Aalen-filtered WKM (AWKM) estimator for rule a is

$$\widehat{S}_a(t) = \begin{cases} 1 & \text{if } t < t_1 \\ \prod_{j \le t} \left(1 - \frac{c_a(j)}{r_a(j)}\right) & \text{if } t \ge t_1 \end{cases}$$

where t_1 is the first event time.

In the full data, the WKM and AWKM estimators are equivalent, and identification is achieved under positivity and sequential ignorability assumptions:

$$Y^*_{a,\bar{d}=0}(t') \perp\!\!\!\perp A(t) \mid W,\ \bar{A}(t-1) = \bar{a}(t-1),\ D(t-1) = 0,\ N(t) = 1$$
$$Y^*_{a,\bar{d}=0}(t') \perp\!\!\!\perp D(t) \mid W,\ D(t-1) = 0,\ Y^*(t-1) = 0,\ \bar{A}(t-1) = \bar{a}(t-1)$$

for all times $t' \ge t$, and

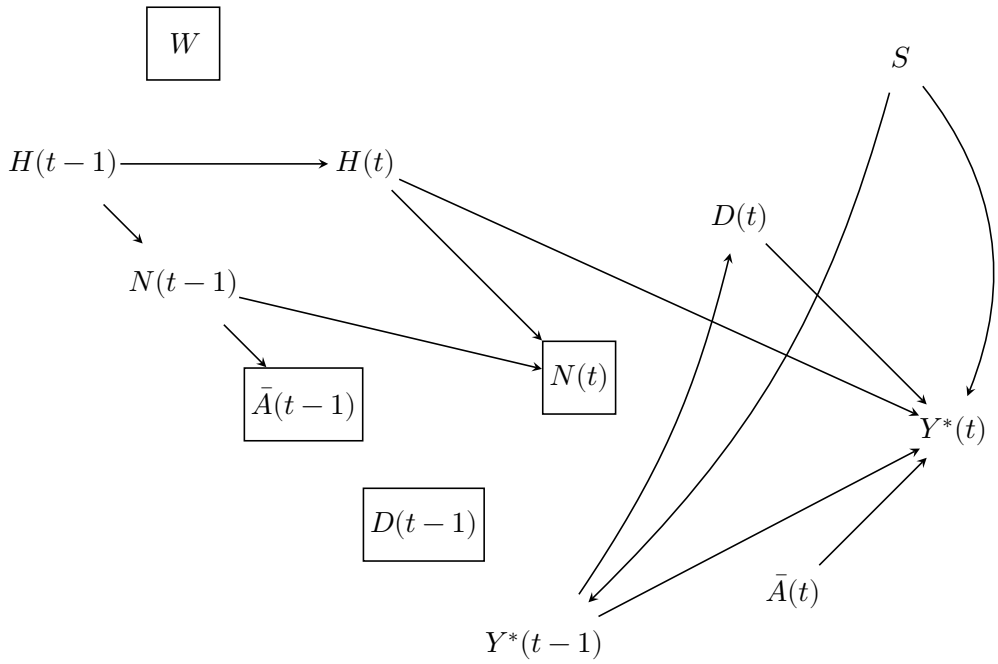
$$0 < \mathbb{P}\left(A(t) = 1 \mid W,\ \bar{A}(t-1) = \bar{a}(t-1),\ D(t-1) = 0,\ N(t) = 1\right) < 1$$

$$0 < \mathbb{P}\left(D(t) = 0 \mid W,\ D(t-1) = 0,\ Y^*(t-1) = 0,\ \bar{A}(t-1) = \bar{a}(t-1)\right) < 1.$$

Graphical representations of the first and second components of the ignorability assumption are presented in Figures 2 and 3 where conditioning on boxed variables are represented by the removal of edges pointing away from those variables. The resulting graphs show the fulfillment of Pearl's

backdoor criterion for the estimation of the causal effects of $\bar{A}(t)$ on $Y^*(t)$ and $D(t)$ on $Y^*(t)$, respectively. Thus, the causal effect of the joint intervention on $(\bar{A}(t), D(t))$ at each time t is identified. Causal identification is not attainable when true cancer status $Y^*(t)$ is not known.

Figure 2: Directed acyclic graph representing the causal relationships encoded in the non-parametric structural equation model at time t after conditioning on $\{W,\ \bar{A}(t-1),\ D(t-1),\ N(t)\}$.



Estimation of weights

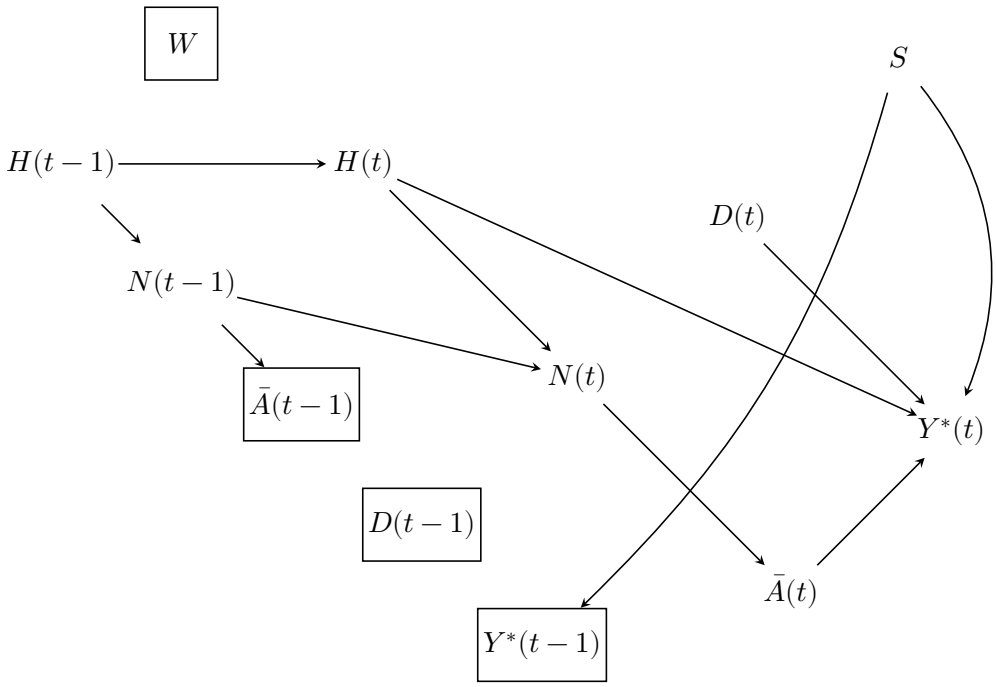
To estimate the weights for the WKM and AWKM estimators, we fit two logistic regressions at each time point $t = 1, \ldots 20$:

$$\text{logit}\left(\mathbb{P}\left(A(t) = 1 \mid W,\ \bar{A}(t-1),\ D(t-1) = 0,\ N(t) = 1\right)\right) = \alpha_0 + W\alpha_1 + A(t-1)\alpha_2$$
$$\text{logit}\left(\mathbb{P}\left(D(t) = 1 \mid W,\ D(t-1) = 0,\ Y(t-1) = 0,\ \bar{A}(t-1)\right)\right) = \beta_0 + W\beta_1 + \bar{A}(t-1)\beta_2$$

The first was fit on data for those alive and at work at time t. The second was among those alive and (observed to be) cancer-free. For each unit at time t, the weight was calculated by taking the inverse of the cumulative probability of following the exposure rule and remaining uncensored:

$$\widehat{w}_a(t) = \left[\prod_{j=1}^{t} \begin{array}{r} \hat{\mathbb{P}}\left\{A(j) = a(j) \mid W,\ \bar{A}(j-1) = \bar{a}(j-1),\ D(j-1) = 0,\ N(j) = 1\right\} \times \\ \hat{\mathbb{P}}\left\{D(j) = 0 \mid W,\ D(j-1) = 0,\ Y(j-1) = 0,\ \bar{A}(j) = \bar{a}(j)\right\} \end{array}\right]^{-1}.$$

Figure 3: Directed acyclic graph representing the causal relationships encoded in the non-parametric structural equation model at time t after conditioning on $\{W,\ \bar{A}(t-1),\ D(t-1),\ Y^*(t-1)\}$.



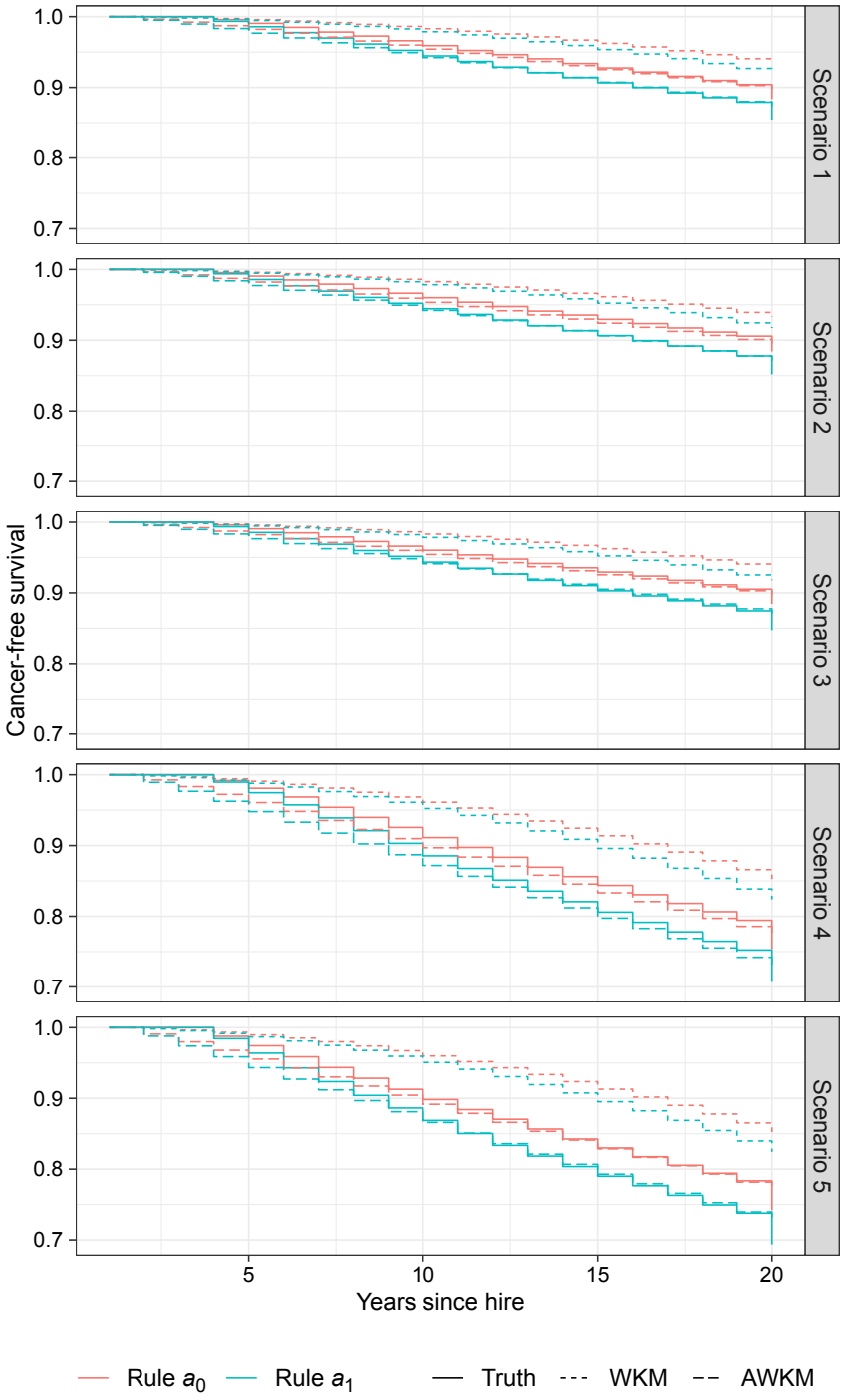
Results

Figure 4 presents the true survival curves as well as the WKM and AWKM survival curves averaged over 250 replications for each intervention rule and scenario. Qualitatively, the WKM estimator consistently over-estimated survival whereas the the AWKM survival curve was much closer to the truth. The bias of the AWKM survival estimator appeared to be larger in earlier follow-up and smaller for later follow-up time points. The bias of the WKM estimator appeared largest in Scenario 5. The bias of the AWKM estimator was similar across the five scenarios

Table 3 presents true and estimated average cancer-free survival times under each intervention rule and scenario. Table 4 presents differences in survival time contrasting rule a_1 to rule a_0. Table 5 presents estimates of the bias of the WKM and AWKM estimators for ψ, the difference in average cancer-free survival time over 20 years of follow-up. These numeric results were consistent with the qualitative interpretations of Figure 4. The WKM estimator over-estimated the difference in cancer-free survival time, resulting in bias toward the null, whereas the AWKM estimator under-estimates the cancer-free survival, resulting in bias away from the null. In every scenario, the bias of the WKM-derived contrast was two to several times larger in magnitude than that of the AWKM-derived contrast.

The qualitative results here were consistent with those of Izano (2017). However, true and estimated survival in the present analysis was larger than those found previously. Furthermore, the true and estimator average mean differences in survival were smaller in magnitude in the present case. The

Figure 4: Cancer-free survival over time since hire in five simulation scenarios. The true (discrete) survival curve is represented by the solid lines. The average inverse probability weighted Kaplan-Meier (WKM) survival curve is represented by the dashed-line with short dashes. The average Aalen-filtered inverse probability weighted Kaplan-Meier (AWKM) survival curve is represented by the dashed-line with long dashes. Estimated survival curves were averaged over 250 replicates. Salmon color indicates survival and survival estimates under rule a_0 when workers are always unexposed. Cyan color indicates those under rule a_1 when workers are always exposed while employed.



magnitudes of the bias estimates were also smaller.

Table 3: True cancer-free survival time μ_a over 20-year follow-up and estimator averages over 250 replicates.

Rule	Estimator	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
a_0	Truth	19.08	19.10	19.10	18.02	17.83
	WKM	19.52	19.51	19.52	18.91	18.90
	AWKM	19.01	19.00	19.01	17.80	17.71
a_1	Truth	18.80	18.79	18.76	17.54	17.29
	WKM	19.41	19.39	19.39	18.68	18.67
	AWKM	18.76	18.76	18.74	17.30	17.22

Table 4: Difference in average cancer-free survival time over 20-year follow-up comparing rule a_1 always exposed to rule a_0 never exposed at work: true value ψ and estimator averages over 250 replicates.

Estimator	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Truth	-0.28	-0.31	-0.34	-0.48	-0.54
WKM	-0.11	-0.12	-0.13	-0.23	-0.23
AWKM	-0.25	-0.24	-0.27	-0.50	-0.50

Table 5: Bias estimates of estimators for ψ, the difference in average cancer-free survival time over 20 years of follow-up.

Estimator	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
WKM	0.17	0.19	0.21	0.25	0.31
AWKM	0.03	0.07	0.07	-0.02	0.04

Application to the UAW-GM Cohort

In the simulation study, we showed that under several scenarios compatible with our hypothetical causal structure, the AWKM survival estimator had a smaller bias than the WKM estimator. The bias was smaller when the cumulative incidence of the outcome was low and at later follow-up time points. Next, we estimated cancer-free survival in a real-world context. Using data from two plants participating in the UAW-GM Cohort study, we followed 26 182 individuals starting from hire to 65 years after hire for incidence of digestive system cancers (colon, rectal, esophageal, or stomach). As

in the simulation, the UAW-GM data were longitudinal data with baseline covariates, time-varying covariates, and a survival outcome.

The exposures of interest were MWF of three types: straight, soluble, and synthetic (Byers 2006; F. Mirer 2003; F. E. Mirer 2010). Straight MWFs are hydrocarbon-based fluids that became widely-used by the 1920s. They continue to occupy a large portion of the MWF market due to their simple formulation. In straight MWFs, hydrocarbons of different lengths are mixed together with other additives to attain different properties. Straight MWFs contain polycyclic aromatic hydrocarbons, long known to be carcinogenic (*IARC Monographs on the Evaluation of Carcinogenic Risk of the Chemical to Man: Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds* 1973). Soluble oils are water-based oil emulsions first introduced in response to rising oil prices. They now make up the largest market share of MWFs (**Childers_2006?**). Soluble MWFs are vulnerable to microbial contamination, so they contain biocides and chlorinated chemicals. Soluble MWFs have carcinogenic potential from both their oil components and their additives, but their high lubricity makes them the most popular fluid type. Synthetic MWFs have the best toxicological profile, have no oil, and have a higher resistance to microbial growth. They were introduced into the MWF market in the second half of the 20th C., but failed to out-perform soluble MWFs in industrial metalworking applications. Synthetic MWFs contain biocides, corrosion inhibitors, and chlorinated compounds, some classified as carcinogenic by the IARC (**IARC_1987?**).

The outcome of interest was digestive system cancer incidence. There is little past research linking digestive system cancers to MWF exposures, but there is some evidence suggesting that straight MWFs cause digestive system cancers (Izano et al. 2019). Cancer incidence was obtained by linkage to Surveillance, Epidemiology, and End Results (SEER), which recorded cancer incidence cases starting on January 1, 1973. The cohort is comprised of individuals hired between 1938 and 1975. Cancer-free survival to the start of the registry was a left-filtering process possibly in the presence of the HWSE, as was the case in simulations. Over the 65 year follow-up period, vital status was obtained through the Social Security Administration, the National Death Index, as well as records provided by the UAW. The exposure rules of interest in the applied analysis were different than those in the simulation study: a_0 having cumulative exposure of more than 0.05 mg/m^3 years and a_1 having no cumulative exposure. Weights were truncated at 1000. Exposure was binary and defined to be whether there was exposure above the median level of exposure to straight, soluble, and synthetic MWFs. Counterfactual survival under rules a_0 and a_1 were estimated using the WKM and AWKM estimators. Treatment and censoring mechanisms were estimated using logistic regression conditional on baseline and time-varying confounders. These logistic regressions were estimated with stratification by every two years of follow-up. Baseline confounders included race, sex, plant, and year of hire. Time-varying confounders included age, cumulative time off, employment status, and exposure to the metalworking fluids exposure from past years (3 years in the case of exposure and 6 years in the case of death due to censoring). Summary statistics for the full study population and those who experienced digestive system cancer are presented in Table 6.

Table 6: Study population characteristics.

	Full cohort		Digestive cancer cases	
n (person-years)	26 182	(695 475)	213	(6000)
Race (%)				
Black	6 017	(23.0)	66	(31.0)
White	20 165	(77.0)	147	(69.0)
Sex (%)				
Female	3 328	(12.7)	15	(7.0)
Male	22 854	(87.3)	198	(93.0)
Plant (%)				
Plant 1	9 092	(34.7)	103	(48.4)
Plant 2	17 090	(65.3)	110	(51.6)
Ever exposed to MWF (%)	13 240	(50.6)	95	(44.6)
Year of hire (mean (SD))	1963	(12.26)	1960	(9.55)
Age at end of follow-up (mean (SD))	55.09	(12.02)	63.58	(9.40)
Cumulative years off (mean (SD))	0.06	(0.15)	0.12	(0.24)

Assumptions

Since we are working with observational data, the evaluation of the no-interference, causal consistency, ignorability, and overlap (positivity) assumptions are critical for causal inference. The stability of our estimation depends on positivity, which we assessed qualitatively by examining the distribution of the weights. The no-interference assumption may be problematized by the fact that there were a finite number of job types in the factory setting. If one worker operates a particular metalworking machine, then the the other workers would not be able to operate that machine at that time. Instead, they may be assigned to assembly tasks, which have lower MWF exposure opportunities. That said, since these factories were quite large, there may be approximate independence. The consistency assumption is also problematic. The MWFs of interest are complex chemical mixtures whose composition underwent changes by design and by nature of their use. Over the last several decades, the formulation of MWFs has changed significantly in reaction to performance needs and toxicity concerns (F. Mirer 2003; Byers 2006). The composition of MWFs also undergoes unintentional changes over the course of their use: MWFs are often applied in contexts where contamination by other substances and microbes is possible and chemical changes due to heat and pressure are likely. In fact, concern over the carcinogenicity of MWFs includes concerns over chemical species formed in MWF mixtures that were not originally added (Hidajat et al. 2020). Concerns regarding the consistency assumption may be abrogated in part by adequate adjustment for secular and factory-level characteristics.

Another key assumption meriting discussion is that of sequential ignorability. In order to achieve identification, even in the absence of left filtering, we need to have conditionally ignorable future

exposure status and ignorable future censoring status at each time point given past data. In occupational cohorts, employment status and health history are strong predictors of future death (Häfner 1987; Halliday 2014; Laliotis and Stavropoulou 2018). Logically, major causes of death first act through employment status before they precipitate death. This dynamic is actually a key component in the setup for HWSE. We are therefore relatively confident that conditional ignorability of censoring due to death is attained given covariate, exposure, and cancer history. Our confidence in the conditional ignorability of exposure given history was not as strong. In particular, workers may be assigned to certain tasks based on their specific skills and knowledge, which may be associated with structural privileges that confer a lower risk of deleterious health outcomes. The potential magnitude of this uncontrolled confounding may be bounded, however. Education level among workers in the cohort was approximately homogeneous, and all cohort members were members of the UAW union, which had uniform procedures in place for equitable access to training, wages, and career advancement (Harbison 1950; Barnard 2005). The presence of UAW policies support the assertion that given time since hire, job types (and therefore exposures) were randomly allocated.

Results

Estimated digestive system cancer-free curves under rules a_0 and a_1 applied to the three MWF types are presented in Figure 5. Surprisingly, the survival curves were more or less overlapping under the two exposure rules. Numeric values for the cancer-free survival and difference in cancer-free survival are presented in Tables 7 and 8. The numeric summaries were consistent with the qualitative interpretation of the estimated survival curves; expected survival time does not differ substantially comparing rules a_0 and a_1 applied to all MWF types. Nonetheless, reducing exposure to straight and soluble MWFs yielded a longer estimated survival time, though the difference was less than a month in time.

Table 7: Estimated cancer-free survival time over 65-year follow-up.

Rule	Estimator	Straight	Soluble	Synthetic	Any
a_0	WKM	55.9808	56.0093	56.2051	55.8072
a_0	AWKM	55.8864	55.8952	56.1300	55.6712
a_1	WKM	56.2258	56.2760	56.1323	
a_1	AWKM	56.0953	56.1824	56.0066	

Figure 5: Cancer-free survival over time since hire under interventions for exposure to straight, soluble, and synthetic metalworking fluids. The estimated inverse probability weighted Kaplan-Meier (WKM) survival curve is represented by the solid. The estimated Aalen-filtered inverse probability weighted Kaplan-Meier (AWKM) survival curve is represented by the dashed-line. Salmon color indicates survival and survival estimates under rule a_0; cyan color indicates those under rule a_1.

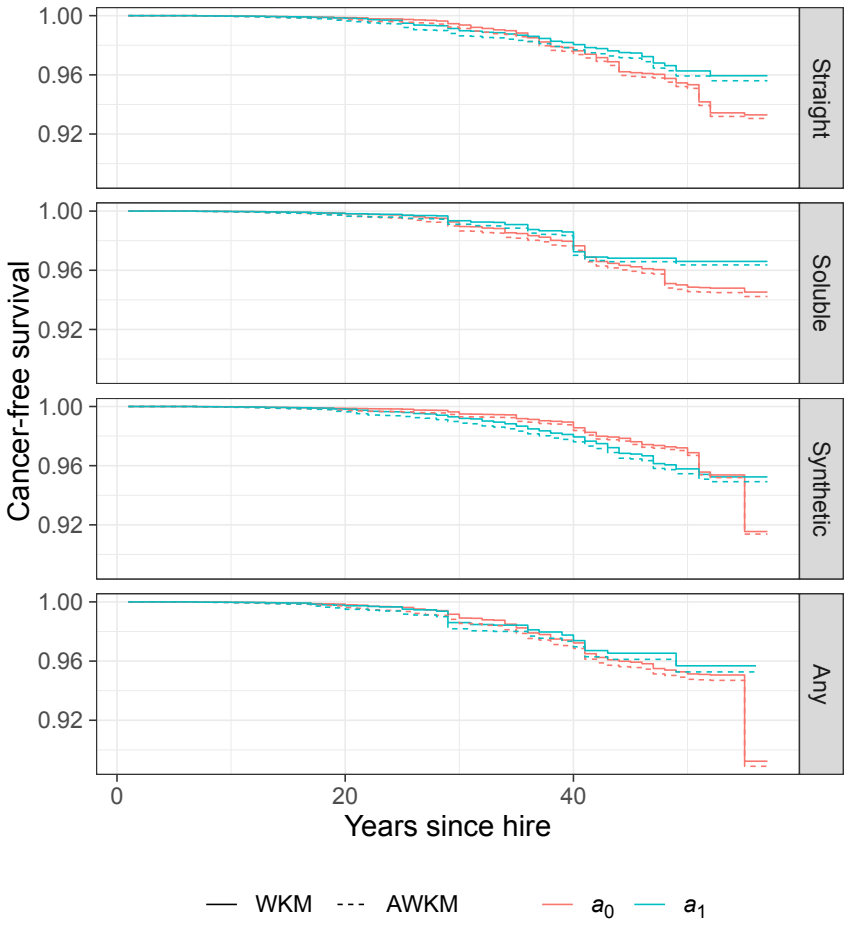


Table 8: Estimated difference in average cancer-free survival time over 65-year follow-up comparing rule a_1 exposed above the median level of exposure with probability 1% to a_0 never exposed.

Estimator	Straight	Soluble	Synthetic	Any
WKM	0.2449	0.2667	-0.0727	
AWKM	0.2089	0.2872	-0.1233	

Figure 6 presents the median cumulative weight applied years since hire with ribbons showing the minimum and maximum weight. The overlap in the distribution of weights under the two rules for synthetic MWF exposure suggests that the model for the treatment and censoring mechanisms were inadequate in distinguishing the units of analysis by their probability of following a certain exposure

rule or of remaining alive. The distribution of the weights was very skewed. Without truncation, they would have been in the order of magnitude of 10^{20} or even higher. Distributional summaries of the cumulative weights without truncation are presented in Table 9. The presence of extremely large weights suggests that our observed data were inadequate for answering the causal questions of interest due to practical violations in overlap (Petersen et al. 2012).

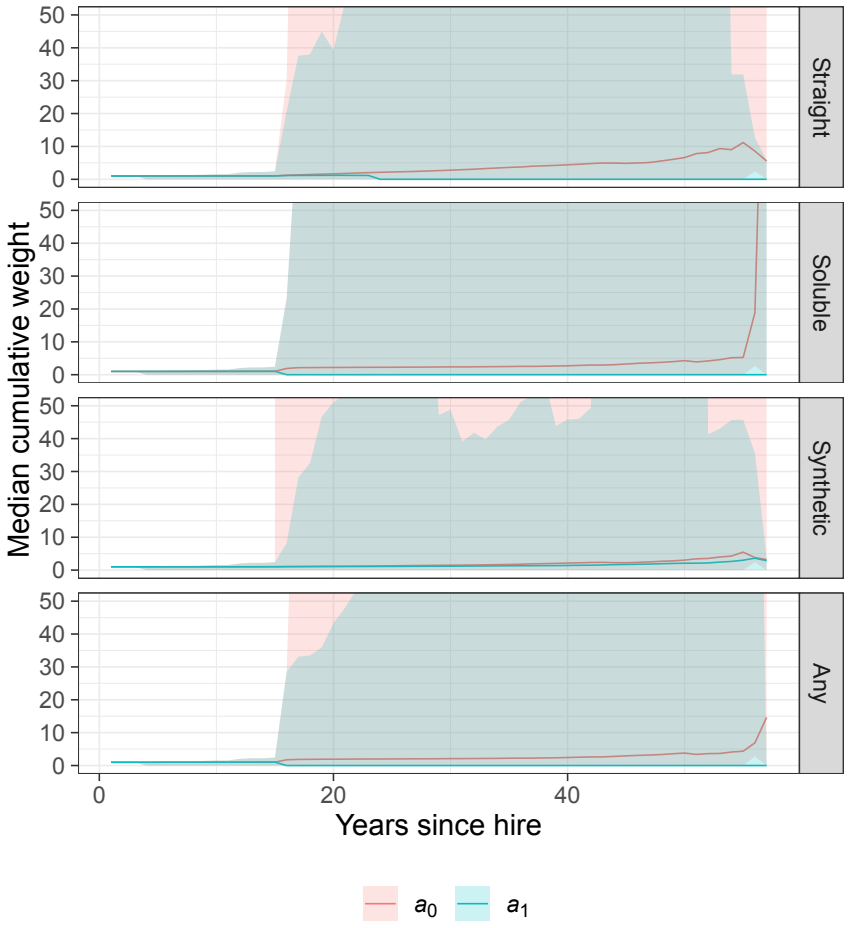
Table 9: Summary statistics for the cumulative weights used for the WKM estimator at $t = 1$ and $t = 65$ years since hire for each metalworking fluid type and exposure rule.

MWF type	Rule	t	Minimum	Q1	Median	Mean	Q3	Maximum
Straight	a_0	1	1	1	1	1	1	1
	a_1	1	1	1	1	1	1	1
Soluble	a_0	1	1	1	1	1	1	1
	a_1	1	1	1	1	1	1	1
Synthetic	a_0	1	1	1	1	1	1	1
	a_1	1	1	1	1	1	1	1
Any	a_0	1	1	1	1	1	1	1
	a_1	1	1	1	1	1	1	1
Straight	a_0	57	0	4.6	5.6	93	2×10^2	3.9×10^2
	a_1	57	0	0	0	2.4	5.2	5.8
Soluble	a_0	57	0	3.9	1.5×10^2	1.7×10^2	3.1×10^2	3.8×10^2
	a_1	57	0	0	0	41	0	3.7×10^2
Synthetic	a_0	57	0	2.6	3.2	97	3.4	8.5×10^2
	a_1	57	0	2.5	2.9	2.4	3.3	3.6
Any	a_0	57	0	3.6	15	1.4×10^2	3×10^2	4.1×10^2
	a_1	57	0	0	0	0	0	0

Discussion

In the simulation study, we showed that the inverse probability of exposure/censoring weighted Kaplan-Meier estimator resulted in lower bias in the estimation of average survival time than did the weighted Kaplan-Meier estimator without the Aalen filter. While the Aalen filter corrects for non-informative left-filtering in the estimation of the discrete hazard by excluding person-years not observed under the cancer registry. These person-years contribute to estimation during the estimation of exposure and censoring weights. Speculatively, the combination of the two extensions to the Kaplan-Meier estimator may result in the partial control of informative left censoring without adjusting for informative left truncation.

Figure 6: Median of the cumulative weights for each year since hire with ribbons delimiting the range of values calculated. Salmon color corresponds to the weights used in the estimation of the survival curve under rule a_0; cyan corresponds to those for rule a_1.



The simulation permitted the evaluation of the estimators in clean, well-behaved scenarios, but the same luxury was not possible when using observed data. Several assumptions used in the simulation study were incompatible with what is known about cancer etiology. Firstly, cumulative incidence in the simulations was close to 15% (or higher) over a 20-year follow-up. This is an extraordinarily high risk of cancer, especially because most workers in the automotive manufacturing industry start their careers at a fairly young age. Digestive system cancers are among the most common forms of cancer in the Unite states, but over 35 years of follow-up, we were only able to observe a cumulative incidence of less than 1%. The simulation results suggested that the bias of the WKM and AWKM estimators is higher when cumulative incidence is higher, but when cumulative incidence is low, there is a different problem: the reliance on few observations to index the risk sets.

There are multiple opportunities for future work. The simulation study can be expanded to investigate subtler exposure-outcome effects. In the present work, the discrete hazard ratio of cancer incidence given exposure was rather high at about 1.28. Furthermore, we assumed the luxury of knowing the true treatment and censoring mechanisms' model forms, but this is quite unrealistic. In future simulations, the effect of model mis-specification should be investigated. Alternatively, we could estimate survival using a doubly robust method. There can also be several improvements made from the subject-matter expertise point-of-view. The exposure rules investigated in the applied analysis were chosen naively. Other dynamic or stochastic exposure interventions may have been of greater interest to occupational health policy, and they may have led to improved numeric performance as well. The present analysis did not lag exposure status, which is standard practice in cancer epidemiology – the biological responses to carcinogens do not occur until several years or decades after exposure. The true causal effects of MWF exposure may not yet be observable after 35 years of follow-up. As follow-up in this cohort study continues, we will have the opportunity to investigate the carcinogenic effects of MWF exposure further.

References

Andersen, P. K., Ø. Borgan, R. D. Gill, and N. Keiding. 1993. *Statistical Models Based on Counting Processes*. Springer Series in Statistics. Springer, New York, NY. https://books.google.com/books?id=kBnvAAAAMAAJ.

Arrighi, H. Michael, and Irva Hertz-Picciotto. 1994. "The Evolving Concept of the Healthy Worker Survivor Effect." *Epidemiology* 5 (2): 189–96. http://www.jstor.org/stable/3702361.

Barnard, John. 2005. *American Vanguard: The United Auto Workers During the Reuther Years, 1935-1970*. Wayne State University Press.

Byers, Jerry P. 2006. *Metalworking Fluids*. CRC Press.

Eisen, Ellen A, Judith Bardin, Rebecca Gore, Susan R Woskie, Marilyn F Hallock, and Richard R Monson. 2001. "Exposure-Response Models Based on Extended Follow-up of a Cohort Mortality Study in the Automobile Industry." *Scandinavian Journal of Work, Environment & Health* 27 (4): 240–49.

Eisen, Ellen A, Paige E Tolbert, Richard R Monson, and Thomas J Smith. 1992. "Mortality Studies of Machining Fluid Exposure in the Automobile Industry I: A Standardized Mortality Ratio Analysis." *American Journal of Industrial Medicine* 22 (6): 809–24.

Garcia, Erika, Sally Picciotto, Sadie Costello, Patrick T Bradshaw, and Ellen A Eisen. 2017. "Assessment of the Healthy Worker Survivor Effect in Cancer Studies of the United Autoworkers-General Motors Cohort." *Occupational and Environmental Medicine* 74 (4): 294–300.

Garcia, Erika, Sally Picciotto, Andreas M Neophytou, Patrick T Bradshaw, John R Balmes, and Ellen A Eisen. 2018. "Lung Cancer Mortality and Exposure to Synthetic Metalworking Fluid and Biocides: Controlling for the Healthy Worker Survivor Effect." *Occupational and Environmental Medicine* 75 (10): 730–35.

Halliday, Timothy J. 2014. "Unemployment and Mortality: Evidence from the PSID." *Soc Sci Med* 113 (July): 15–22. https://doi.org/10.1016/j.socscimed.2014.04.038.

Harbison, Frederick H. 1950. "The General Motors-United Auto Workers Agreement of 1950." *Journal of Political Economy* 58 (5): 397–411.

Häfner, H. 1987. "Unemployment and Health." *Dtsch Med Wochenschr* 112 (37): 1428–32. https://doi.org/10.1055/s-2008-1068265.

Hidajat, Mira, Damien Martin McElvenny, Peter Ritchie, Andrew Darnton, William Mueller, Raymond M Agius, John W Cherrie, and Frank de Vocht. 2020. "Lifetime Cumulative Exposure to Rubber Dust, Fumes and n-Nitrosamines and Non-Cancer Mortality: A 49-Year Follow-up of UK Rubber Factory Workers." *Occup Environ Med* 77 (5): 316–23. https://doi.org/10.1136/oemed-2019-106269.

IARC Monographs on the Evaluation of Carcinogenic Risk of the Chemical to Man: Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds. 1973. Vol. 3. World Health Organization International Agency for Research on Cancer.

Izano, Monika A. 2017. "Estimating Causal Effects of Occupational Exposures." PhD thesis, University of California, Berkeley; University of California, Berkeley.

Izano, Monika A, Oleg A Sofrygin, Sally Picciotto, Patrick T Bradshaw, and Ellen A Eisen. 2019. "Metalworking Fluids and Colon Cancer Risk: Longitudinal Targeted Minimum Loss-Based Estimation." *Environmental Epidemiology* 3 (1): e035.

Kaplan, Edward L, and Paul Meier. 1958. "Nonparametric Estimation from Incomplete Observations." *Journal of the American Statistical Association* 53 (282): 457–81.

Laliotis, Ioannis, and Charitini Stavropoulou. 2018. "Crises and Mortality: Does the Level of Unemployment Matter?" *Soc Sci Med* 214 (October): 99–109. https://doi.org/10.1016/j.socscimed.2018.08.016.

Mirer, Franklin. 2003. "Updated Epidemiology of Workers Exposed to Metalworking Fluids Provides Sufficient Evidence for Carcinogenicity." *Applied Occupational and Environmental Hygiene* 18 (11): 902–12.

Mirer, Franklin E. 2010. "New Evidence on the Health Hazards and Control of Metalworking Fluids Since Completion of the OSHA Advisory Committee Report." *American Journal of Industrial Medicine* 53 (8): 792–801.

Naimi, Ashley I, Stephen R Cole, Michael G Hudgens, M Alan Brookhart, and David B Richardson. 2013. "Assessing the Component Associations of the Healthy Worker Survivor Bias: Occupational Asbestos Exposure and Lung Cancer Mortality." *Annals of Epidemiology* 23 (6): 334–41.

Petersen, Maya L, Kristin E Porter, Susan Gruber, Yue Wang, and Mark J van der Laan. 2012. "Diagnosing and Responding to Violations in the Positivity Assumption." *Statistical Methods in Medical Research* 21 (1): 31–54. https://doi.org/10.1177/0962280210386207.

Sofrygin, Oleg, Mark J. van der Laan, and Romain Neugebauer. 2021. *Stremr: Streamlined Estimation for Static, Dynamic and Stochastic Treatment Regimes in Longitudinal Data*. https://github.com/osofr/stremr.

Xie, Jun, and Chaofeng Liu. 2005. "Adjusted Kaplan–Meier Estimator and Log-Rank Test with Inverse Probability of Treatment Weighting for Survival Data." *Statistics in Medicine* 24 (20): 3089–3110.