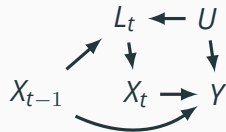# Concepts and Methods for Healthy Worker Survivor Bias

Alex Keil

December 2024
Earl Stadtman Investigator, National Cancer Institute

$$L_t \leftarrow U$$

$$X_{t-1} \quad X_t \rightarrow Y$$

What to expect

- History
- Theory: Causal diagrams (DAGs)
- Practice: Replicable example of diagnosis and adjustment (https://github.com/alexpkeil1/2024_EPICOH)

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*

Employment and health

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

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
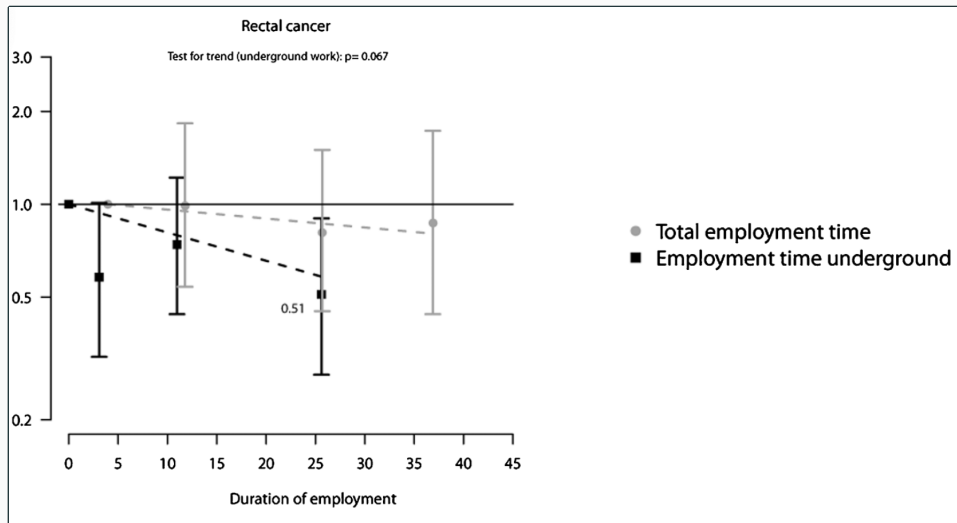
Björ et al. (2013) *Am J Ind Med*

*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 Jr (2000) *Am J Epidemiol*

Arsenic and cardiovascular disease among 8,014 copper smelter workers: comment

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

Hertz-Picciotto, Hu, and Arrighi (2000) *Am J Epidemiol*

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[a] (95% CI) No exposure	Excess deaths per 1,000[b] (95% CI)		
		Natural course	If at work, light exposure	If at work, medium exposure	If at work, heavy exposure
Age 60					
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)
Age 70					
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.
[a]Cumulative incidence × 1,000.
[b]Risk difference × 1,000 (relative to no exposure; negative values imply that higher exposures would decrease the risk of mortality).

Keil and Richardson (2017) *Env Health Persp*

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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.

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Keil and Richardson (2017) *Env Health Persp*

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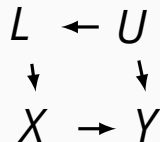
To sharpen the distinction, it is helpful to see the structure

Concepts: the structure of healthy worker survivor bias

Healthy worker survivor bias: a structural problem

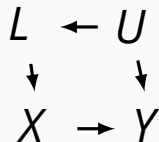Confounders and confounding in directed acyclic
graphs (DAGs)

$$
\begin{array}{ccc}
L & \leftarrow & U \\
\downarrow & & \downarrow \\
X & \rightarrow & Y
\end{array}
$$

U=unmeasured "healthiness", L=employment, X=exposure, Y=outcome

Confounders and confounding in directed acyclic
graphs (DAGs)

- Is U a confounder?
- Is L a confounder?
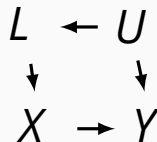- Is there confounding by U after adjusting for L?

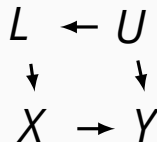$$L \leftarrow U$$
$$\downarrow \quad\quad \downarrow$$
$$X \rightarrow Y$$

U=unmeasured "healthiness", L=employment, X=exposure, Y=outcome

Confounders and confounding in directed acyclic graphs (DAGs)

- Is U a confounder? Yes
- Is L a confounder?
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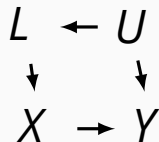
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Healthy worker survivor bias: a structural problem

Confounders and confounding in directed acyclic
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- Is U a confounder?
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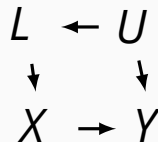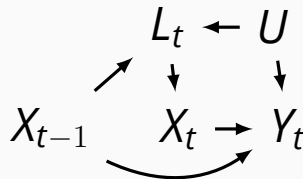- Is there confounding by U after adjusting for L?

$$L \leftarrow U$$
$$\downarrow \qquad \downarrow$$
$$X \rightarrow Y$$

U=unmeasured "healthiness", L=employment, X=exposure, Y=outcome

Confounders and confounding in directed acyclic graphs (DAGs)

- Is U a confounder?
- Is L a confounder?
- Is there confounding by U after adjusting for L?
  No

$$L \leftarrow U$$
$$\downarrow \qquad \downarrow$$
$$X \rightarrow Y$$

U=unmeasured "healthiness", L=employment, X=exposure, Y=outcome

Healthy worker survivor bias: a structural problem

Confounders and confounding in directed acyclic graphs (DAGs)

$$L \leftarrow U$$
$$\downarrow \qquad \downarrow$$
$$X \rightarrow Y$$

Conclusion: if we can adjust for L, we do not need to measure U

U=unmeasured "healthiness", L=employment, X=exposure, Y=outcome

Healthy worker survivor bias: a structural problem

- DAG for HWSB

- Employment status = confounder (adjust)

$$L \leftarrow U$$
$$\downarrow \qquad \downarrow$$
$$X \rightarrow Y$$

U=unmeasured "healthiness", L=employment, X=exposure, Y=outcome
Buckley et al. (2015) *Epidemiology*

- Employment status = confounder (adjust)

$$L_{t-1} \qquad L_t \leftarrow U$$
$$\downarrow \qquad \downarrow \qquad \downarrow$$
$$X_{t-1} \qquad X_t \rightarrow Y_t$$

U=unmeasured "healthiness", L=employment, X=exposure, Y=outcome
Buckley et al. (2015) *Epidemiology*

- Employment status = collider (don't adjust)

$$L \leftarrow U$$
$$X \nearrow \qquad \downarrow$$
$$X \qquad\qquad Y$$

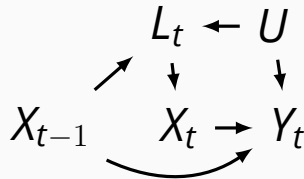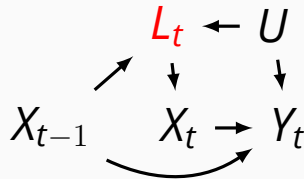
U=unmeasured "healthiness", L=employment, X=exposure, Y=outcome
Buckley et al. (2015) *Epidemiology*

Healthy worker survivor bias: a structural problem

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

$$L_t \leftarrow U$$
$$\nearrow \quad \downarrow \quad \downarrow$$
$$X_{t-1} \quad X_t \rightarrow Y_t$$

U=unmeasured "healthiness", L=employment, X=exposure, Y=outcome
Buckley et al. (2015) *Epidemiology*

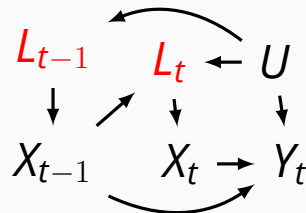## Healthy worker survivor bias: a structural problem

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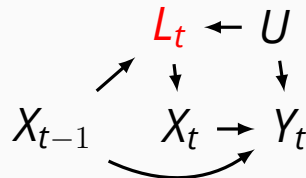- Employment status = time-varying confounder affected by prior exposure

$L_t \leftarrow U$

$X_{t-1} \quad X_t \rightarrow Y_t$

U=unmeasured "healthiness", L=employment, X=exposure, Y=outcome
Buckley et al. (2015) *Epidemiology*

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

U=unmeasured "healthiness", L=employment, X=exposure, Y=outcome
Buckley et al. (2015) *Epidemiology*

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[1]

If exposure impacts employment   g-methods

 G-methods   g-estimation[2], g-formula/g-computation[3], inverse probability
         weighting[4]

_____

[1]Naimi, Cole, and Kennedy (2017) *Int J Epidemiol*
[2]Keil, Richardson, and Troester (2015) *Am J Epidemiol*
[3]Keil et al. (2018) *Epidemiology*
[4]Keil et al. (2024) *Am J Epidemiol*

G-methods for healthy worker survivor bias in cohort studies

G-methods for healthy worker survivor bias in cohort studies

G-methods for healthy worker survivor bias in cohort studies

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,[1,2] Miguel Ángel Hernán,[1] and Babette Brumback[2]

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)

Marginal Structural Models and Causal Inference in Epidemiology

James M. ~~Brumback²~~

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

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)

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

JOURNAL ARTICLE   ACCEPTED MANUSCRIPT

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

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

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Inverse probability weighting for HWSB is possible with recent developments

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 (simulated) 10,000 worker cohort

- Two outcomes : mimicking lung cancer ($D1$) and other-cause ($D2$) mortality based on US mortality rates (race/gender/age/year specific)[5]
- 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

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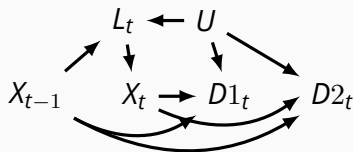
[5]Rates available in LTASR R package
Full code available at https://github.com/alexpkeil1/2024_EPICOH

Synthetic example: study questions

- What is the association (i.e. hazard ratio) between cumulative exposure and mortality? (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)

Synthetic data: first 15 observations

id	atwork	x	cumx	wagestatus	gender	race	age	year	d1	d2
1	1	0.577	0.577	1	F	N	25	1956	0	0
1	1	1.297	1.874	1	F	N	26	1957	0	0
1	1	1.138	3.012	1	F	N	27	1958	0	0
1	1	0.991	4.003	1	F	N	28	1959	0	0
1	1	0.878	4.881	1	F	N	29	1960	0	0
1	1	0.884	5.766	1	F	N	30	1961	0	0
1	1	1.008	6.773	1	F	N	31	1962	0	0
1	1	1.256	8.030	1	F	N	32	1963	0	0
1	1	0.848	8.878	1	F	N	33	1964	0	0
1	1	1.161	10.039	1	F	N	34	1965	0	0
1	1	0.962	11.001	1	F	N	35	1966	0	0
1	1	1.097	12.098	1	F	N	36	1967	0	0
1	1	1.126	13.225	1	F	N	37	1968	0	0
1	1	1.941	15.166	1	F	N	38	1969	0	0
1	1	0.939	16.104	1	F	N	39	1970	0	0

Step 1: 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; 459,000 person-years

Variable	N	Pct	Mean	SD
Age			23	3.48
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		
Never exposed (X=0)	2950	30		
Years of follow-up			45.9	13.1
Average X (at work)			0.931	0.656
Cumulative X			20.8	21.9
Years worked			23.4	15.6
D1	727	7.3		
D2	5090	51		
Survived	4183	42		

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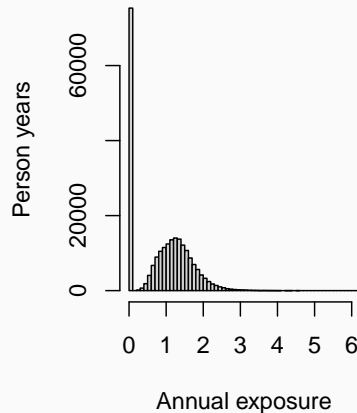
Should healthy worker survivor bias be a concern?
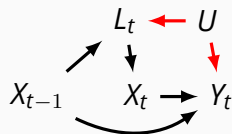
Should healthy worker survivor bias be a concern?

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

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

                 coef  exp(coef)  se(coef)      z          p
cumatwork  -0.033074   0.967467  0.005166  -6.402  1.53e-10
cxl         0.042144   1.043045  0.003200  13.169   < 2e-16
wagestatus  0.814132   2.257215  0.096816   8.409   < 2e-16
male        0.616845   1.853073  0.090030   6.852  7.31e-12
year       -0.022570   0.977683  0.008853  -2.550    0.0108

Likelihood ratio test=642.1  on 5 df, p=< 2.2e-16
n= 459114, number of events= 727
```

$$L_t \longleftarrow U$$
$$X_{t-1} \quad X_t \longrightarrow Y_t$$

Is employment associated with mortality, given past exposures and confounders?
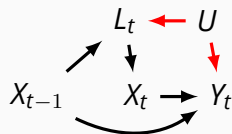**The hazard of $D1$ is lower for each additional year of employment**

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

                 coef exp(coef)  se(coef)       z        p
cumatwork  -0.033074  0.967467  0.005166  -6.402  1.53e-10
cxl         0.042144  1.043045  0.003200  13.169  < 2e-16
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Likelihood ratio test=642.1  on 5 df, p=< 2.2e-16
n= 459114, number of events= 727
```

Is exposure associated with leaving work, given confounders?
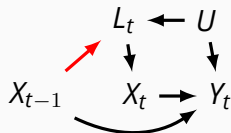
Cumulative exposure increases the hazard of leaving work

```
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         0.0128555  1.0129385  0.0006291  20.434  <2e-16
wagestatus -0.0122375  0.9878371  0.0230387  -0.531   0.595
male        0.0177102  1.0178679  0.0218276   0.811   0.417
year       -0.0035572  0.9964491  0.0024427  -1.456   0.145

Likelihood ratio test=446  on 4 df, p=< 2.2e-16
n= 243167, number of events= 8778
```

$$L_t \leftarrow U$$
$$X_{t-1} \quad X_t \rightarrow Y_t$$

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           0.1132628  1.1199262  0.0210034   5.393  6.95e-08
cxl2         0.0098854  1.0099344  0.0008869  11.146   < 2e-16
wagestatus  -0.0183339  0.9818331  0.0230791  -0.794     0.427
male         0.0042062  1.0042151  0.0220344   0.191     0.849
year        -0.0024602  0.9975428  0.0024549  -1.002     0.316

Likelihood ratio test=468.6  on 5 df, p=< 2.2e-16
n= 243167, number of events= 8778
```
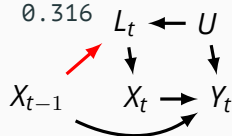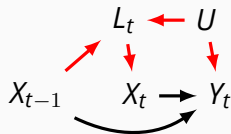
We have evidence that the **components**[6] of healthy worker survivor bias are in place (time-varying confounder affected by prior exposure)

---

[6]Naimi et al. (2013) *Ann Epidemiol*

Inverse probability weighting, generally

Intuition:

- 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[7]
- Each "arm" is a *time-fixed* exposure, eliminating time-varying-confounding

---

Clone-censor-weight approach to HWSB

Approach to weighting

- "Standard" inverse probability weighting for studying cumulative exposure-response curves *is not generally possible* for HWSB[8]
- Instead, we can use inverse probability weighting to study effects of hypothetical exposure limits[9]
- Example: "If at work, annual exposure can be no more than 2.0 units"[10]
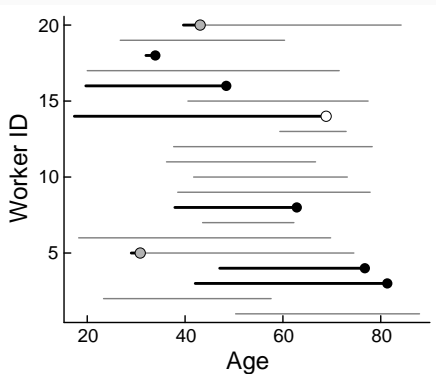- Sometimes called a "clone-censor-weight" approach

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[8]Robins, Hernan, and Brumback (2000) *Epidemiology*
[9]Hernán et al. (2006) *Basic clin pharm & tox*
[10]Joffe (2012) *Epidemiology*

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**

Censor Censor clones in when they exceed the limit

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

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

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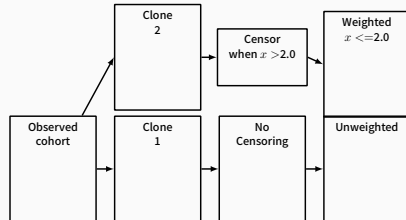
Make a copy of the cohort data and create a
unique ID so the clones do not get
confused with observed data

```
clones <- sim_cohort %>%
  mutate(
    limit = as.numeric(2.0),
    cloneid = paste0("clone2.0_", id)
  )
```

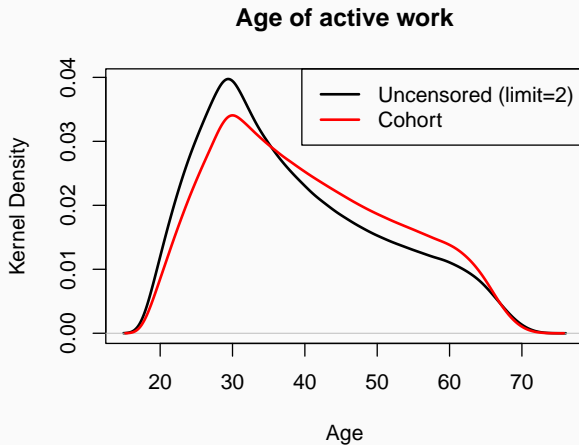## Clone-censor-weight approach to HWSB: Censoring

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
  )
```

- Employment status is a confounder
- Weighting: low exposure individuals must represent the full distribution of confounders in the data
- Here: those with X<2.0 have the same range of employment age as the full cohort, supporting positivity for a limit of 2.0
- This assumption is *crucial*

Age of active work

Legend:
- Uncensored (limit=2)
- Cohort

x-axis: Age
y-axis: Kernel Density

If we had non-positivity, the red line would flatten out before the black line

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
  )
```

Intuition: as individuals are censored, the weights of uncensored individuals increase to represent those individuals, had they remained below the limit

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"
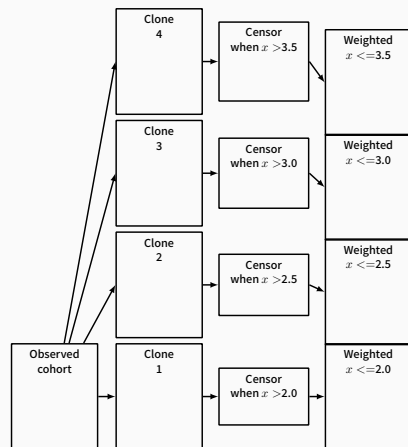- Cox model with exposure level as only predictor
- "marginal structural model"

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

Marginal structural models

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)
```

Results: standard Cox model vs. clone-censor-weight

Model	Outcome	HR	(95% CI)[11]	Interpretation
Adjusted Cox model, 1 unit increase in cumulative exposure	D1	1.027	(1.024, 1.030)	HR$>$1 $\rightarrow$ harmful
	D2	0.996	(0.995, 0.997)	

---

[11] Cluster robust confidence intervals to account for weighting

[12] Limits range from 1.7 to 2.9, with mean cumulative exposures ranging from 3.1 to 13.2

Results: standard Cox model vs. clone-censor-weight

Model	Outcome	HR	(95% CI)[11]	Interpretation
Adjusted Cox model, 1 unit increase in cumulative exposure	D1	1.027	(1.024, 1.030)	HR>1 → harmful
	D2	0.996	(0.995, 0.997)	
Clone/censor/weight, 2.0 limit vs. none (ref)	D1	0.645	(0.542, 0.767)	HR<1→ harmful
	D2	0.989	(0.931, 1.052)	

[11]Cluster robust confidence intervals to account for weighting
[12]Limits range from 1.7 to 2.9, with mean cumulative exposures ranging from 3.1 to 13.2

Results: standard Cox model vs. clone-censor-weight

Model	Outcome	HR	(95% CI)[11]	Interpretation
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	D2	0.996	(0.995, 0.997)	
Clone/censor/weight, 2.0 limit vs. none (ref)	D1	0.645	(0.542, 0.767)	HR$<$1$\rightarrow$ harmful
	D2	0.989	(0.931, 1.052)	
Clone/censor/weight, 1 unit increase in limit[12]	D1	1.627	(1.390, 1.906)	HR$>$1 $\rightarrow$ harmful
	D2	0.995	(0.944, 1.047)	

---

[11] Cluster robust confidence intervals to account for weighting

[12] Limits range from 1.7 to 2.9, with mean cumulative exposures ranging from 3.1 to 13.2

Summary

- Key: understanding structural components
- Bias often downward, if not through the null (e.g. outcome D2)
- Cohort data are required for addressing
- G-methods like IPCW can address in general
- HWSB adjusted dose-response models are necessarily different
- Public health: "policy-response" model

Discussion of inverse probability weighting

Limitations

- Can have high variance
- Sparse data/non-positivity = 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

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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).

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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.

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

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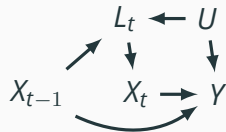
Concepts and Methods for Healthy Worker Survivor Bias

Alex Keil

December 2024
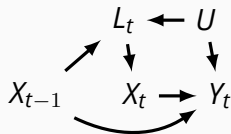Earl Stadtman Investigator, National Cancer Institute

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[13]
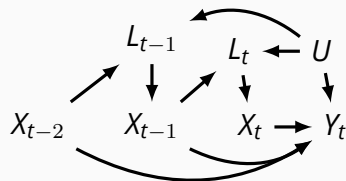- Other factors to consider: job title, work area/tasks[14]

$$L_t \leftarrow U$$
$$X_{t-1} \nearrow \quad \downarrow \quad \downarrow$$
$$X_{t-1} \quad X_t \rightarrow Y_t$$

---

[13]e.g. Neophytou et al. (2014) *Am J Epidemiol*
[14]Pearce, Checkoway, and Kriebel (2007) *Occ Env Med*

Examples

$$L_{t-1} \quad L_t \leftarrow U$$
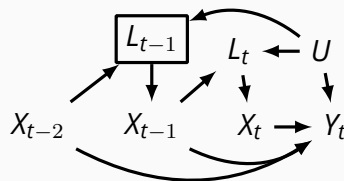
$$X_{t-2} \quad X_{t-1} \quad X_t \rightarrow Y_t$$

[15]Applebaum, Malloy, and Eisen (2011) *Epidemiology*
[16]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; use incident hires [15] or modified cumulative exposure [16]

- **Depletion of susceptibles** U will be an effect measure modifier and prevalent workers will be healthier/less susceptible (external validity)
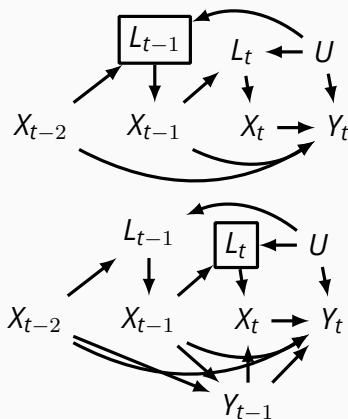

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[15] Applebaum, Malloy, and Eisen (2011) *Epidemiology*

[16] e.g. Keil, Richardson, and Troester (2015) *Am J Epidemiol*
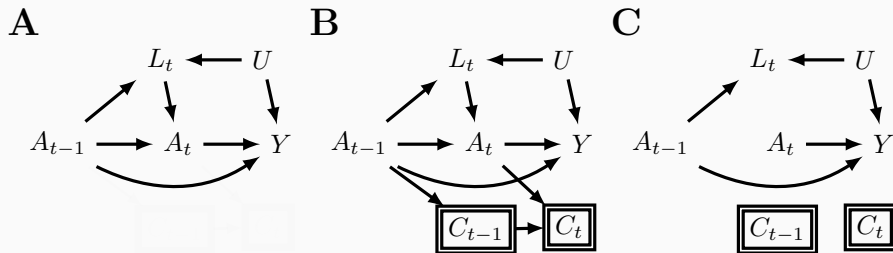
Selection issues and selection bias

Examples

- **Reverse causation** Cross sectional studies of workers, those with previous events may have lower exposures

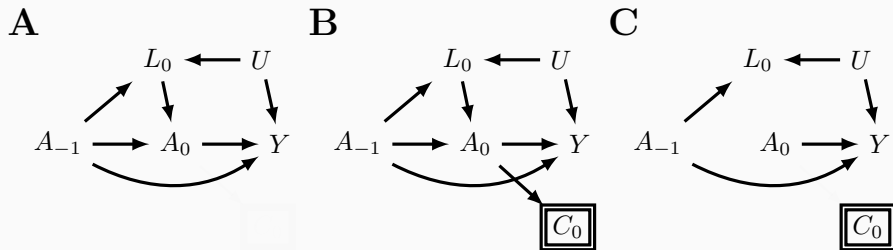## Clone-censor-weight for a single occupational annual limit

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)

Keil et al. (2024) *Am J Epidemiol*

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)

Keil et al. (2024) *Am J Epidemiol*

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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