G-ESTIMATION OF STRUCTURAL NESTED MODELS

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Learning objectives At the end of this lecture you will be able to

- Specify a structural nested model for a continuous outcome
- Conduct g-estimation to estimate the parameters of a structural nested model
- Describe the relation between g-estimation and instrumental variable estimation

- Key concepts
  - G-estimation
  - Structural nested mean models

Study population

- 1629 cigarette smokers
- Aged 25-74 years when interviewed in 1971-75 (baseline)
- Interviewed again in 1982
- Known sex, age, race, weight, height, education, alcohol use, and smoking intensity at both baseline and follow-up visits, and who answered the general medical history questionnaire at baseline

Key variables

Treatment A	Quit smoking between baseline and 1982 1: yes, 0: no
Continuous outcome Y	Weight gain, kg Weight in 1982 minus baseline weight Available for 1566 individuals
Baseline (pre-treatment) covariates	Age, sex, race, alcohol use, intensity of smoking, weight…
Censoring C	Missing weight in 1982 1: yes, 0: no

Formal version of causal question: First define the counterfactual means

if everybody had quit smoking

- $E[Y^{a=1}]$
- $Y^{a=1}$ is an individual's outcome under $a=1$

if nobody had quit smoking

- $E[Y^{a=0}]$
- $Y^{a=0}$ is an individual's outcome under $a=0$

Then the formal question is:

- What is the average causal effect $E[Y^{a=1}] - E[Y^{a=0}]$?
  - ignore censoring for now

Average causal effect can be defined marginally or conditionally

- Marginal: Effect in the entire population
  - $E[Y^{a=1}] - E[Y^{a=0}]$
  - Methods: Standardization, IP weighting of MSMs, Instrumental variable estimation (under homogeneity)
- Conditional: Effects in subsets defined by effect modifiers
  - $E[Y^{a=1}|V=v] - E[Y^{a=0}| V=v]$ for all values l
  - All of the above combined with stratification
- Conditional: Effects in subsets defined by *all* confounders
  - $E[Y^{a=1}|L=l] - E[Y^{a=0}|L=l]$ for all values l
  - Methods: stratification, outcome regression, and g-estimation of structural nested models

Footnote: Average causal effects can also be conditional on PS

- Just replace the individual covariates L by the propensity score PS
  - $E[Y^{a=1}|PS=p] - E[Y^{a=0}|PS=p]$ for all values p
  - Methods: stratification and outcome regression using PS rather than L

Some new terms

- Structural nested models:
  - Models with parameter(s) that can be interpreted as the magnitude of the causal effect conditional on covariates
- G-estimation:
  - Method to estimate the parameters of structural nested models

Plan for this lecture

A. Review
- Conditional exchangeability

B. Structural nested models

C. G-estimation

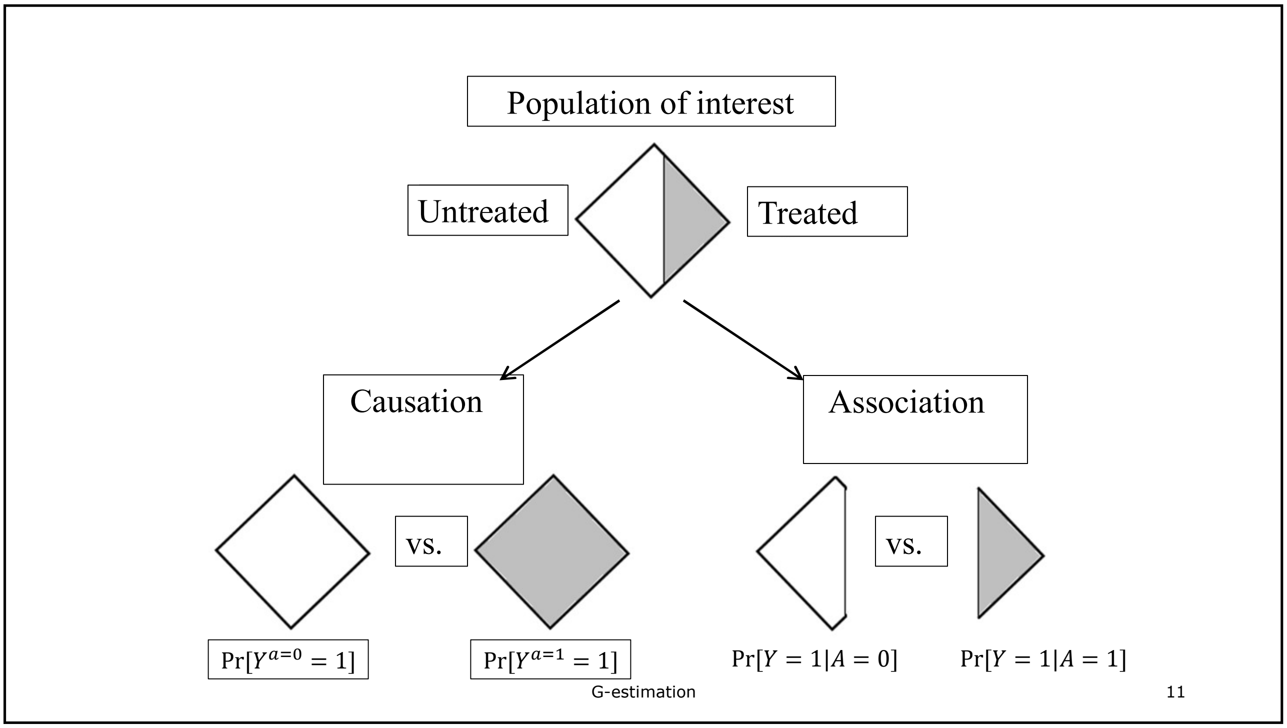
D. Adjustment for selection bias

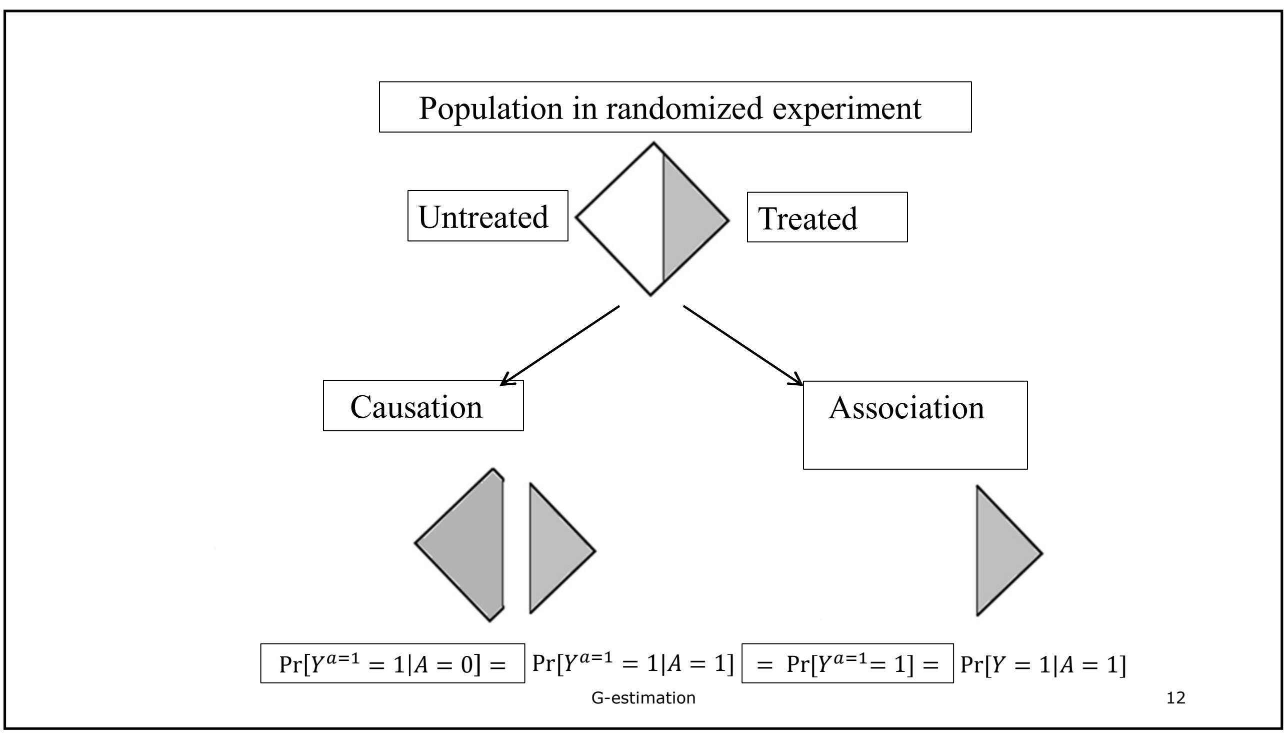
E. G-estimation and IV estimation

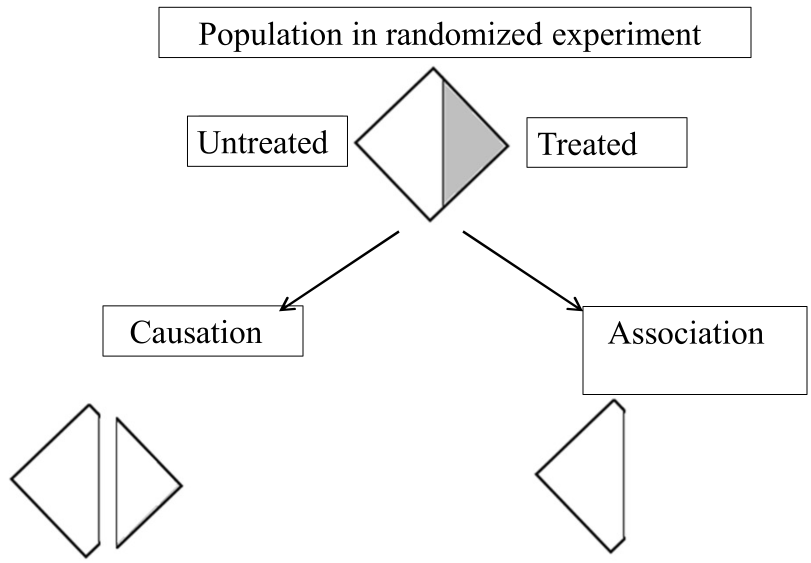
Conditional exchangeability
Formal definition

$$Y^a \coprod A | L = l \text{ for all a}$$

- Conditional exchangeability is equivalent to randomization within levels of the variables in L
  - e.g., smoking cessation occurred at random within levels of age, sex, race, smoking intensity, etc.
- Also known as the assumption of no unmeasured confounding


Population of interest
Untreated
Treated
Causation
Association
vs.
vs.
$\Pr[Y^{a=0} = 1]$
$\Pr[Y^{a=1} = 1]$
$\Pr[Y = 1|A = 0]$
$\Pr[Y = 1|A = 1]$
G-estimation
11


Population in randomized experiment
Untreated
Treated
Causation
Association
$\Pr[Y^{a=1} = 1|A = 0] =$
$\Pr[Y^{a=1} = 1|A = 1]$
$= \Pr[Y^{a=1} = 1] =$
$\Pr[Y = 1|A = 1]$
G-estimation
12



$\Pr[Y^{a=0} = 1 | A = 0] \; \boxed{= \Pr[Y^{a=0} = 1 | A = 1]} \; \boxed{= \Pr[Y^{a=0} = 1] =} \; \Pr[Y = 1 | A = 0]$

Clarification:
Average causal effect for continuous outcomes

- Only mean exchangeability is required
  - within levels of the covariates L, treated individuals would have had the same mean outcome as the untreated individuals had they being untreated, and vice versa
  - mean counterfactual outcome is the same in the treated and the untreated with the same value of L
- For dichotomous outcomes, exchangeability and mean exchangeability are the same

An equivalent expression of conditional exchangeability

$$Y^a \coprod A | L = l \text{ for all a}$$

$$\Pr[A = 1 | L = l, Y^{a=1}] = \Pr[A = 1 | L = l,\ Y^{a=0}]$$

$$= \Pr[A = 1 | L = l]$$

- That is, conditional on the measured covariates, the probability of treatment does not depend on the value of the counterfactual outcome

Dream with me for a minute

- Suppose conditional exchangeability given L holds
- Suppose we know the values of the counterfactual outcomes $Y^{a=1}$ and $Y^{a=0}$ for all subjects
- Suppose that we fit a logistic model for treatment that includes one of the counterfactual outcomes as a covariate
  - $\text{logit} \Pr[A=1|L, Y^a] = \alpha_0 + \alpha_1 Y^a + \alpha_2 L$
  - For either $a=0$ or $a=1$

What would be the value of the coefficient α_1 for $Y^{a=0}$?

$\text{logit Pr}[A = 1|L, Y^{a=0}] = \alpha_0 + \alpha_1 Y^{a=0} + \alpha_2 L$

0

Zero — 0%

Greater than zero — 0%

Less than zero — 0%

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What would be the value of the coefficient α_1 for $Y^{a=1}$?

$\text{logit Pr}[A = 1|L, Y^{a=1}] = \alpha_0 + \alpha_1 Y^{a=1} + \alpha_2 L$

0

Zero — 0%

Greater than zero — 0%

Less than zero — 0%

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We can test whether conditional exchangeability holds by fitting a propensity score model with counterfactual outcomes as covariates and then checking the value of α_1.

0

True

0%

False

0%

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Reminder:
Different notation, different concepts

- Conditional exchangeability of treated and untreated is represented by

$$Y^a \coprod A | L = l$$

- Conditional independence of treatment and outcome is represented by

$$Y \coprod A | L = l$$

Under the sharp null, these two statements are expected to be true:

$Y^a \perp\!\!\!\perp A | L = l$

$Y \perp\!\!\!\perp A | L = l$

where L is the vector of measured variables in our study

0

True

0%

False

0%

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Plan

A. Review
- Conditional exchangeability assumption

B. Structural nested models

C. G-estimation

D. Adjustment for selection bias

E. G-estimation and IV estimation

Average causal effect within levels of the confounders

- These conditional effects are represented by
  - $\mathrm{E}[Y^{a=1}|L=l] - \mathrm{E}[Y^{a=0}|L=l]$ for all values l
- Or, equivalently
  - $\mathrm{E}[Y^{a=1} - Y^{a=0}|L=l]$
- Outcome regression
  - models for the conditional mean outcome $\mathrm{E}[Y^{a}|L=l] = \mathrm{E}[Y|A=a, L=l]$
- Structural nested models
  - models for the conditional average effect $\mathrm{E}[Y^{a=1} - Y^{a=0}|L=l]$

Outcome regression One dichotomous confounder L

- If effect modification

$$\mathrm{E}[Y|A=a, L=l] = \beta_0 + \beta_1 A + \beta_2 AL + \beta_3 L$$

  - Effect in stratum $L=0$: β_1
  - Effect in stratum $L=1$: $\beta_1 + \beta_2$

- If no effect modification

$$\mathrm{E}[Y|A=a, L=l] = \beta_0 + \beta_1 A + \beta_3 L$$

  - Effect in all strata : β_1

Structural nested mean model
One dichotomous confounder L

- ☐ If effect modification

$$E[Y^a - Y^{a=0} | A=a, L=l] = \beta_1\, a + \beta_2\, aL$$

  - Effect in stratum L=0 : β_1
  - Effect in stratum L=1 : $\beta_1 + \beta_2$

- ☐ If no effect modification

$$E[Y^a - Y^{a=0} | A=a, L=l] = \beta_1\, a$$

  - Effect in all strata : β_1

Structural nested models have fewer parameters than outcome regression models

- ☐ Because SNMs model the causal effect directly
  - That is, the difference in mean outcomes rather than the mean outcomes
- ☐ No intercept and no parameters for the confounders
- ☐ Fewer opportunities of having bias due to model misspecification

Structural nested models vs. Marginal structural models

- For time-varying treatments, structural nested models allow product terms between treatment and time-varying covariates
  - marginal structural models do not
- For point treatments (like in our data), both classes of models can be used
  - MSMs estimate marginal effect or conditional effects, SNMs estimate conditional effects only

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G-estimation

- The procedure to estimate the parameters of structural nested models
- Next we describe, in 5 steps, g-estimation to estimate β_1 in a structural nested mean model
  - $\mathrm{E}[Y^a - Y^{a=0} | A=a, L=l] = \beta_1 a$
  - under no effect modification by any confounders
    - Aside: in the presence of EM, there are multiple parameters to be identified: $\mathrm{E}[Y^a - Y^{a=0} | A = a, L = l] = \beta_1 a + \beta_2 aL$

Step 1: Mean model transformed into an individual-level, rank-preserving model

$$Y^a - Y^{a=0} = \psi_1 a$$

- This step is not really necessary for g-estimation but simplifies teaching the method
- This rank-preserving model has stronger assumptions than the mean model
- The estimate of ψ_1 obtained via g-estimation for the rank-preserving model is also valid for the mean model

This model assumes constant treatment effect
$Y^a - Y^{a=0} = \psi_1 a$
That is, the individual causal effect ψ_1 is the same for all individuals and equal to the average causal effect β_1

0

True
0%

False
0%

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Step 2: Some rearranging

$$Y^{a=0} = Y^a - \psi_1\, a$$

- We'll see why later
- Still too many unknowns in the model

Step 3: Model linked to the observed data

$$Y^{a=0} = Y - \psi_1 A$$

- The observed outcome Y equals the counterfactual outcome Y^a when a is equal to the observed treatment A
  - By consistency of counterfactuals

- How can we validly estimate ψ_1?

Step 4: Suppose that a friend of yours knows the value of ψ_1

- But they only tell you that ψ_1 is one of the following
  - $\psi^\dagger = -1.11$, $\psi^\dagger = 0$, or $\psi^\dagger = 3.46$
- How can you identify the true value ψ_1 among the 3 possible values $\psi^\dagger$?
- For each subject, compute $H(\psi^\dagger) = Y - \psi^\dagger A$ for each of the three possible values $\psi^\dagger$
- The newly created variables $H(-1.11)$, $H(0)$, and $H(3.46)$ are candidate counterfactuals
  - One of them is the counterfactual outcome $Y^{a=0}$
  - $H(\psi^\dagger) = Y^{a=0}$ if $\psi^\dagger = \psi_1$

Computing $H(\psi^{\dagger})$ from our observed data

$Y^{a=0} = Y - \psi_1 A$

$H(\psi^{\dagger}) = Y - \psi^{\dagger} A$

Recall that ψ_1 is one of the following: $\psi^{\dagger} = -1.11$, $\psi^{\dagger} = 0$, or $\psi^{\dagger} = 3.46$

ID	A	L	Y
1	0	0	3.5
2	1	1	1.2
3	1	1	2.7
…	…	…	…

Computing $H(\psi^{\dagger})$ from our observed data

$Y^{a=0} = Y - \psi_1 A$

$H(\psi^{\dagger}) = Y - \psi^{\dagger} A$

Recall that ψ_1 is one of the following: $\psi^{\dagger} = -1.11$, $\psi^{\dagger} = 0$, or $\psi^{\dagger} = 3.46$

ID	A	L	Y	$H(\psi^{\dagger}=-1.11)$
1	0	0	3.5	3.5 – (-1.11)(0) = 3.5
2	1	1	1.2	1.2 – (-1.11)(1) = 2.31
3	1	1	2.7	2.7 – (-1.11)(1) = 3.81
…	…	…	…	…

Computing $H(\psi^\dagger)$ from our observed data

$Y^{a=0} = Y - \psi_1 A$

$H(\psi^\dagger) = Y - \psi^\dagger A$

Recall that ψ_1 is one of the following: $\psi^\dagger = -1.11$, $\psi^\dagger = 0$, or $\psi^\dagger = 3.46$

ID	A	L	Y	$H(\psi^\dagger$=-1.11)	$H(\psi^\dagger$=0)
1	0	0	3.5	3.5 – (-1.11)(0) = 3.5	3.5 – 0(0) = 3.5
2	1	1	1.2	1.2 – (-1.11)(1) = 2.31	1.2 – 0(1) = 1.2
3	1	1	2.7	2.7 – (-1.11)(1) = 3.81	2.7 – 0(1) = 2.7
…	…	…	…	…	…

Computing $H(\psi^\dagger)$ from our observed data

$Y^{a=0} = Y - \psi_1 A$

$H(\psi^\dagger) = Y - \psi^\dagger A$

Recall that ψ_1 is one of the following: $\psi^\dagger = -1.11$, $\psi^\dagger = 0$, or $\psi^\dagger = 3.46$

ID	A	L	Y	$H(\psi^\dagger$=-1.11)	$H(\psi^\dagger$=0)	$H(\psi^\dagger$=3.46)
1	0	0	3.5	3.5 – (-1.11)(0) = 3.5	3.5 – 0(0) = 3.5	3.5 – 3.46(0) = 3.5
2	1	1	1.2	1.2 – (-1.11)(1) = 2.31	1.2 – 0(1) = 1.2	1.2 – 3.46(1) = -2.26
3	1	1	2.7	2.7 – (-1.11)(1) = 3.81	2.7 – 0(1) = 2.7	2.7 – 3.46(1) = -0.76
…	…	…	…	…	…	…

Step 5: Test all the candidates, choose the true value

- To identify which candidate $H(\psi^{\dagger})$ is the counterfactual $Y^{a=0}$, fit 3 models

$$\text{logit } \Pr[A=1|L, H(\psi^{\dagger})] = \alpha_0 + \alpha_1 H(-1.11) + \alpha_2 L$$
$$\text{logit } \Pr[A=1|L, H(\psi^{\dagger})] = \alpha_0 + \alpha_1 H(0) + \alpha_2 L$$
$$\text{logit } \Pr[A=1|L, H(\psi^{\dagger})] = \alpha_0 + \alpha_1 H(3.46) + \alpha_2 L$$

- Remember the assumption of conditional exchangeability?
  - and its relation to the parameter α_1 in the model

$$\text{logit } \Pr[A=1|L, Y^{a=0}] = \alpha_0 + \alpha_1 Y^{a=0} + \alpha_2 L$$

Which candidate $H(\psi^{\dagger})$ is equal to the counterfactual outcome?
Recall: $\text{logit } \Pr[A=1|L, H(\psi^{\dagger})] = \alpha_0 + \alpha_1 H(\psi^{\dagger}) + \alpha_2 L$

0

Come on. This is hopeless. 0%

The candidate $H(\psi^{+})$ with α_1=0 0%

The candidate $H(\psi^{+})$ with α_1>0 0%

The candidate $H(\psi^{+})$ with α_1<0 0%

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Which $\psi^\dagger$ is equal to the causal parameter ψ_1?
Recall: $\text{logit Pr}[A = 1|L, H(\psi^\dagger)] = \alpha_0 + \alpha_1 H(\psi^\dagger) + \alpha_2 L$

0

(A) The ψ^+ with α_1=0 when used to compute the candidate $H(\psi^+)$
0%

(B) The ψ^+ with α_1>0 when used to compute the candidate $H(\psi^+)$
0%

(C) The ψ^+ with α_1<0 when used to compute the candidate $H(\psi^+)$
0%

Done: That was g-estimation

- Search over all possible values of $\psi^\dagger$ until you find one that results in $H(\psi^\dagger)$ with α_1=0
  - The candidate $H(\psi^\dagger)$ with α_1=0 is the counterfactual and the corresponding $\psi^\dagger$ is the true value ψ_1
- In practice, use more sophisticated search methods
  - Need some additional coding
- Sometimes the estimator has closed form
  - No need to search or optimize
  - e.g., linear models like the ones considered here

To get the 95% confidence interval for ψ_1

- Invert the test for α_1=0
  - Find the set of values of $\psi^\dagger$ that result in a *P*-value>0.05 when testing for α_1=0
  - The 95% confidence limits are the limits of that set of values
  - Can use Wald test, Score test…
- Bootstrapping

Back to our data: Point estimate for ψ_1

- Point estimate: 3.5 *See gestimation.R, lines 19-42*
  - Value of $\psi^\dagger$ that produces the value of α_1 closest to 0
  - Or, equivalently, p-value closest to 1
- Adjusting for baseline covariates:
  - Sex, age, race, education, smoking intensity, duration of smoking, exercise, active lifestyle, baseline weight

95% confidence interval for estimate of ψ_1

- 95% CI: 2.6, 4.4 approx
- By inversion of the test: values of $\psi^\dagger$ for which the test for α_1=0 has *P*-value>0.05 in model
  - We might not be able to find the value of $\psi^\dagger$ that corresponds to exactly p-value=0.05
  - Select next closest $\psi^\dagger$ with p-value<0.05 to give us a (conservative) 95% CI

See gestimation.R, lines 19-42

ψ_1	**p-value**
2.5	0.028
2.6	0.049
2.7	0.081
…	…
3.4	0.888
3.5	0.929
3.6	0.750
…	…
4.2	0.091
4.3	0.055
4.4	0.032

More efficient g-estimators exist (narrower 95% CIs)

- Doubly-robust estimators are more efficient
  - Require a model for the mean of $H(\psi^\dagger)$ given the confounders L
- G-estimation based on functions of $H(\psi^\dagger)$ may be more efficient
  - e.g., we could use the model

$$\text{logit Pr}[A=1|L, H(\psi)] = \alpha_0 + \alpha_1 [H(\psi^\dagger)]^3 + \alpha_2 L$$

Causal questions of interest

1. What is the effect of smoking cessation on weight gain?

2. What is the effect of smoking cessation on risk of death? ⇨

- G-estimation cannot be generally used with logistic models, particularly in the time-varying setting
- Can use log models under rare disease assumption

Plan

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Key variables

Treatment A	Quit smoking between baseline and 1982 1: yes, 0: no
Continuous outcome Y	Weight gain, kg Weight in 1982 minus baseline weight Available for 1566 individuals
Baseline (pre-treatment) covariates	Age, sex, race, alcohol use, intensity of smoking, weight…
Censoring C	Missing weight in 1982 1: yes, 0: no

Causal question

- Estimate the counterfactual mean weight gain if nobody's outcome had been censored
  - $E[Y^{a=1,c=0}]$
  - $E[Y^{a=0,c=0}]$
- Estimate the average causal effect
  - $E[Y^{a=1,c=0}] - E[Y^{a=0,c=0}]$
- Conditional on confounders when using g-estimation

G-estimation + IP weighting

- G-estimation to adjust for confounding
- IP weighting to adjust for selection bias

- First, use IP weighting to estimate IP weights W^C
  - The weights create a pseudo-population without selection bias by measured covariates
  - i.e., no arrows from *L* and *A* into *C*

G-estimation + IP weighting

- Second, use g-estimation to adjust for confounding in the pseudo-population
  - Find the value of ψ that produces the value of α_1 closest to 0 in the IP weighted model

    $\text{logit } \Pr[A=1|L, H(\psi^\dagger)] = \alpha_0 + \alpha_1 H(\psi^\dagger) + \alpha_2 L$
  - using estimates of the weights W^C

- Need to use robust variance estimator
  - Conservative 95% confidence interval

Back to our data: Point estimate for ψ_1

- Point estimate: 3.4 *See gestimation.R, lines 44-104*
- 95% CI: 2.5, 4.5 approx
- Adjusting for baseline covariates:
  - Sex, age, race, education, smoking intensity, duration of smoking, exercise, active lifestyle, baseline weight

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G-estimation to consistently estimate the parameter ψ_1

- From the model $Y^{a=0} = Y - \psi_1 A$
- Compute $H(\psi^\dagger) = Y - \psi^\dagger A$
  - for a range of possible values $\psi^\dagger$
  - The variables $H(\psi^\dagger)$ are candidate counterfactuals
  - One of them is the counterfactual outcome $Y^{a=0}$
    - $H(\psi^\dagger) = Y^{a=0}$ if $\psi^\dagger = \psi_1$
- We just need to identify the value $\psi^\dagger$ that makes $H(\psi^\dagger) = Y^{a=0}$

How to identify the value $\psi^\dagger$ that makes $H(\psi^\dagger) = Y^{a=0}$?

- We said that **IF** conditional exchangeability holds

$$Y^a \coprod A | L = l$$

- Then ψ_1 is the value $\psi^\dagger$ that makes α_1=0 in the model
  $\text{logit } \Pr[A=1|L, H(\psi^\dagger)] = \alpha_0 + \alpha_1 H(\psi^\dagger) + \alpha_2 L$
- But there is another way
  - If we have an instrumental variable Z

How to identify the value of ψ that makes $H(\psi^\dagger) = Y^{a=0}$?

- **By definition** of IV, (unconditional) exchangeability is expected to hold

$$Y^a \coprod Z$$

- Then the true value of ψ is the one that makes $\alpha_1=0$ in the model $\text{logit}\ \Pr[Z=1|H(\psi)] = \alpha_0 + \alpha_1 H(\psi^\dagger)$

IV estimation as a particular case of g-estimation

- G-estimation based on the IV is mathematically equivalent to the standard IV estimand
  - Defined in last week's notes
- The standard IV estimator consistently estimates the parameter ψ^* from our structural mean model
  - Under instrumental assumptions (i)-(iii) and assumption of no additive effect modification (iv)
  - See Chapter 16 of *Causal Inference: What If.*

Within the g-estimation framework, IV becomes a more general method that allows

- Use of baseline covariates
  - To increase efficiency
    - Especially if covariates are strongly associated with Y and weakly associated with A
  - To address violations of condition (iii)
- Use of multiplicative models and assumption of no multiplicative effect modification (iv)
- Extensions to time-varying treatments and time-varying instruments, survival analyses

Conclusion

- We have studied (essentially) all available methods to adjust for confounding
- Of those, IP weighting, standardization/g-formula, and g-estimation can be generally used with time-varying treatments

IP weighting, standardization, or g-estimation?

- Why do we have to choose?
  - If possible, use all methods separately and doubly-robust versions when available
  - Similar effect estimates increase our confidence in the results
  - Different effect estimates will make us examine our modeling assumptions
- See EPI207 for more about these methods

Readings

- *Causal Inference: What If*. Chapter 14

Progress report

1. Introduction to modeling
2. Stratified analysis:
   - Outcome regression
   - Propensity scores
3. Standardization
4. Inverse probability weighting
   - Marginal structural models
5. Instrumental variable estimation
6. G-estimation
7. Causal survival analysis