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Sentinel

Inverse probability weighting for effect estimation in observational research: Weight Weight… Tell Me!

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Sentinel Innovation and Methods Seminar Series

September 30, 2021

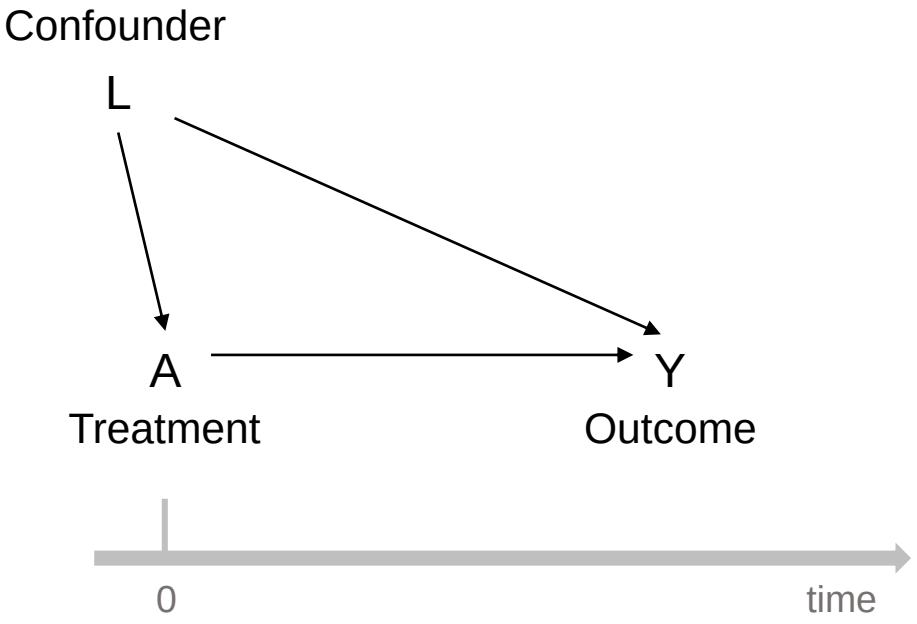
DEPARTMENT OF POPULATION MEDICINE

HARVARD MEDICAL SCHOOL

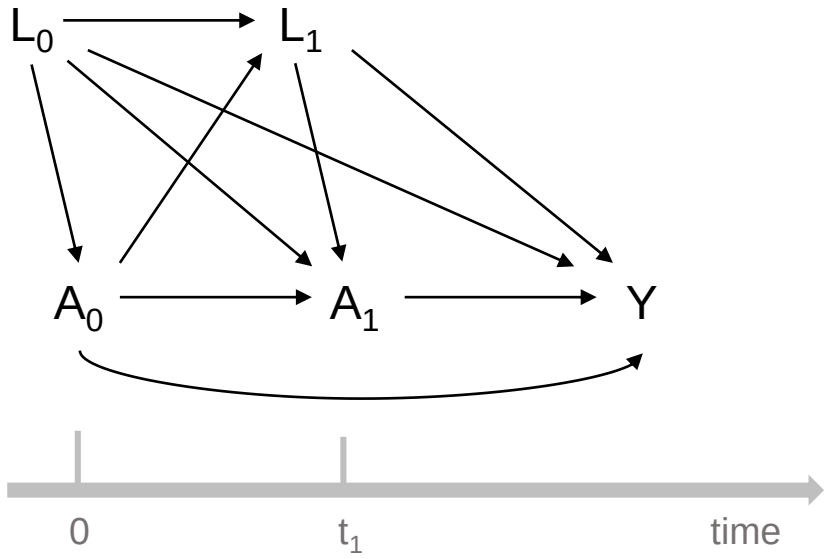
Harvard Pilgrim Health Care Institute

Inverse probability weighting a versatile way to confounding control in observational studies

Time-fixed exposure



Time-varying exposure

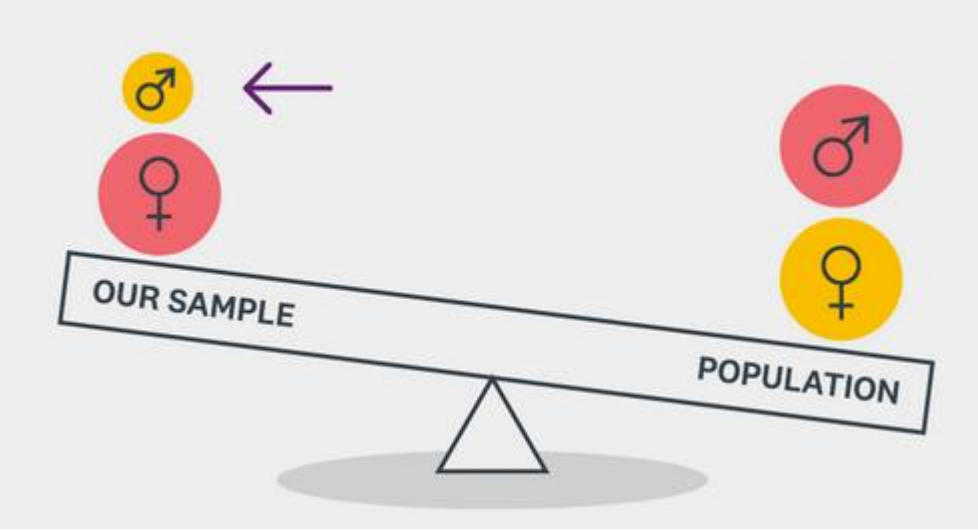


Overview

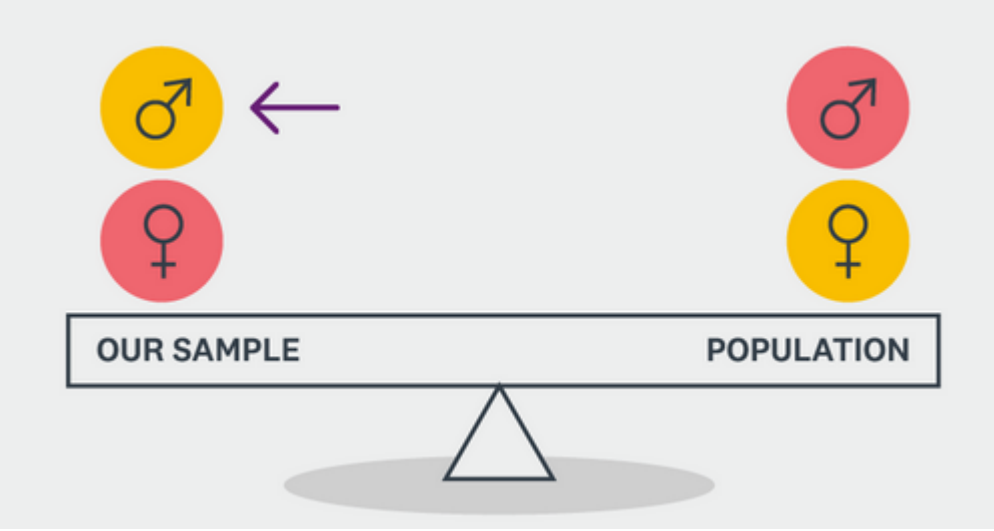
- Inverse probability weighting (time-fixed setting)
- Inverse probability weighted estimator of marginal structural models (extension to time-varying setting)
- Opportunities and considerations

Inverse probability weighting as standardization

- First developed for **survey sampling** – make a sample surveyed look more like the population



Before weighting

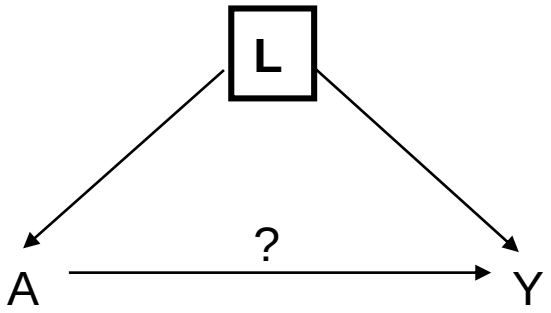


After weighting

Horvitz & Thompson. *J Am Stat Assoc* 1952;47: 663-85
Source: https://www.surveymonkey.com/mp/survey-methodology/

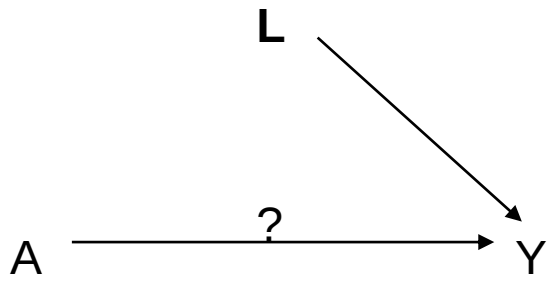
Confounding adjustment in comparative studies

- Standard methods, such as matching, stratification, or regression adjustment, can be used to **control for** confounding



Confounding adjustment via inverse probability weighting

- Inverse probability weighting is another approach, by creating pseudo-population in which the association between treatment and measured confounders is removed



Inverse probability weighting as standardization

- **survey sampling** – make a sample surveyed look more like the population

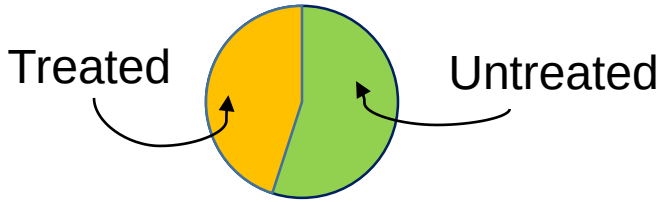
- Inverse probability of treatment weights – re-weight each exposure group to look like the entire observed population
  - sharing the same covariate distribution
  - IPTW: standard population = observed population/study sample
  - SRW: standard population = observed treated population

Horvitz & Thompson. *J Am Stat Assoc* 1952;47: 663-85
Sato & Matsuyama. *Epidemiology* 2003; 14: 680-686

IPTW = inverse probability of treatment weighting
SMRW = standardized mortality ratio weighting

Visualizing end-product of inverse probability weighting

Original



Observed population, N

Weighted

Treated, N

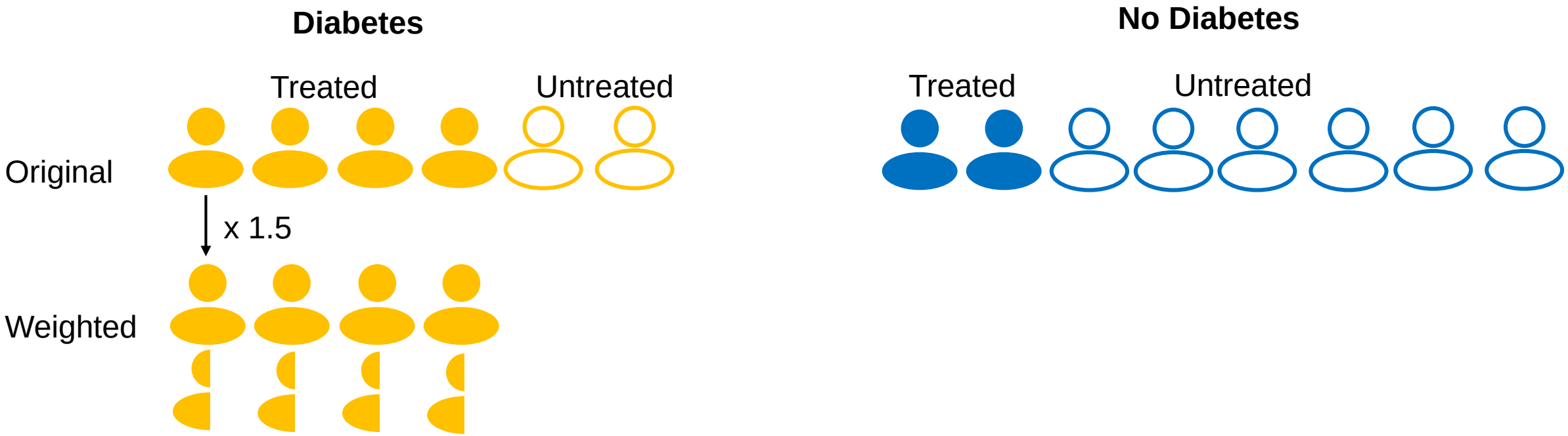
Untreated, N

Covariate distribution

Pseudo-population, 2N

Adapted from http://www.baileydebarmore.com/epicode/calculating-ipw-and-smr-in-sas

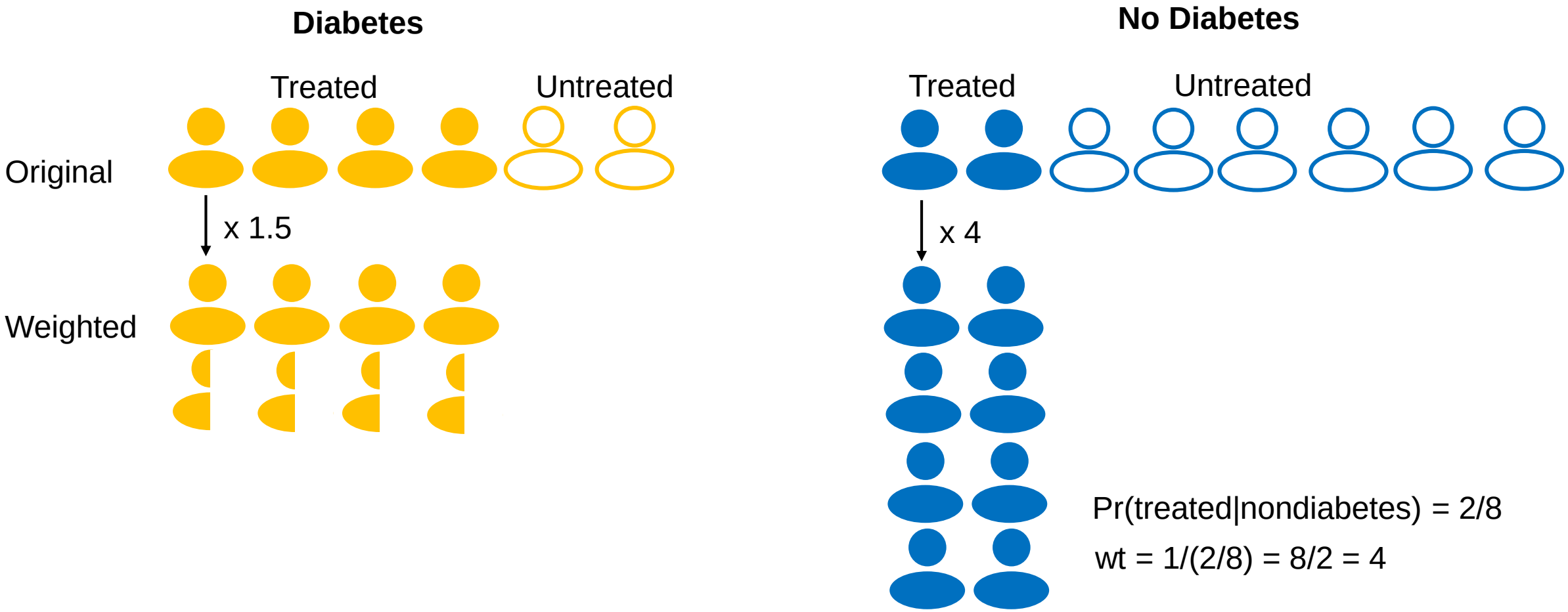
	Pr(diabetes)	Pr(diabetes|treated)	Pr(diabetes|untreated)	
Original	6/14 = 43%	4/6 = 67%	2/8 = 25%	Imbalanced



Pr(treated|diabetes) = 4/6

wt = 1/(4/6) = 6/4 = 1.5

	Pr(diabetes)	Pr(diabetes|treated)	Pr(diabetes|untreated)	
Original	6/14 = 43%	4/6 = 67%	2/8 = 25%	Imbalanced



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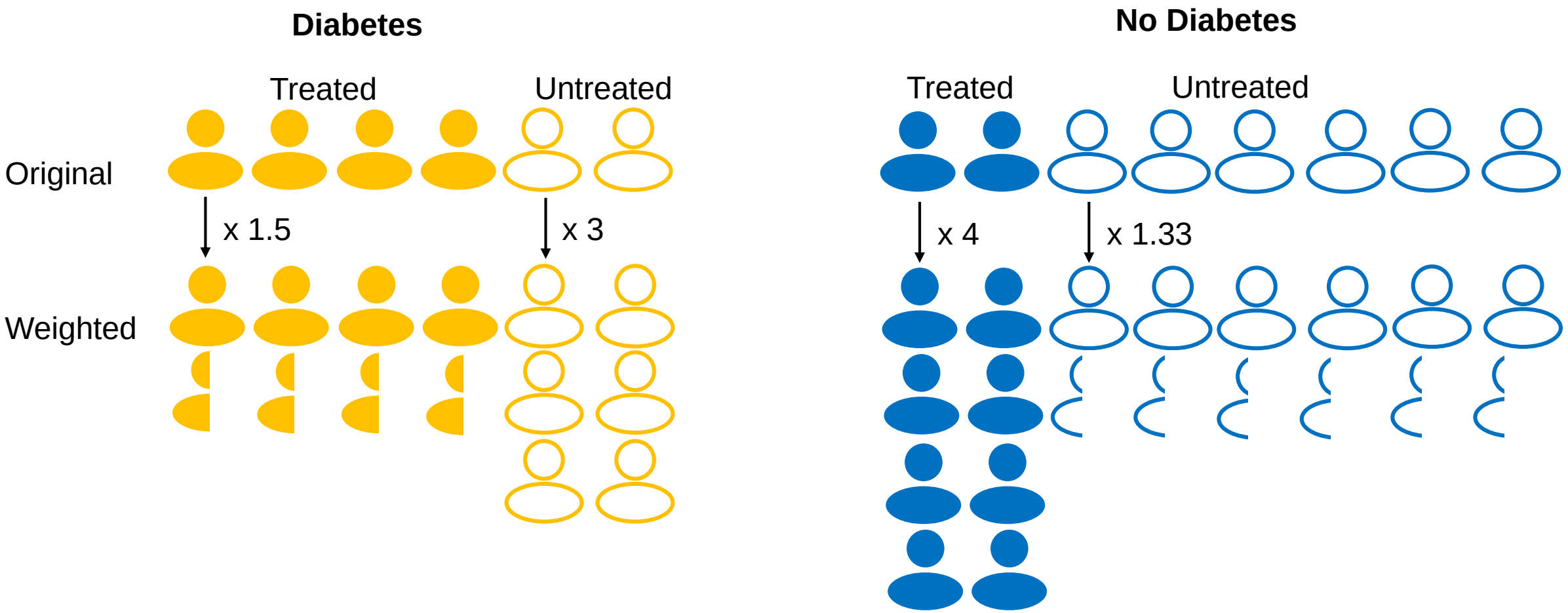

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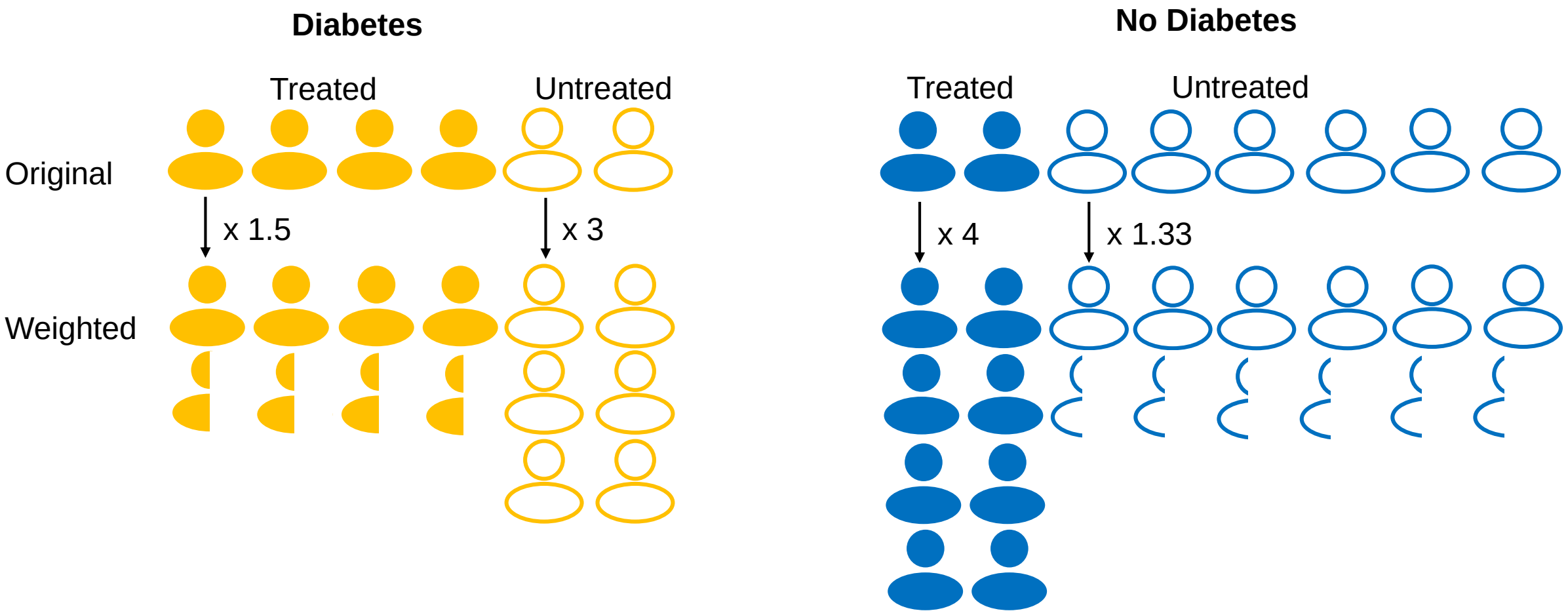

	Pr(diabetes)	Pr(diabetes|treated)	Pr(diabetes|untreated)	
Original	6/14 = 43%	4/6 = 67%	2/8 = 25%	Imbalanced
Weighted	12/28 = 6/14	4*1.5/(4*1.5+2*4)=6/14	2*3/(2*3+6*1.33) = 6/14	Balanced

Estimate treatment effect in the weighted sample

We can just use 2x2 table to get the disease incidence or means to do the analysis in the pseudo-population

	Outcome	**No event**	**Risk**	**Risk ratio**	**Risk difference**
a = 1	D_1	14-D_1	$D_1/14$	D_1/D_1	$(D_1-D_2)/14$
a = 0	D_2	14-D_2	$D_2/14$	reference	reference

Implementation of inverse probability weighted estimation

1. Model exposure as function of confounders/covariates

2. Assign each individual weight, $W = \frac{1}{f(A|L)}$

3. Obtain measure of disease incidence/association of interest in the weighted sample
   - use robust variance estimator (or bootstrap) for variance/confidence intervals

Inverse probability weighting and propensity sores

- The denominator of the weights $f(A|L)$ links closely to propensity score $f(A = 1|L)$
  - Treated: W $= \frac{1}{P(A_i=1|L_i)} = \frac{1}{PS}$
  - Untreated: W $= \frac{1}{P(A_i=0|L_i)} = \frac{1}{1-PS}$

- Inverse probability weighting and propensity score based weighting methods can be very flexible

Rosenbaum & Rubin. *Biometriika* 1983a;70: 41--55
Sato & Matsuyama. *Epidemiology* 2003; 14: 680-686

Inverse probability weighted estimation of marginal structural models

- After weighting, instead of 2x2 table, one can **fit a model** to the pseudo-population

- Often considered as a tool for longitudinal time-varying exposures, marginal structural models can be used in point exposure settings

- Using a weighted model to estimate the parameters of a marginal structural model
  - e.g. weighted logistic (Cox) model to estimate a marginal structural logistic (Cox) model
  - Adjusting for all confounding through weights
  - Model has no covariates → estimating a marginal effect; avoid potential bias through adjusting in time-varying setting

Robins. 1997 *Proceedings of the Section on Bayesian Statistical Inference* 1998:1-10
Robins et al. *Epidemiology* 2000; 11: 550-560
Sato & Matsuyama. *Epidemiology* 2003; 14: 680-686

Stabilized weights to improve efficiency

- Common issue: large weights → unstable weighted estimator
  - treated individuals with low propensity score, or
  - untreated individuals with high propensity score

- Solution: stabilized weights, $SW = \frac{f(A)}{f(A|L)}$ vs $W = \frac{1}{f(A|L)}$
  - marginal probability of treatment in the numerator
  - preserve sample size, while unstabilized weights double sample size
  - good check – mean=2 for IPTW; 1=sIPTW

- Solution: re-assess propensity score model
  - trim non-overlapping propensity score region
  - weight truncation

Xu et al. *Value Health* 2010; 13(2): 273-277
Lee et al. *PLOS One* 2011; 6(3): e18174

Overview

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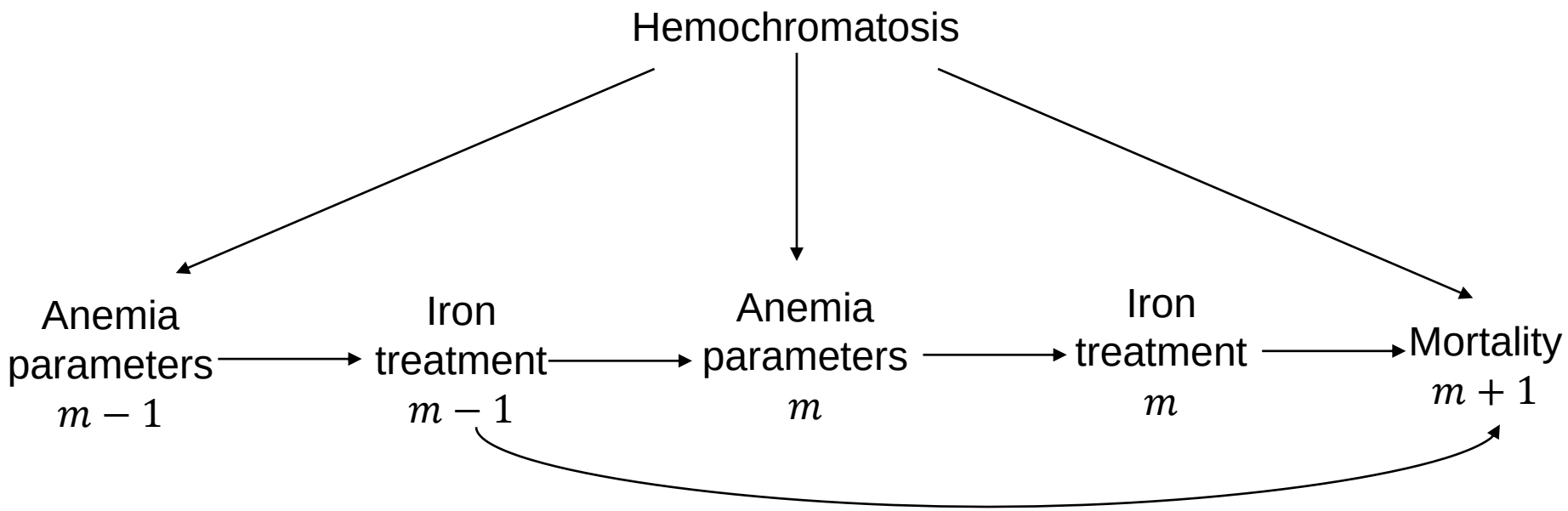
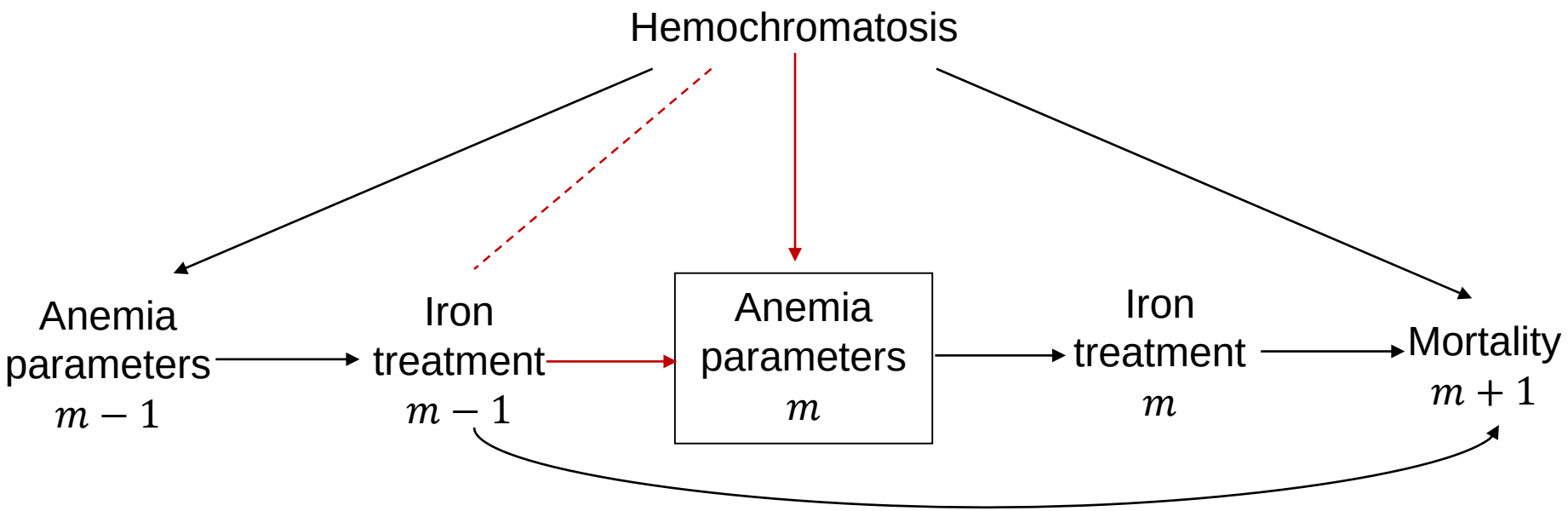
Inverse probability weighting for time-varying setting

- treatment-confounder feedback loop



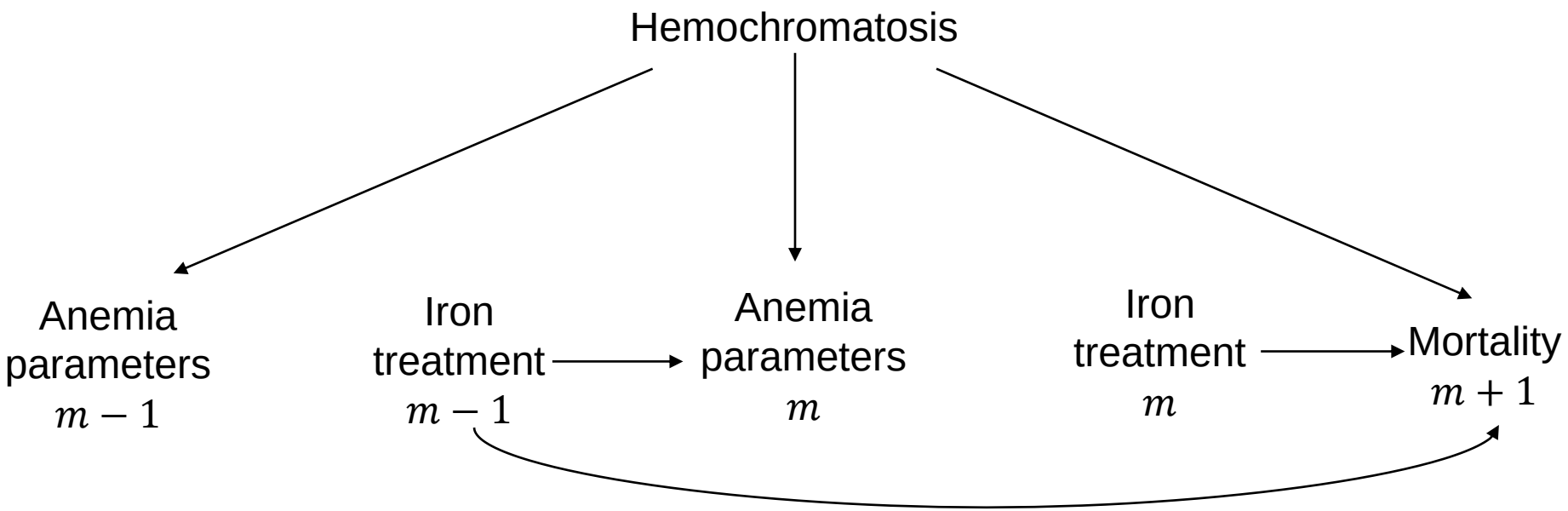
Hernán et al. *Epidemiology* 2004; 15:615-625
Li et al. *Curr Epidemiol Rep* 2017; 4(4): 288-297

Standard regression methods fail



Hernán et al. *Epidemiology* 2004; 15:615-625
Li et al. *Curr Epidemiol Rep* 2017; 4(4): 288-297

Inverse probability weighting can work



Hernán et al. *Epidemiology* 2004; 15:615-625
Li et al. *Curr Epidemiol Rep* 2017; 4(4): 288-297

IPW in the time-varying setting – treatment weights

- Need to estimate time-varying weights
- Standard weights: $W^A(t) = \prod_{k=0}^{t} \frac{1}{f\left\{[A(k)\middle|\bar{A}(k-1), \bar{L}(k)\right\}}$
- Stabilized weights: $SW^A(t) = \prod_{k=0}^{t} \frac{f\{A(k)|\bar{A}(k-1), V\}}{f\{A(k)|\bar{A}(k-1), \bar{L}(k)\}}$

Hernán et al. *Epidemiology* 2004; 15:615-625
Fewell et al. *Stata Journal* 2004; 4(4):402-420

IPW in the time-varying setting – censoring weights

- Censoring weights:

$$SW^C(t) = \prod_{k=0}^{t} \frac{f\{C(k)|\bar{C}(k-1) = \bar{0}, \bar{A}(k), V\}}{f\{C(k)|\bar{C}(k-1) = \bar{0}, \bar{L}(k)\}}$$

- Lost to follow-up, drop out, administrative censoring, etc.
- Nonadherence (to estimate sustained treatment effects)
- Final weights: $SW(t) = SW^A(t) * SW^C(t)$

Hernán et al. *Epidemiology* 2004; 15:615-625
Fewell et al. *Stata Journal* 2004; 4(4):402-420

Fitting the outcome model

- Bootstrap or robust variance estimator to account for dependence between observations from the same subject introduced by the weighting process

- Variables V included in the numerator of the stabilized weight should be included in the outcome model

Hernán et al. *Epidemiology* 2000; 11(5):561-570

Select applications of IPW estimation of MSM

- Effect of continuous treatment on risk of outcome
  - Adjusting for nonadherence
  - Toh et al. *Epidemiology* 2010; 21: 528-539
- Effect of cumulative dose on risk of outcome
  - Zhang et al. *CJASN* 2009; 4(3):636-644
- Effect of treatment initiation versus no initiation on risk of outcome
  - Time-varying indication
  - HIV-CAUSAL Collaboration. *AIDS* 2010; 24:123-137
- Comparative effectiveness of dynamic treatment strategies
  - Cain et al. *Int J Biostat* 2010; 6(2):18
- Comparative effectiveness of static treatment strategies
  - Schnitzer et al. *Stat Med* 2020; 39(29):4538-4550

A clone-censor-weight approach to estimate effect of treatment duration on survival outcomes

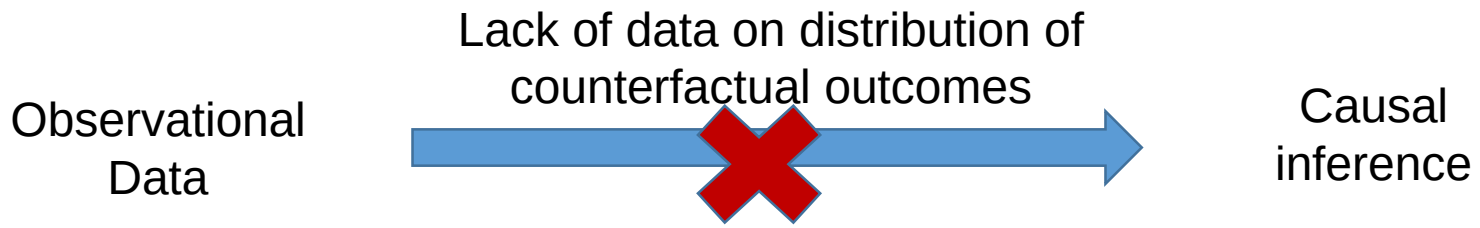
Create a pseudo-cohort

- Step 1 – define strategies and make copies of the original data with one copy for each strategy of interest
- Step 2 – artificially censor observations when they first deviate from the index strategy
- Step 3 – estimate weights to adjust for potential selection bias introduced by artificial censoring for strategy deviation
- Step 4 – compute risk by end of follow-up under the specified strategy

Hernán. *BMJ* 2018; 360:k182
Cain et al. *Int J Biostat* 2010; 6(2):18
Li et al. *Curr Epidemiol Rep* 2017; 4(4): 288-297

Validity of causal inference requires conditions

- Exchangeability
- Consistency
- Positivity
- No measurement error
- No model misspecification



Hernán & Robins. *J Epidemiol Community Health* 2006; 60(7):578-586
VanderWeele. Epidemiology. 2009;20(6):880-3
Orellana et al. *Int J Biostat* 2010; 6(2):8
Platt et al. *Stat Med* 2013; 32(8)

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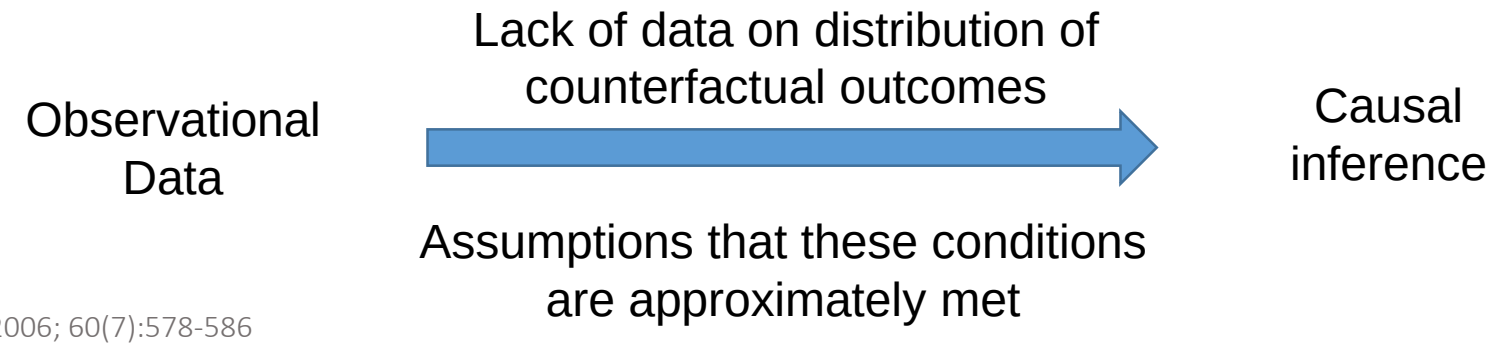

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VanderWeele. Epidemiology. 2009;20(6):880-3
Orellana et al. *Int J Biostat* 2010; 6(2):8
Platt et al. *Stat Med* 2013; 32(8)

Limitations of IPW of MSM

- Only achieve balance on measured variables
- Number of balancing variables may be limited by sample size
- Prone to positivity violation and unstable weights
- Tends to produce wider confidence intervals

Strengths of IPW of MSM

- Easier to explain
- Less computationally intensive
- Less prone to model misspecification
- Can directly estimate parameters encoding null hypothesis
- Easier to identify positivity violations

Other methods for time-varying exposure

- Methods that derive from Robins' g-formula can generate unbiased estimates of causal treatment effects

- g-formula = counterfactual outcome mean/risk associated with a time-varying treatment strategy
  - Function of baseline and time-varying data
  - Contrasts in this function for different strategies = unbiased estimates of causal effects

- Various methods to estimate the g-formula
  - Parametric g-formula
  - Inverse probability weighting of marginal structural models
  - G-estimation of structural nested models
  - Doubly robust estimation; Targeted maximum likelihood estimation

"g-methods"

Robins 1986; Robins 2004; Robins 2000, Hernan 2000, Robins 1998; van der Laan 2006 Schuler & Rose 2017

Overview

- Inverse probability weighting (time-fixed setting)
- Inverse probability weighted estimator of marginal structural models (extension to time-varying setting)
- Opportunities and considerations

Opportunities

- Many questions in observational comparative studies involve time-varying treatments
- Long-term effects involves (non)adherence
- Ability to provide answers on more clinically-relevant questions

Applications of inverse probability weighting

- Selection into the study population → sampling bias or generalizability
- Receipt of a treatment/exposure → confounding
- Observation at a visit → missing data
- Remaining under observation → censoring (selection)

Horvitz & Thompson. *J Am Stat Assoc* 1952;47;663-85
Hernán & Robins. *J Epidemiol Community Health* 2006;60:578-86
Robins & Finkelstein. *Biometrics* 2004; 75:45-49
Seaman & White. *Stat Methods Med Res* 2013; 22:278-95
Cole & Stuart. *Am J Epidemiol* 2010; 172:107-15

Consideration in applying these methods for observational research

Table 3 Some considerations before applying g-methods for treatment effects estimation in pharmacoepidemiologic studies

Study question	Is your research question well defined? 1. What treatment effect are you trying to estimate? 2. Do you have well-defined interventions? 3. How many interventions are you comparing? 4. Do these questions align well with real-world clinical decisions?
Study variables	Can you draw causal diagrams to identify relations amongst variables? 1. Which variables are confounders? Which ones are time-fixed, time-varying, or time-varying and also affected by past treatment? 2. Which variables do you need to control to provide valid treatment effect of interest?
Data consideration	Do you have all the necessary information captured for your analysis? 1. Do you have longitudinal data? 2. Which variables are unmeasured? Do you have proxies for them? 3. What is the accuracy of measurement? 4. What is the frequency of measurement (visit process)? 5. What is the temporal order of the variables? 6. Employ visualization tools to understand the complexity of the data if necessary

Li et al. *Curr Epidemiol Rep* 2017; 4(4): 288-297
Hernán & Robins. *Am J Epidemiol* 2016; 183(8):758-64

Data needed for implementation of IP weighting

Treatment

start date
end date
switch date
(changes of dose, change of frequency, if relevant)

Confounder

baseline confounders
time-varying: prognostic factors, comorbidities, concomitant treatments, determinants of adherence

Outcome

occurrence
time of occurrence
count
measurement

Specific considerations for database studies

- Data fit-for-purpose?
  - potential for unmeasured confounding
  - determinants of noncompliance
- Measurement error
  - date of discontinuation
- Visit process, time-varying monitoring
  - Non-equal intervals
- Model misspecification
  - Treatment, censoring model
- Positivity violations

Hernán et al. *Stat Methods Med Res* 2009;18(1):27–52

Conclusions

- Inverse probability weighting is a standardization approach
- Conventional methods provide biased estimates in the presence of treatment-confounder feedback
- Inverse probability weighted estimation of marginal structural models appropriately adjust for such complex time-varying confounding

For more information

- Causal Inference Methods for Patient Centered Outcomes Using Observational Data
  - http://cimpod.org/
- Inverse probability weighting
  - Hernán MA, Robins JM (2020). Chapter 12. Causal Inference: What If. Boca Raton: Chapman & Hall/CRC
- Marginal structural models
  - Robins, et al. Epidemiology 2000; 11:550-70
- Time-varying treatment
  - Robins JM, Hernán MA. Estimation of the causal effects of time-varying exposure. 2008. p. 553-99.
- Dynamic treatment strategies
  - Hernán et al, Basic Clin Pharmacol Toxicol 2006;98(3):237–42

Thank you!

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