Inverse Probability of Autopsy Weighting – Moving Toward Best Practices

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Outline

- Introduce counterfactual theory of causal inference
- Introduce inverse probability of treatment weighting
- Introduce inverse probability of censoring weighting
- Review use of inverse probability of autopsy weighting in the literature
- Make recommendations for best practices

Intuitive definition of cause

Alice finds a mysterious bottle labelled "Drink Me." Naturally, she consumes the unknown substance right away, as you do. Alice shrinks into tiny Alice.

Had Alice not consumed the substance, **all other things being equal**, she would not be tiny.

Did the "Drink Me" substance have a causal effect on Alice's size?

Counterfactual Theory

- We define the relationship between an exposure/treatment/intervention and an outcome as "causal" when the potential outcomes under the treatment are not equal

- Potential outcomes may be written as $Y^{A=a}$, which is interpreted as the value of Y when treatment takes the value "a"

- Thus, $Y^{A=a} \neq Y^{A\neq a}$ is interpreted to mean there is a causal effect of treatment A on outcome Y

Fundamental problem of causal inference

- We can only observe one potential outcome for any individual, the one corresponding to their observed treatment (SUTVA)

- We cannot evaluate $Y^{A=a} \neq Y^{A\neq a}$ for any individual

G-Methods

- Methods based on counterfactual theory, rely on **strong** identifiability assumptions
  - Consistency (If A_i=a then $Y_i^a = Y^{A_i} = Y_i$)
  - Exchangeability ($Y^a \perp A$)
  - Positivity (Pr[A=a]>0)
  - *No model misspecification*
  - *No measurement error*

Average causal effects

- Thus, $E[Y^{a=1} - Y^{a=0}]$ cannot be evaluated, but

- $E[Y^{a=1}] - E[Y^{a=0}]$ is equal to

  $E[Y^{a=1} - Y^{a=0}]$

- When identifiability conditions hold, $E[Y^{a=1}] - E[Y^{a=0}] =$

  $E[Y|A=1] – E[Y|A=0]$

Conditional Exchangeability

– Exchangeability ($Y^a \perp A \mid L$)

$$E[Y^{a=1}] - E[Y^{a=0}] =$$

$$E[Y \mid A=1, L=\ell] - E[Y \mid A=0, L=\ell]$$

Inverse probability of treatment weighting

- Addresses unequal probabilities of treatment in observational studies
- Observations are weighted by their conditional (on L) probability of receiving treatment A=a
- Unlike prediction modeling, the goal is not to find the model with the smallest residual; goal is identify the set L

IPT Weights

- Observations are weighted by the inverse of the conditional probability of their observed treatment: $W^A=1/(f(A|L)$
- Stabilized weights are recommended: $SW^A=f(A)/(f(A|L)$

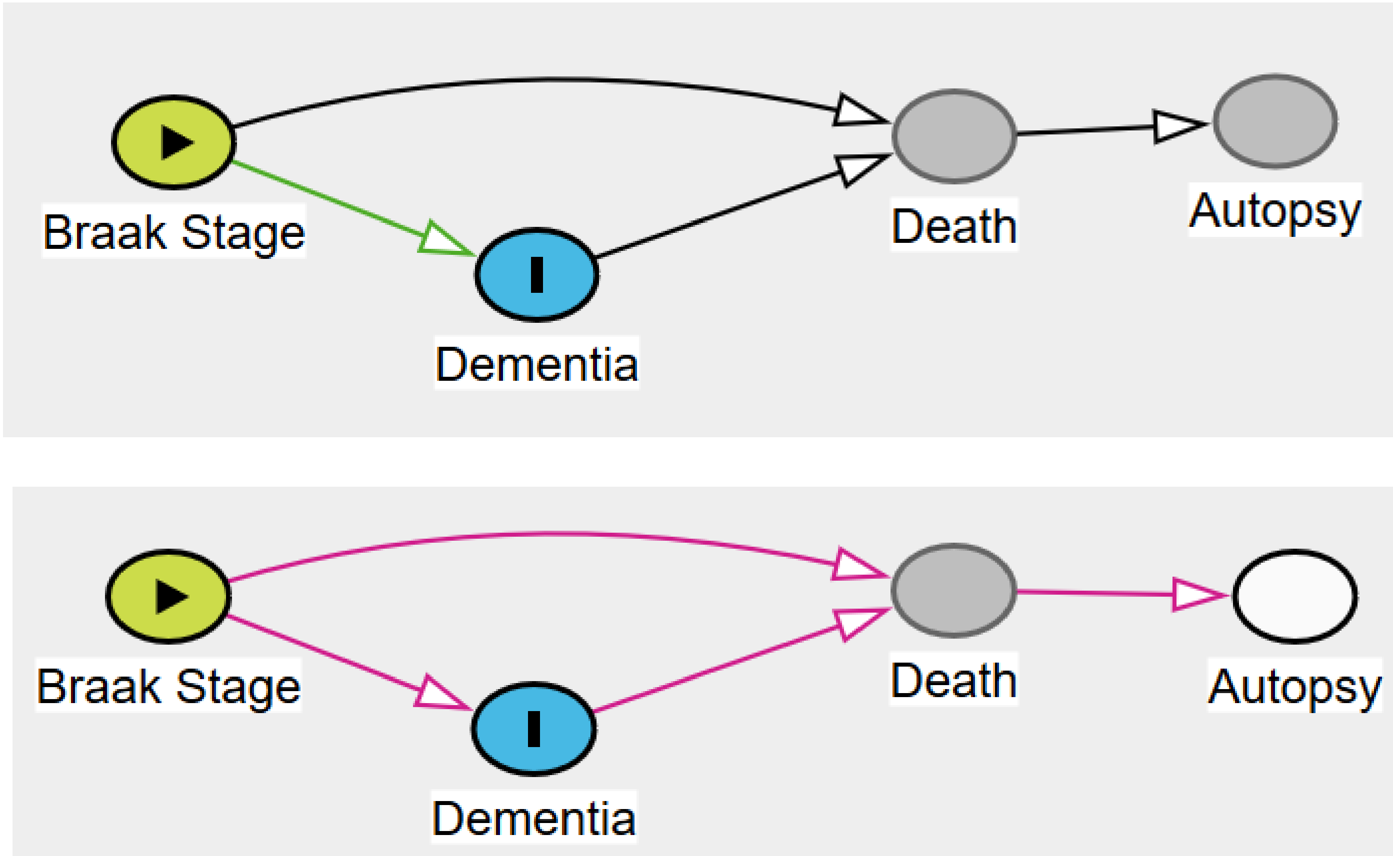
Pseudo-population

- By weighting, a pseudo-population is produced: every person is exposed, and every person is unexposed. Thus, if $Y^a \perp A | L$, the association can be interpreted as causal.

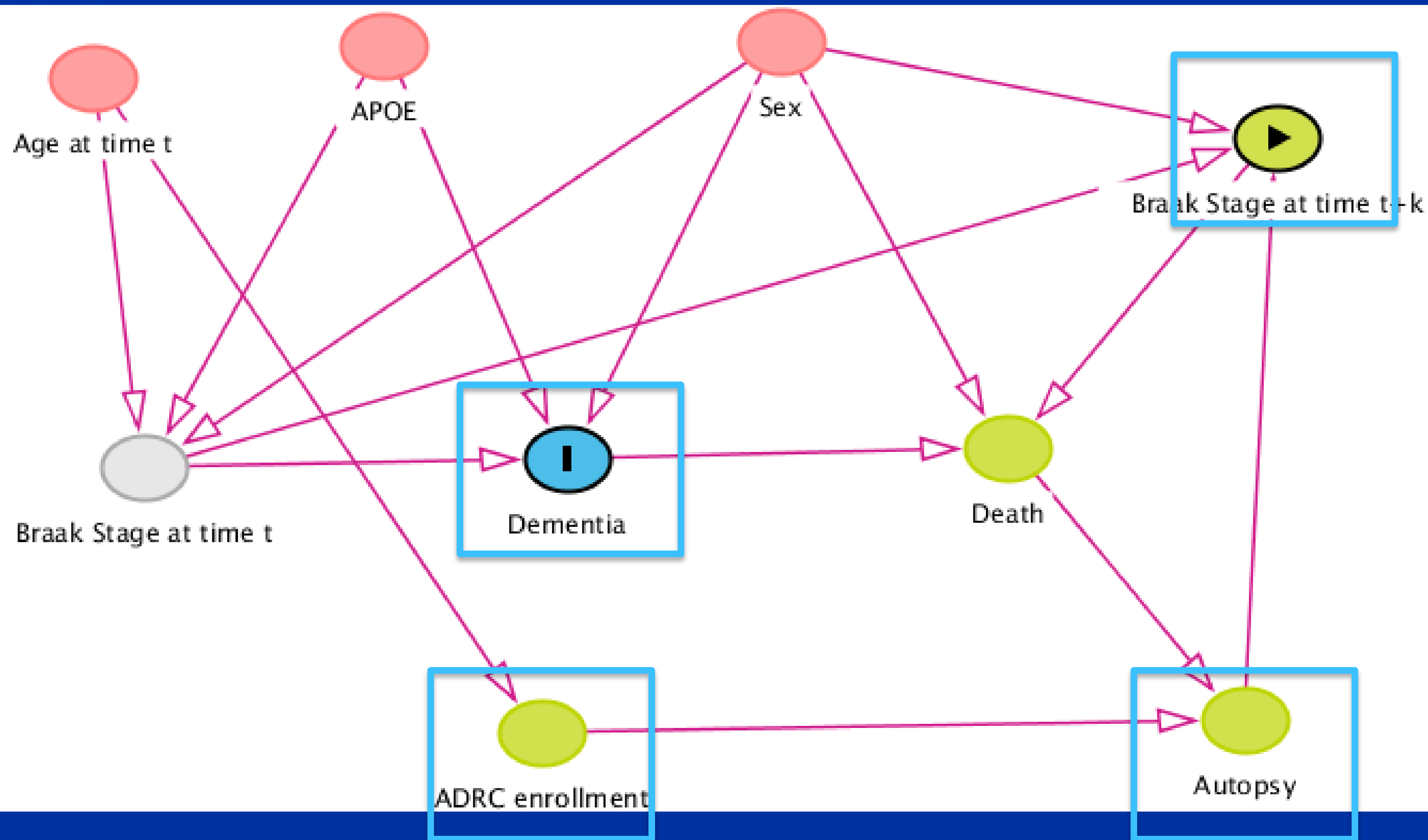
- Stabilization ensures the pseudo-population is roughly the same size as the original population.

Selection Bias

- In addition to confounding, observational studies are plagued by selection biases
- Occurs when we condition on a common effect of two variables, one of which is the treatment or is associated with the treatment, <u>and</u> one of which is the outcome or associated with the outcome



(Over-simplified) causal diagram depicting hypothesized causal relation between Braak stage and dementia; since Braak stage cannot be observed without autopsy, we are forced to condition on autopsy, which introduces selection bias



(Still over-simplified) causal diagram depicting hypothesized causal relation between Braak stage and dementia status

IPCW

- Goal is either:
  - to create a pseudo-population that represents the entire uncensored original population *before* censoring
  - or, to create a pseudo-population the same size as the uncensored population, but without selection bias (stabilized IPCW)

- Often, the causal estimand we are really interested in is:

  $E[Y^{a=1,c=0}] - E[Y^{a=0,c=0}] =$

  $E[Y|C=0,A=1,L=\ell] -$

  $E[Y|C=0,A=0,L=\ell]$

- In our case, we want to know what the association is in a world where either everyone is autopsied, or autopsy occurs at random

Joint Weights

- We can address confounding and selection bias by computing treatment weights and censoring weights, and taking their product

- IPW is a powerful analytic tool!

With great power…

comes great responsibility

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IPW Best Practices

- **IPW is only valid if the assumptions hold**
- Assess consistency assumption
  - Outside the data; based on expert knowledge
- Assess exchangeability
  - Directed acyclic graphs
  - Examine distribution of weights
  - Evaluation of weighted data for balance
- Assess positivity
  - Based on the data; expert knowledge

Inverse Probability of Autopsy Weights

- Introduced by Haneuse et al., 2009
- Applied IPAW to autopsied ACT participants
- Used in at least 8 published studies since, usually ACT or NACC data

IPAW in the Literature

- Papers that have applied IPAW to date have not provided explicit evaluation the identifiability conditions
- Although the weighting model is usually specified, no justification for the model is provided
- The distribution of weights is not examined; rather, the weighting model results are provided
- Nature of the weights (stabilized or unstabilized) is not mentioned

Recommendations for using/reviewing IPAW

- Specify variables in the weighting model; provide rationale
- State whether weights are stabilized; provide rationale
- Don't report measure of association results from the weighting model
- Evaluate the identifiability conditions for IPW
- Evaluate the distribution of weights
  - Means for stabilized IPAW should be ~1.00

Summary

- The nature of clinico-pathologic studies means we must condition on a common effect of the exposure and outcome, which induces selection bias
- IPAW is appealing tool to mitigate this selection bias
- But, IPAW is based on very strong assumptions that must be evaluated each time it is used
- Careful assessment and reporting of these assumptions will increase the rigor of our research

Thank you!

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