

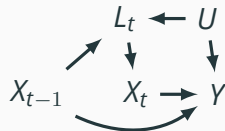
# Concepts and Methods for Healthy Worker Survivor Bias

---

Alex Keil

December 2024

Earl Stadtman Investigator, National Cancer Institute



# What to expect

- Didactic
- Fast
- Replicable

## History: healthy worker survivor effect

---

Mortality has long been observed to be lower among populations of active workers

The weaker individuals, and those whose health is failing them, are thus being constantly drafted out of each industrial occupation, and especially out of those which require much vigour; and the consequence is that the death-rates in these latter occupations are unfairly lowered, as compared with the death-rates in occupations of an easier character, and still more as compared with the death-rates among those persons who are returned as having no occupation at all. A very considerable proportion of those who

---

Ogle (1885) *Supplement to the Forty-Fifth Annual Report of the Registrar-General of Births, Deaths, and Marriages in England*

Mortality has long been observed to be lower among populations of active workers

The weaker individuals, and those whose health is failing them, are thus being constantly drafted out of each industrial occupation, and especially out of those which require much vigour; and the consequence is that the death-rates in these latter occupations are unfairly lowered, as compared

activity in those that follow them. Such industries are in fact carried on by a body of comparatively picked men; stronger in the beginning, and maintained at a high level by the continual drafting out of those whose strength falls below the mark.

---

Ogle (1885) *Supplement to the Forty-Fifth Annual Report of the Registrar-General of Births, Deaths, and Marriages in England*

*Brit. J. prev. soc. Med.* (1976), 30, 225-230

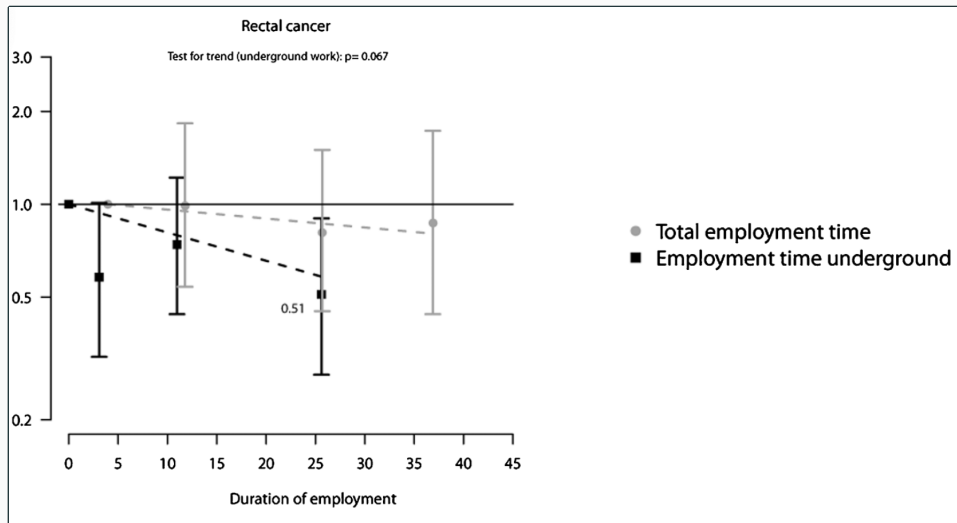
# Low mortality rates in industrial cohort studies due to selection for work and survival in the industry

A. J. FOX AND P. F. COLLIER

*Office of Population Censuses and Surveys and the Employment Medical Advisory Service,  
Health and Safety Executive, London*

**industry. The survivor population effect for men who were alive 15 years after entry was measured by comparing the mortality patterns of those who had left the industry before the 15 years were completed with those for men still in the industry 15 years after entering. The SMR for past workers including retired workers was 108·4 compared with 74·0 for those employees who were still in the industry.**

# Longer employment predicts lower risk in 13,623 iron miners



Björ et al. (2013) *Am J Ind Med*



## Arsenic and cardiovascular disease among 8,014 copper smelter workers

*There were **no significant trends in the relative risks** with the various measures of cumulative arsenic exposure. However, relative risks for 5–14, 15–24, and 25 years and more after cessation of employment were 0.80, 0.66, and 0.41, respectively, compared with 1–4 years after cessation of employment. These results do not suggest a relation between cardiovascular disease and cumulative arsenic exposure, but do suggest that **cardiovascular disease “caused the retirement.”***

*Lubin and Fraumeni as suggest[ed] that cardiovascular disease “caused the retirement.” This is an **excellent description of how the healthy survivor effect operates...***

# Arsenic and cardiovascular disease in 8,014 copper smelter workers, reanalysis

**Table 2.** Cause-specific and all-cause mortality per 1,000 and excess deaths per 1,000 at age 60 and age 70.

Age (years)/ Cause of mortality	Deaths per 1,000 <sup>a</sup> (95% CI)		Excess deaths per 1,000 <sup>b</sup> (95% CI)		
	No exposure	Natural course	If at work, light exposure	If at work, medium exposure	If at work, heavy exposure
<b>Age 60</b>					
All causes	224 (211, 239)	14 (5.0, 22.3)	12 (4.1, 20)	27 (14, 40)	60 (33, 88)
Respiratory cancer	17 (13, 20.2)	1.7 (-0.4, 3.9)	1.6 (-0.5, 3.7)	4.0 (0.6, 7.3)	10 (2.6, 20)
Heart disease	65 (58, 73)	4.8 (0.2, 9.1)	4.1 (-0.4, 8.4)	8.7 (1.4, 16)	18 (2.8, 34)
Other causes	143 (132, 156)	7.3 (-0.1, 15)	6.5 (-0.3, 14)	14 (2.3, 26)	32 (8.0, 58)
<b>Age 70</b>					
All causes	441 (423, 460)	22 (10, 35)	20 (8.3, 31)	42 (23, 62)	89 (51, 128)
Respiratory cancer	42 (35, 50)	4.0 (-0.8, 8.2)	3.6 (-0.7, 7.4)	8.9 (0.7, 16)	21 (2.3, 43)
Heart disease	138 (126, 152)	7.2 (-1.1, 15)	6.4 (-1.2, 13)	13 (-0.9, 26)	25 (-2.5, 54)
Other causes	261 (244, 279)	11 (0.0, 23)	9.9 (-0.7, 21)	20 (1.8, 40)	43 (4.2, 83)

CI, confidence interval.

The cohort comprised 8,014 copper smelter workers, Anaconda, Montana, 1938–1990.

<sup>a</sup>Cumulative incidence  $\times$  1,000.

<sup>b</sup>Risk difference  $\times$  1,000 (relative to no exposure; negative values imply that higher exposures would decrease the risk of mortality).

## To address healthy worker survivor bias, methods matter

**Table 2.** Cause-specific and all-cause mortality per 1,000 and excess deaths per 1,000 at age 60 and age 70.

Age (years)/ Cause of mortality	Deaths per 1,000 <sup>a</sup> (95% CI)		Excess deaths per 1,000 <sup>b</sup> (95% CI)		
	No exposure	Natural course	If at work, light exposure	If at work, medium exposure	If at work, heavy exposure
<b>Age 60</b>					
All causes	224 (211, 239)	14 (5.0, 22.3)	12 (4.1, 20)	27 (14, 40)	60 (33, 88)
Respiratory cancer	17 (13, 20.2)	1.7 (-0.4, 3.9)	1.6 (-0.5, 3.7)	4.0 (0.6, 7.3)	10 (2.6, 20)
Heart disease	65 (58, 73)	4.8 (0.2, 9.1)	4.1 (-0.4, 8.4)	8.7 (1.4, 16)	18 (2.8, 34)
Other causes	143 (132, 156)	7.3 (-0.1, 15)	6.5 (-0.3, 14)	14 (2.3, 26)	32 (8.0, 58)
<b>Age 70</b>					
All causes	441 (423, 460)	22 (10, 35)	20 (8.3, 31)	42 (23, 62)	89 (51, 128)
Respiratory cancer	42 (35, 50)	4.0 (-0.8, 8.2)	3.6 (-0.7, 7.4)	8.9 (0.7, 16)	21 (2.3, 43)
Heart disease	138 (126, 152)	7.2 (-1.1, 15)	6.4 (-1.2, 13)	13 (-0.9, 26)	25 (-2.5, 54)
Other causes	261 (244, 279)	11 (0.0, 23)	9.9 (-0.7, 21)	20 (1.8, 40)	43 (4.2, 83)

CI, confidence interval.

The cohort comprised 8,014 copper smelter workers, Anaconda, Montana, 1938–1990.

<sup>a</sup>Cumulative incidence × 1,000.

<sup>b</sup>Risk difference × 1,000 (relative to no exposure; negative values imply that higher exposures would decrease the risk of mortality).

I use “**healthy worker survivor bias**” rather than “healthy worker survivor effect” because it is a **structural bias of specific parameters** that is amenable to control, rather than a singular effect.

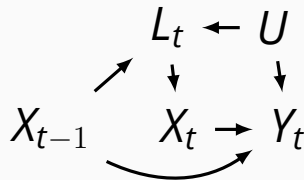
To sharpen the distinction, it is helpful to see the structure

## **Concepts: the structure of healthy worker survivor bias**

---

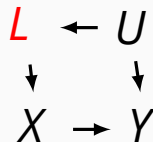
# Healthy worker survivor bias: a structural problem

- DAG for HWSB



# Healthy worker survivor bias: a structural problem

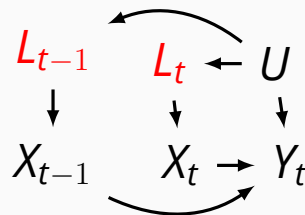
- Employment status = **confounder** (adjust)





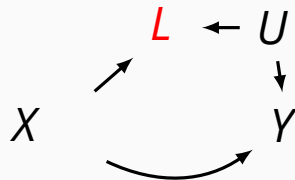
# Healthy worker survivor bias: a structural problem

- Employment status = **confounder** (adjust)



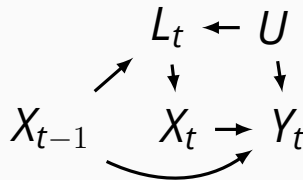
# Healthy worker survivor bias: a structural problem

- Employment status = **collider** (don't adjust)



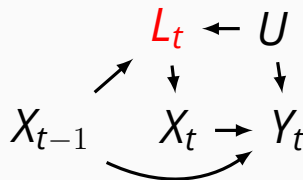
# Healthy worker survivor bias: a structural problem

- Cumulative exposure =  $\dots + X_{t-1} + X_t$



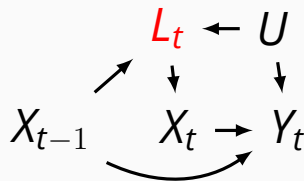
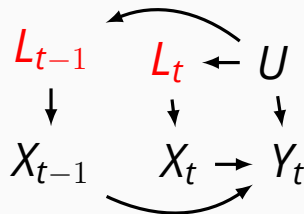
# Healthy worker survivor bias: a structural problem

- Employment status = **confounder** (adjust)
- Employment status = **collider** (don't adjust)
- Cumulative exposure =  $\dots + X_{t-1} + X_t$
- Employment status = time-varying **confounder**  
**affected by prior exposure**



# Healthy worker survivor bias: a structural problem

- **Healthy worker survivor bias** **Confounding** by employment status that *may* be complicated by impacts of exposure on employment



## Healthy worker survivor bias: a structural problem summary

**Confounding** The bias to control

**Collider stratification bias** The bias to avoid when controlling confounding

**Cumulative exposure** We are interested in effects of multiple exposures at once, so we must concern ourselves with both of these biases at once

## **Methods for healthy worker survivor bias in cohort studies**

---

# Methods for healthy worker survivor bias in cohort studies

**If exposure does not impact employment** regression, g-methods<sup>1</sup>

**If exposure impacts employment** g-methods

**G-methods** g-estimation<sup>2</sup>, g-formula/g-computation<sup>3</sup>, inverse probability weighting<sup>4</sup>

---

<sup>1</sup>Naimi, Cole, and Kennedy (2017) *Int J Epidemiol*

<sup>2</sup>Keil, Richardson, and Troester (2015) *Am J Epidemiol*

<sup>3</sup>Keil et al. (2018) *Epidemiology*

<sup>4</sup>Keil et al. (2024) *Am J Epidemiol*



# G-methods for healthy worker survivor bias in cohort studies

g-computation or g-formula|



Search

[Advanced](#) [Create alert](#) [Create RSS](#)

[User Guide](#)

Save

Email

Send to

Sort by:

Best match



Display options

1,272 results



Page

1

of 128



("healthy worker"[All Fields] AND "g-computation"[All Fields]) OR ("health



Search

[Advanced](#) [Create alert](#) [Create RSS](#)

[User Guide](#)

Save

Email

Send to

Sort by:

Best match



Display options

16 results



Page

1

of 2



# G-methods for healthy worker survivor bias in cohort studies

× Search

[Advanced](#) [Create alert](#) [Create RSS](#) [User Guide](#)

Save Email Send to

Sort by: Best match ⬆

Display options ⚙

169 results

⏪ < Page 1 of 17 > ⏩

× Search

[Advanced](#) [Create alert](#) [Create RSS](#) [User Guide](#)

Save Email Send to

Sort by: Best match ⬆

Display options ⚙

17 results

⏪ < Page 1 of 2 > ⏩

# G-methods for healthy worker survivor bias in cohort studies

× Search

[Advanced](#) [Create alert](#) [Create RSS](#) [User Guide](#)

Save

Email

Send to

Sort by: 

Best match

Display options

16,767 results

<< < Page 

1

 of 1,677 > >>

× Search

[Advanced](#) [Create alert](#) [Create RSS](#) [User Guide](#)

Save

Email

Send to

Sort by: 

Best match

Display options

5 results

<< < Page 

1

 of 1 > >>

## Compared with other g-methods, inverse probability weighting

- Is simpler
- Is less computationally demanding
- Reduces modeling assumptions
- Is conceptually clearer
- Is easier to interpret

# Marginal Structural Models and Causal Inference in Epidemiology

*James M. Robins,<sup>1,2</sup> Miguel Ángel Hernán,<sup>1</sup> and Babette Brumback<sup>2</sup>*

---

In observational studies with exposures or treatments that vary over time, standard approaches for adjustment of confounding are biased when there exist time-dependent confounders that are also affected by previous treatment. This paper introduces marginal structural models, a new class of

causal models that allow for improved adjustment of confounding in those situations. The parameters of a marginal structural model can be consistently estimated using a new class of estimators, the inverse-probability-of-treatment weighted estimators. (Epidemiology 2000;11:550–560)

**Keywords:** causality, counterfactuals, epidemiologic methods, longitudinal data, structural models, confounding, intermediate variables

---

# Marginal Structural Models and Causal Inference in Epidemiology

James M.

Brumback<sup>2</sup>

## 11. Limitations of Marginal Structural Models


It is shown in Ref 2 and Appendix 2 that our IPTW estimators will be biased and thus MSMs should not be used in studies in which at each time  $k$  there is a covariate level  $l_k$  such that all subjects with that level of the covariate are certain to receive the identical treatment  $a_k$ . For example, this circumstance implies that MSMs should not be used in occupational cohort studies. To see why, consider an occupational cohort study

improved adjustment of con-  
The parameters of a marginal  
stently estimated using a new  
verse-probability-of-treatment  
iology 2000;11:550–560)

In observational studies with  
vary over time, standard app  
founding are biased when the  
founders that are also affecte  
paper introduces marginal str

Keywords: causality, counterfactuals, epidemiologic methods, longitudinal data, structural models, confounding, intermediate variables

# Inverse Probability Weighting to Estimate Impacts of Hypothetical Occupational Limits on Radon Exposure to Reduce Lung Cancer

Alexander P Keil , Yi Li, Qing Lan, Stephen Bertke, Robert D Daniels, Jessie K Edwards, Kaitlin Kelly-Reif

*American Journal of Epidemiology*, kwae299, <https://doi.org/10.1093/aje/kwae299>

**Published:** 21 August 2024      **Article history** ▼

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).



Hernán et al. and Cain et al. introduced the basic foundation for inverse probability weighting for *dynamic regimes*, which is a formal term for what I describe today.

---

Hernán et al. (2006) *Basic clin pharm & tox*

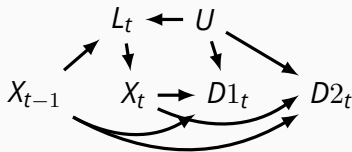
Cain et al. (2010) *The international journal of biostatistics*

## **A worked example with inverse probability weighting**

---

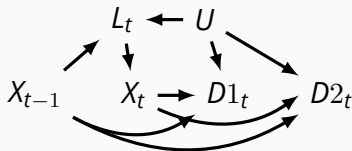
## Synthetic example: effects of exposure in 10,000 worker cohort

- Full code available at [https://github.com/alexpkeil1/EPICOH\\_2024](https://github.com/alexpkeil1/EPICOH_2024)
- Two outcomes : mimicking lung cancer ( $D1$ ) and other-cause ( $D2$ ) mortality based on US mortality rates (race/gender/age/year specific)
- One occupational exposure of interest ( $X$ ) for chronic effects on lung cancer outcome  $D1$
- Covariates: race, gender, age, year, wage status (salary vs. wage at hire), employment status  $L_t$



## Synthetic example: study questions

- What is the association (i.e. hazard ratio) between cumulative exposure and mortality, adjusted for baseline exposure? (Cox model)
- What is the impact (i.e. hazard ratio) of a personal exposure limit on mortality (clone-censor-weight)
- What is the effect of any feasible personal exposure limit on mortality (clone-censor-weight + marginal structural model)



## First 15 observations

id	atwork	x	cumx	wagestatus	gender	race	age	year	d1	d2
1	1	3.252	3.252	1	F	N	31	1956	0	0
1	1	0.936	4.188	1	F	N	32	1957	0	0
1	1	1.269	5.457	1	F	N	33	1958	0	0
1	1	2.230	7.687	1	F	N	34	1959	0	0
1	0	0.000	7.687	1	F	N	35	1960	0	0
1	0	0.000	7.687	1	F	N	36	1961	0	0
1	0	0.000	7.687	1	F	N	37	1962	0	0
1	0	0.000	7.687	1	F	N	38	1963	0	0
1	0	0.000	7.687	1	F	N	39	1964	0	0
1	0	0.000	7.687	1	F	N	40	1965	0	0
1	0	0.000	7.687	1	F	N	41	1966	0	0
1	0	0.000	7.687	1	F	N	42	1967	0	0
1	0	0.000	7.687	1	F	N	43	1968	0	0
1	0	0.000	7.687	1	F	N	44	1969	0	0
1	0	0.000	7.687	1	F	N	45	1970	0	0

## Create variables for analyses (R code with dplyr)

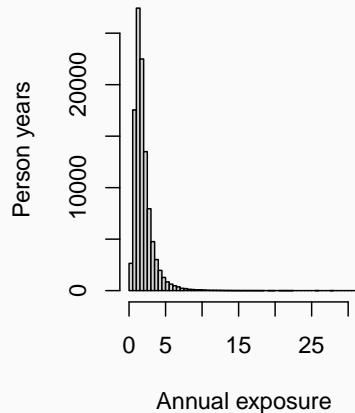
```
sim_cohort <- sim_cohort %>%
  group_by(id) %>%
  mutate(
    one = 1,
    time = cumsum(one),
    timein = time-1,
    agein = age-1,
    xl = lag(x, default=0),
    cxl = lag(cumx, default=0),
    cumatwork = cumsum(atwork),
    cumatworkl = lag(cumatwork, default=0),
    atworkl = lag(atwork, default=0),
    leftwork = as.numeric(atworkl==1 & atwork == 0),
    cxl2 = lag(cxl, default=0),
  ) %>%
  select(-one) %>%
  ungroup()
sim_cohort <- sim_cohort %>%
  group_by(id) %>%
  mutate(
    male = as.numeric(gender == 'M')
  ) %>%
  ungroup()
```

← Define helpful variables for  
time-dependent analysis (time on  
study, lagged variables)

# Cohort characteristics at baseline, exposure and mortality by end of follow-up

N=10,000; 264,000 person-years

Variable	N	Pct	Mean	SD
Age			28	6.35
Calendar year			1954	2.915
Waged	7039	70		
Salaried	2961	30		
Gender F	5052	51		
Gender M	4948	49		
White race	7476	75		
Non-white race	2524	25		
Years of follow-up			26.4	16.9
Average X (at work)			1.89	0.797
Cumulative X			17.2	15.3
Years worked			9.07	7.67
D1	601	6		
D2	7931	79		
Survived	1468	15		



## Should healthy worker survivor bias be a concern?



# Should healthy worker survivor bias be a concern?

Is employment associated with mortality, given past exposures and confounders?

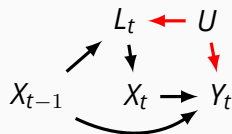
**The hazard of  $D1$  is lower for each additional year of employment**

Call:

```
coxph(formula = Surv(agein, age, d1) ~ cumatwork + cxl + wagestatus +  
      male + year, data = sim_cohort)
```

	coef	exp(coef)	se(coef)	z	p
cumatwork	-0.008939	0.991100	0.014611	-0.612	0.54066
cxl	0.019431	1.019621	0.006887	2.821	0.00478
wagestatus	0.921821	2.513863	0.104730	8.802	< 2e-16
male	0.825716	2.283516	0.100563	8.211	< 2e-16
year	-0.001291	0.998710	0.006003	-0.215	0.82971

Likelihood ratio test=284.7 on 5 df,  $p < 2.2e-16$   
n= 458152, number of events= 601



# Should healthy worker survivor bias be a concern?

Is exposure associated with leaving work, given confounders?

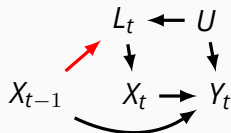
**Cumulative exposure is inversely related to leaving work (due to HWSB!)**

Call:

```
coxph(formula = Surv(agein, age, leftwork) ~ cxl + wagestatus +  
      male + year, data = filter(sim_cohort, atwork == 1 | leftwork ==  
      1))
```

	coef	exp(coef)	se(coef)	z	p
cxl	0.0141371	1.0142375	0.0014321	9.872	<2e-16
wagestatus	-0.0445361	0.9564411	0.0223938	-1.989	0.0467
male	-0.0057580	0.9942586	0.0220583	-0.261	0.7941
year	-0.0007632	0.9992371	0.0027040	-0.282	0.7778

Likelihood ratio test=220.8 on 4 df, p=< 2.2e-16  
n= 115616, number of events= 9589



# Should healthy worker survivor bias be a concern?

Is exposure associated with leaving work, given past exposures and confounders?

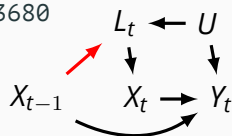
**Recent exposure increases the hazard of leaving work**

Call:

```
coxph(formula = Surv(agein, age, leftwork) ~ xl + cxl2 + wagestatus +  
      male + year, data = filter(sim_cohort, atwork == 1 | leftwork ==  
      1))
```

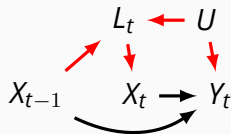
	coef	exp(coef)	se(coef)	z	p
xl	0.071436	1.074049	0.006276	11.383	< 2e-16
cxl2	0.011064	1.011125	0.001480	7.476	7.65e-14
wagestatus	-0.048541	0.952619	0.022392	-2.168	0.0302
male	-0.020670	0.979542	0.022081	-0.936	0.3492
year	0.002456	1.002459	0.002728	0.900	0.3680

Likelihood ratio test=298.4 on 5 df, p=< 2.2e-16  
n= 115616, number of events= 9589



## Should healthy worker survivor bias be a concern? Yes

We have evidence that the **components**<sup>5</sup> of healthy worker survivor bias are in place  
(time-varying confounder affected by prior exposure)



---

<sup>5</sup>Naimi et al. (2013) *Ann Epidemiol*

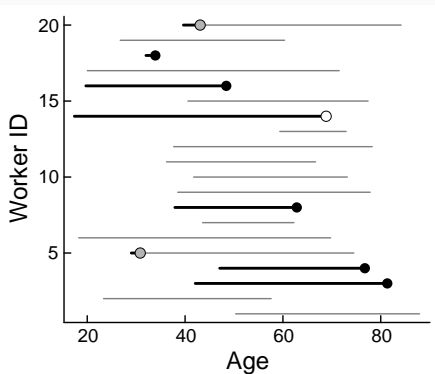
## Intuition of weighting

- All estimates can be conceptualized as a result of an experiment
- Observational data are not experiments
- By weighting observational data, we create a “pseudo-population”
- Each pseudo-population represents an arm of an experiment<sup>6</sup>

---

<sup>6</sup>Under causal assumptions, e.g. Hernán and Robins (2006) *Journal of Epidemiology & Community Health*

# Clone-censor-weight approach to HWSB



From Keil et al. (2024) *Am J Epidemiol*: Person-time of 20 workers. **black line**: observed; **gray line**: observed but artificially censored; **gray dot**: artificially censored during follow-up; **black dot**: death while following regime; **white dot**: alive at end of study

## Strategy:

Clone the cohort data for each hypothetical **exposure limit<sup>a</sup>**

Censor Censor clones in when they exceed the limit<sup>b</sup>

Weight Estimate weights based on the probability of *not* being censored

Weighted data  $\approx$  cohort, had the exposure limit been in place

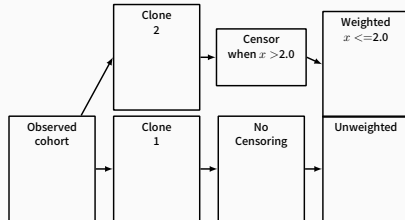
<sup>a</sup> Joffe (2012) *Epidemiology*

<sup>b</sup> Hernán et al. (2006) *Basic clin pharm & tox*

# Clone-censor-weight approach to HWSB: Analysis

## Estimating an effect of exposure

- The original data (with weights = 1) and the uncensored “clones” (with inverse-probability of censoring weights) are combined
- Set “exposed” to 1 in the clones and “exposed” to 0 in the original data
- Fit a weighted model (e.g. weighted Cox model) to the combined data with the “exposed” variable as the sole predictor



## Clone-censor-weight approach to HWSB: Cloning

Make a copy of the cohort data and create a unique ID so the clones do not get confused with observed data

```
clones <- sim_cohort %>%  
  mutate(  
    limit = as.numeric(1.0),  
    cloneid = paste0("clone2.0_", id)  
  )
```



## Clone-censor-weight approach to HWSB: Censoring

An individual is censored in the observation when a worker first exceeds an annual limit. Keep the observation in which censoring occurs (for now) and set “cens=1”.

```
cens_data <- clones %>%  
  group_by(cloneid) %>%  
  mutate(  
    cens = pmin(1, cumsum(x > limit)),  
    drop = pmin(2, cumsum(cens))  
  ) %>%  
  ungroup() %>%  
  filter(  
    drop < 2  
  )
```

# Clone-censor-weight approach to HWSB: predicting censoring

## Separately model

- the “cens” variable at baseline (a “confounding” weight)
- the “cens” variable after baseline (a “censoring” weight)

```
# "censored at baseline" model
confdmod <- glm(cens~
  year + rcspline.eval(year, knots=yearkn0) +
  age + rcspline.eval(age, knots=agekn0) +
  wagestatus + male + race,
  data = cens_data, weight=conf_weight, family=binomial())

# "censored during follow-up" model
censdmod <- glm(cens~ cxl + cumatworkl +
  age + rcspline.eval(age, knots=agekn) +
  wagestatus + male + race , data = cens_data, weight=fu_weight,
  family=binomial())
```

---

Note: the weights used here are 1/0 weights that are just used to subset the data to baseline and non-baseline observations

## Clone-censor-weight approach to HWSB: calculating estimated weights

The weight “ipw” is the time-specific, inverse, cumulative probability of *not* being censored and is set to zero when censoring occurs

```
cens_data$dconf = cens_data$conf_weight*as.numeric(predict(confdmod, type="response"))
cens_data$dcens = cens_data$fu_weight*as.numeric(predict(censdmod, type="response"))
cens_data$nconf = cens_data$conf_weight*as.numeric(predict(confnmod, type="response"))
cens_data$ncens = cens_data$fu_weight*as.numeric(predict(censnmod, type="response"))
cens_data <- cens_data %>%
  mutate(
    wtcontr = case_when(
      ((fobs_____ == 1) & (atwork==1)) ~ (1-cens)*(1-nconf)/(1-dconf),
      ((fobs_____ == 0) & (atwork==1)) ~ (1-cens)*(1-ncens)/(1-dcens),
      .default=1
    )
  ) %>%
  group_by(cloneid) %>%
  mutate(
    ipw = cumprod(wtcontr),
    ipwt = pmin(10, cumprod(wtcontr)) # sometimes truncated weights are advocated
  )
```

## Clone-censor-weight approach to HWSB: Effect estimation

This code fits a cox model comparing the hazard under the “natural course” vs. the hazard under the intervention “limit annual exposures to 2.0 units at work”

```
sim_cohort$exposed = 0
cens_data$exposed = 1
sim_cohort$ipw = 1
sim_cohort$cloneid = paste0("cloneobs_", sim_cohort$id)
combined_data <- bind_rows(sim_cohort, cens_data)

coxph(Surv(agein, age, d1)~exposed,
      data=filter(combined_data, ipw != 0), weight=ipw,
      id=cloneid, cluster=id) %>%
  summary %>% print
```

---

Note: the “cluster” argument is necessary to get the robust variance, which accounts for the fact that individuals appear in the data more than once. Bootstrapping is another option.

## Clone-censor-weight: more than 2 “interventions”

- Clone-censor-weight for exposure-response
- Combine many (30) weighted datasets with assigned exposure “level”
- Cox model with exposure level as only predictor
- “marginal structural model”

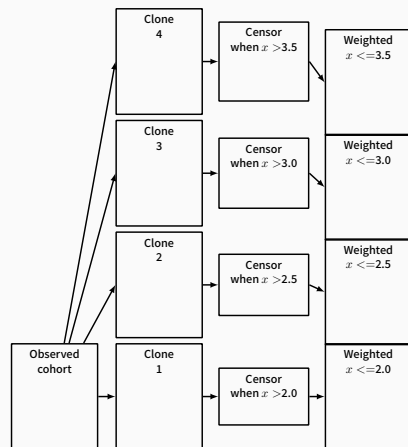


Figure: Conceptual model of clone-censor-weight approach with 4 interventions

This code fits a Cox model estimating the hazard ratio for a 1 unit increase in the occupational limit

```
ttr = coxph(Surv(agein, age, d1)~limit, data=filter(combined_wtd_data, ipw>0),  
            id=cloneid, weight=ipw, cluster=id)
```

Model	Outcome	HR	(95% CI)	Interpretation
Adjusted Cox model, 1 unit increase in cumulative exposure	D1	1.015	(1.012, 1.019)	HR>1, exposure harmful
Clone/censor/weight, 2.0 limit vs. none (ref)	D1	0.12	(0.038, 0.37)	HR<1, exposure harmful
Clone/censor/weight, 1 unit increase in limit <sup>7</sup>	D1	1.098	(1.043, 1.16)	HR>1, exposure harmful

<sup>7</sup>Limits range from 2.2 to 5.7, with mean cumulative exposures ranging from 4 to 14

### Summary

- Key: understanding structural components
- Bias often downward, if not through the null
- Cohort data are required for addressing
- G-methods like IPCW can address in general
- Example demonstrates a "policy-response" model
- HWSB adjusted dose-response models are necessarily different



# Discussion of inverse probability weighting

## Limitations

- Can have high variance
- Sparse data = problematic
- Unfamiliar relative to mortality models with cumulative exposure

## Strengths

- Addresses a key bias (HWSB)
- Simpler than other g-methods
- Weaker modeling assumptions
- Many published examples in other areas, e.g. with diagnostics
- Focuses effect estimates on worker health

## References

---

Katie M Applebaum, Elizabeth J Malloy, and Ellen A Eisen. “Left truncation, susceptibility, and bias in occupational cohort studies”. In: *Epidemiology* 22.4 (2011), pp. 599–606.

H Michael Arrighi and Irva Hertz-Picciotto. “The evolving concept of the healthy worker survivor effect”. In: *Epidemiology* 5.2 (1994), pp. 189–196.

Ove Björ et al. *Reduced mortality rates in a cohort of long-term underground iron-ore miners*. 2013.

Jessie P Buckley et al. “Evolving methods for inference in the presence of healthy worker survivor bias”. In: *Epidemiology* 26.2 (2015), pp. 204–212.

Lauren E Cain et al. “When to start treatment? A systematic approach to the comparison of dynamic regimes using observational data”. In: *The international journal of biostatistics* 6.2 (2010).

Miguel A Hernán and James M Robins. “Estimating causal effects from epidemiological data”. In: *Journal of Epidemiology & Community Health* 60.7 (2006), pp. 578–586.

Miguel A Hernán et al. “Comparison of dynamic treatment regimes via inverse probability weighting”. In: *Basic clin pharm & tox* 98.3 (2006), pp. 237–242.

I Hertz-Picciotto, SW Hu, and HM Arrighi. “Re:” Does arsenic exposure increase the risk for circulatory disease?”-The authors’ reply”. In: *Am J Epidemiol* 152.3 (2000), pp. 293–293.

Marshall M Joffe. “Commentary: Structural Nested Models, G-Estimation, and the Healthy Worker Effect: The Promise (Mostly Unrealized) and the Pitfalls”. In: *Epidemiology* 23.2 (2012), pp. 220–222.

Alexander P Keil and David B Richardson. “Reassessing the link between airborne arsenic exposure among anaconda copper smelter workers and multiple causes of death using the parametric g-formula”. In: *Env Health Persp* 125.4 (2017), pp. 608–614.

Alexander P Keil, David B Richardson, and Melissa A Troester. “Healthy worker survivor bias in the Colorado Plateau uranium miners cohort”. In: *Am J Epidemiol* 181.10 (2015), pp. 762–770.

Alexander P Keil et al. “Estimating the impact of changes to occupational standards for silica exposure on lung cancer mortality”. In: *Epidemiology* 29.5 (2018), pp. 658–665.

Alexander P Keil et al. “Inverse probability weighting to estimate impacts of hypothetical occupational limits on radon exposure to reduce lung cancer”. In: *Am J Epidemiol* (2024), kwae299.

Jay H Lubin and Joseph F Fraumeni Jr. “Re:“Does arsenic exposure increase the risk for circulatory disease?”” In: *Am J Epidemiol* 152.3 (2000), pp. 290–293.

Ashley I Naimi, Stephen R Cole, and Edward H Kennedy. “An introduction to g methods”. In: *Int J Epidemiol* 46.2 (2017), pp. 756–762.

Ashley I Naimi et al. “Assessing the component associations of the healthy worker survivor bias: occupational asbestos exposure and lung cancer mortality”. In: *Ann Epidemiol* 23.6 (2013), pp. 334–341.

Andreas M Neophytou et al. “Marginal structural models in occupational epidemiology: application in a study of ischemic heart disease incidence and PM2. 5 in the US aluminum industry”. In: *Am J Epidemiol* 180.6 (2014), pp. 608–615.

William Ogle. “Letter to the Registrar-General on the mortality in the registration districts of England and Wales during the ten years 1871–80”. In: *Supplement to the Forty-Fifth Annual Report of the Registrar-General of Births, Deaths, and Marriages in England* (1885).

Neil Pearce, Harvey Checkoway, and David Kriebel. “Bias in occupational epidemiology studies”. In: *Occ Env Med* 64.8 (2007), pp. 562–568.

James Robins. “A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect”. In: *Mathematical modelling* 7.9-12 (1986), pp. 1393–1512.

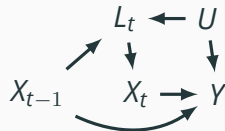
# Concepts and Methods for Healthy Worker Survivor Bias

---

Alex Keil

December 2024

Earl Stadtman Investigator, National Cancer Institute



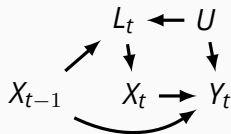
## Extra topics

---



## Employment status is a lever, but not the only one

- Bias is ultimately confounding by underlying health status
- If health status can be measured directly, then employment status is not needed<sup>8</sup>
- Other factors to consider: job title, work area/tasks<sup>9</sup>

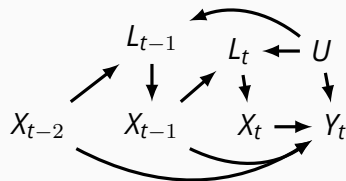


<sup>8</sup>e.g. Neophytou et al. (2014) *Am J Epidemiol*

<sup>9</sup>Pearce, Checkoway, and Kriebel (2007) *Occ Env Med*

# Selection issues and selection bias

## Examples



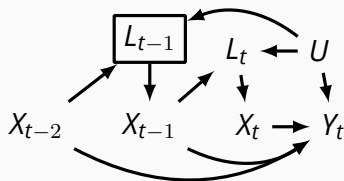
<sup>10</sup>Applebaum, Malloy, and Eisen (2011) *Epidemiology*

<sup>11</sup>e.g. Keil, Richardson, and Troester (2015) *Am J Epidemiol*

# Selection issues and selection bias

## Examples

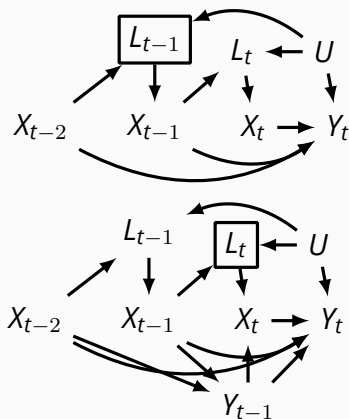
- **Bias from left truncation** Population selected among prevalent workers at a given time; incident hires<sup>10</sup> or use modified cumulative exposure<sup>11</sup>
- **Depletion of susceptibles**  $U$  will be an effect measure modifier and prevalent workers will be healthier/less susceptible (external validity)



<sup>10</sup>Applebaum, Malloy, and Eisen (2011) *Epidemiology*

<sup>11</sup>e.g. Keil, Richardson, and Troester (2015) *Am J Epidemiol*

## Examples

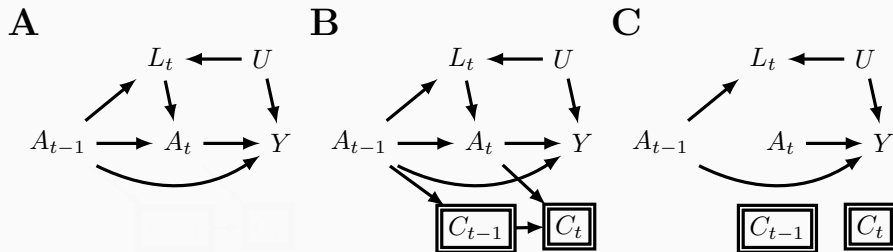


- **Reverse causation** Cross sectional studies of workers, restrict to only recent exposures

<sup>10</sup>Applebaum, Malloy, and Eisen (2011) *Epidemiology*

<sup>11</sup>e.g. Keil, Richardson, and Troester (2015) *Am J Epidemiol*

# Clone-censor-weight for a single occupational annual limit



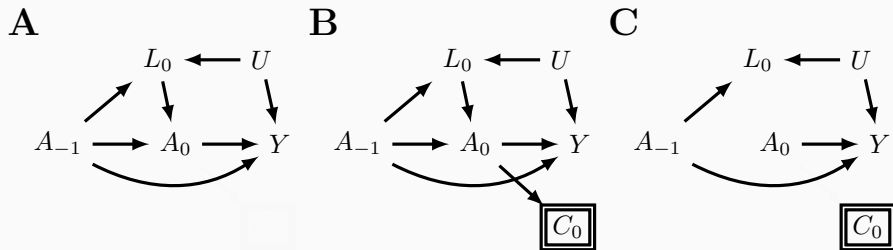
**A** Cloned (same as observed data)

**B** Censored (remove observations from  $t - T$  if exceed limit in time  $t$ )

**C** Weighted ("intervention" on censoring, a deterministic node)

## Artificial “censoring” at baseline

Note: mortality follow-up began after some workers had been exposed



**A** Cloned (same as observed data)

**B** Censored (remove worker if exceed limit in first observation)

**C** Weighted (“intervention” on entry into pseudo-cohort)

# Inverse probability weighting to estimate effects of occupational limits

- IPW is much less reliant on modeling assumptions
- Could be a routinely implemented (contrasted with other g-methods)
- More work: specifying a policy MSM for more principled extrapolation