Welcome to the Sentinel Innovation and Methods Seminar Series

The webinar will begin momentarily

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Note: closed-captioning for today's webinar will be available on the recording posted at the link above.

Sentinel

An Introduction to Negative Control and Proximal Causal Learning

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Acknowledgment

Yifan Cui
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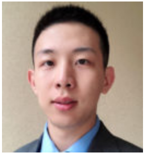
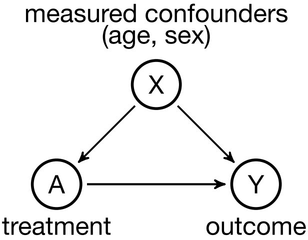


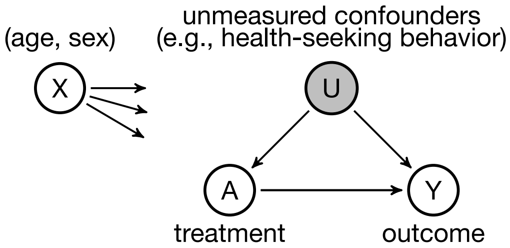
Andrew Ying
U of Pennsylvania

The "randomized" scenario in causal inference



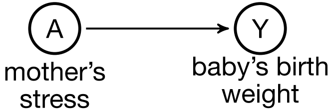
- Estimand: the average treatment effect ATE = $E[Y(1)] - E[Y(0)]$
- Key identification assumption: no unmeasured confounding
  - "Randomized" within each stratum of X
  - Not empirically verifiable

Unmeasured confounding: a threat to causal inference



- Hereafter all arguments are made implicitly conditional on X
- Unmeasured confounders *U*
  - At the center of much skepticism about observational studies
  - The instrumental variable (IV) methods require randomization
- A hidden treasure: negative control variable

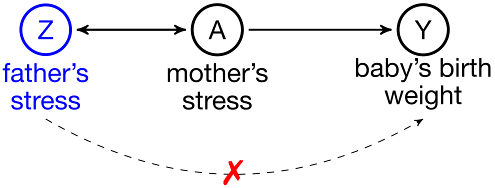
Does stress during pregnancy affect birth weight?



- Observational study on effect of mother’s stress on birth weight

Davey Smith 2008, 2012

Does stress during pregnancy affect birth weight?



- Observational study on effect of mother's stress on birth weight
- No effect from father's stress after adjusting for mother's stress
    - Nonzero effect of father's stress indicates hidden bias

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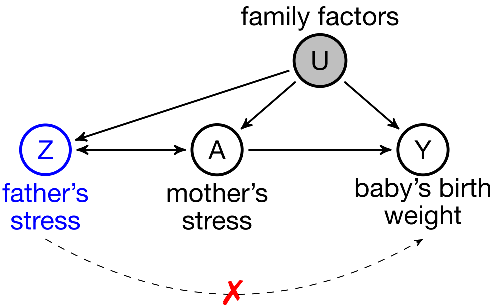
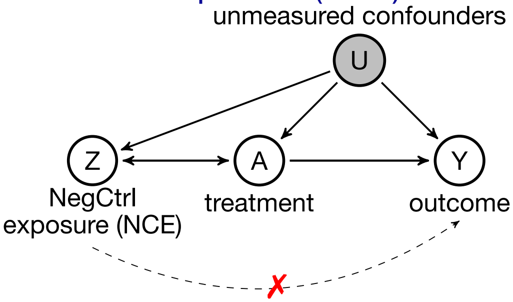
Does stress during pregnancy affect birth weight?



- Observational study on effect of mother's stress on birth weight
- No effect from father's stress after adjusting for mother's stress
    - Nonzero effect of father's stress indicates hidden bias
- Family factors could be an unmeasured confounder

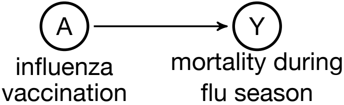
Davey Smith 2008, 2012

Negative control exposure (NCE)



- Z is an NCE if $\boxed{Y(a,z) = Y(a) \text{ and } Z \perp\!\!\!\perp Y(a) \mid U}$
  - (1) It does not causally affect Y
  - (2) It is associated with $Y(a)$ only through U

Does flu shot prevent 50% death in the elderly?



- Observational study on flu vaccine effectiveness
  - found 50% reduction in risk of all cause mortality during winter

Jackson et al. 2006; also considered using injury/trauma hospitalization to detect unmeasured confounding bias

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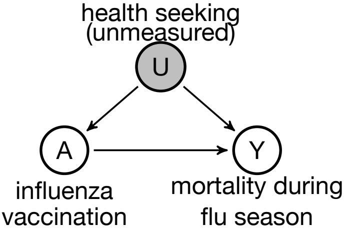

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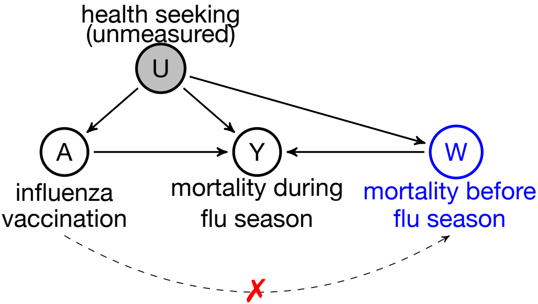
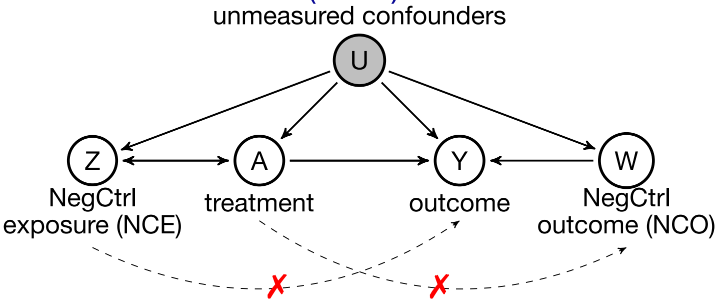
Does flu shot prevent 50% death in the elderly?



- Observational study on flu vaccine effectiveness
    - found 50% reduction in risk of all cause mortality during winter
- Potential unmeasured confounding by health seeking behavior
- Use mortality before flu season to detect confounding bias

Jackson et al. 2006; also considered using injury/trauma hospitalization to detect unmeasured confounding bias

Negative control outcome (NCO)



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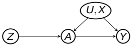
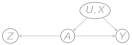
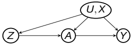
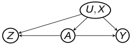
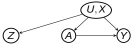
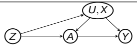
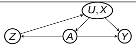
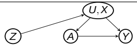
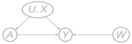
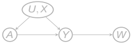
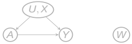
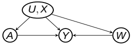
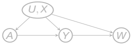
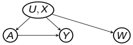
  (1) It does not causally affect Y
  (2) It is associated with $Y(a)$ only through U
- W is an NCO if $\boxed{W(a,z) = W \text{ and } W \perp\!\!\!\perp (A,Z) \mid U}$
  (1) It is not causally affected by A
  (2) It is associated with (A,Z) only through U

More examples that encode the NC assumptions

<table>
<tr><th colspan="4">Examples of NCE</th></tr>
<tr><td></td><td>$Z \to A$ (pre-treatment)</td><td>$A \to Z$ (post-treatment)</td><td>$Z \perp\!\!\!\perp A$</td></tr>
<tr><td>No arrow between U and Z (may violate U-comparability)</td><td>Instrumental variable (IV)
</td><td></td><td></td></tr>
<tr><td>$U \to Z$</td><td>Invalid IV
</td><td>Post-treatment proxy of U
</td><td>Proxy of U
</td></tr>
<tr><td rowspan="2">$Z \to U$</td><td colspan="3">May violate Assumptions if there is $W \to U$</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><th colspan="4">Examples of NCO</th></tr>
<tr><td></td><td>$W \to Y(a)$</td><td>$Y(a) \to W$</td><td>$Y(a) \perp\!\!\!\perp W \mid (U,X)$</td></tr>
<tr><td>No arrow between U and W (violate U-comparability)</td><td></td><td>Violate NCO definition
</td><td></td></tr>
<tr><td>$U \to W$</td><td></td><td>Violate NCO definition
</td><td></td></tr>
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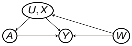
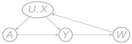
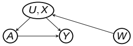
<tr><td></td><td>Violate NCO definition
</td><td></td></tr>
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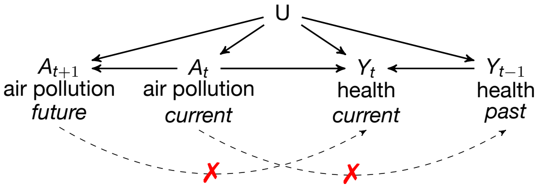
Examples of Z, A, U and W, Y, U relationships. Grey indicates violation of assumptions. (Shi, Miao, and Tchetgen 2020)

Negative controls are widely available

- Air pollution and health outcomes: the future $\not\Rightarrow$ the past [1]
  - NCE = future exposure; NCO = past outcome



- Genetics research and batch effect [2]
  - Use control genes to remove unwanted variation
- Drug/vaccine comparative effectiveness and safety [3]
  - Use secondary treatments or outcomes in electronic health records
  - Can combine multiple binary negative control variables

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[1] Flanders et al. 2011 [2] Gagnon-Bartsch and Speed 2012 [3] Schuemie et al. 2014

Detection, reduction, and correction of bias

Limitation: application focused on bias detection; methods may require strong assumptions

Detect	[1]: Time-series study.
	[2]: invalid NCE.
Reduce	[3]: Time-series study.
	[4]: Standardized mortality ratio in occupational cohort study.
	[5]: Drug–outcome pairs with no plausible causal effect.
Correct	[6]: Time-to-event outcome.
	[7]: Generalized difference-in-differences using NCO.
	[8]: Calibration using NCO.
	[9]: Removing unwanted variation in gene-expression analysis.
	[10]: Nonparametric identification using double negative control.

[1] Flanders et al. 2011.

[2] Davey Smith 2012; Weisskopf, Tchetgen Tchetgen, and Raz 2016.

[3] Flanders, Strickland, and Klein 2017; Miao and Tchetgen Tchetgen 2017.

[4] Richardson et al. 2015.

[5] Schuemie et al. 2014, 2018.

[6] Richardson et al. 2014; Tchetgen Tchetgen, Sofer, and Richardson 2015.

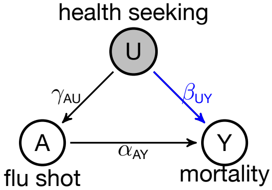
[7] Sofer et al. 2016; Glynn and Ichino 2019.

[8] Tchetgen Tchetgen 2014.

[9] Gagnon-Bartsch and Speed 2012; Jacob, Gagnon-Bartsch, and Speed 2016; Wang et al. 2017.

[10] Miao, Shi, and Tchetgen Tchetgen 2018; Miao, Geng, and Tchetgen Tchetgen 2018; Shi, Miao, and Tchetgen Tchetgen 2020.

Intuition behind identification



- Confounding bias is a product of *U*-*A* and *U*-*Y* association ($\gamma_{AU}\beta_{UY}$)

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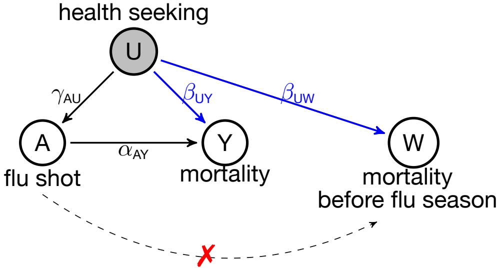

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  - *A*-*W* association is a product of *U*-*A* and *U*-*W* association ($\gamma_{AU}\beta_{UW}$)
  - Problem solved if *U*-*Y* association = *U*-*W* association

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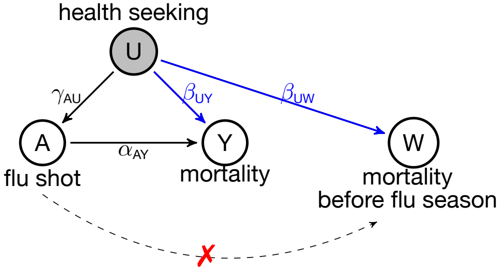

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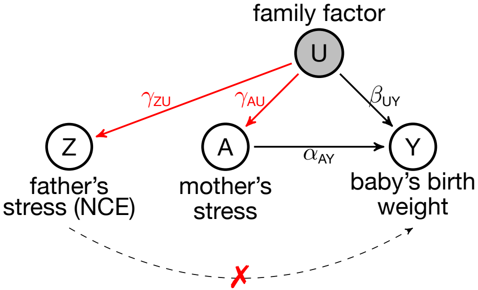
  - Problem solved if *U*-*Y* association = *U*-*W* association
- Regress $\underbrace{Y \text{ on } A,}_{\alpha_{AY}+\gamma_{AU}\beta_{UY}}$ and $\underbrace{W \text{ on } A}_{\gamma_{AU}\beta_{UW}}$, then ATE = diff in coefs of *A*
- A special case: the difference-in-difference method[11]

[11] Richardson et al. 2014, 2015; Tchetgen Tchetgen, Sofer, and Richardson 2015; Sofer et al. 2016.

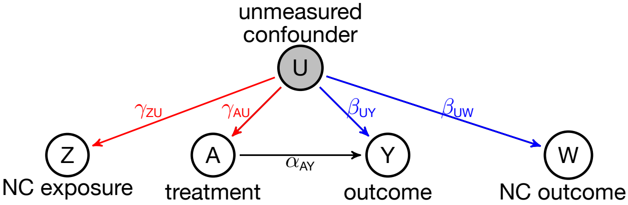
Intuition behind identification



- Confounding bias is a product of *U*-*A* and *U*-*Y* association ($\gamma_{AU}\beta_{UY}$)
  - *Z*-*Y* association is a product of *U*-*Z* and *U*-*Y* association ($\gamma_{ZU}\beta_{UY}$)
  - Problem solved if *U*-*A* association = *U*-*Z* association
- Regress $\underbrace{Y \text{ on } A}_{\alpha_{AY} + \gamma_{AU}\beta_{UY}}$ and $\underbrace{Z}_{\gamma_{ZU}\beta_{UY}}$, then ATE = diff in coefs of *A* and *Z*
- A special case: air pollution studies[12]

[12] Flanders et al. 2011; Flanders, Strickland, and Klein 2017; Miao and Tchetgen Tchetgen 2017.

Intuition behind identification



- What if $\beta_{UY} \neq \beta_{UW}$ and $\gamma_{AU} \neq \gamma_{ZU}$?
  - *A*-*W* association ($\gamma_{AU}\beta_{UW}$) recovers the confounding bias ($\gamma_{AU}\beta_{UY}$) up to a scale $\frac{\beta_{UY}}{\beta_{UW}}$
  - We cannot identify either β_{UY} or β_{UW}, but we can identify the ratio

[13] Miao, Shi, and Tchetgen Tchetgen 2018; Miao, Geng, and Tchetgen Tchetgen 2018; Shi, Miao, and Tchetgen 2020; Shi, Miao, and Tchetgen Tchetgen 2020; Tchetgen et al. 2020.

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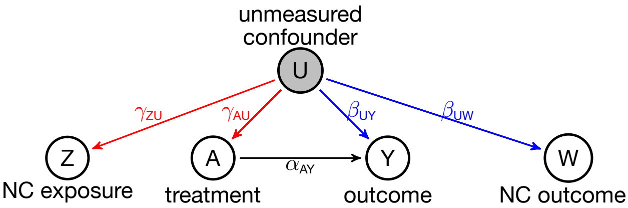

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  - We cannot identify either β_{UY} or β_{UW}, but we can identify the ratio
- Double negative control: use both an NCE and an NCO[13]
  - Identify the ratio using the NCE: $\frac{\beta_{UY}}{\beta_{UW}} = \frac{Z\text{-}Y \text{ association}}{Z\text{-}W \text{ association}} = \frac{\gamma_{ZU}\beta_{UY}}{\gamma_{ZU}\beta_{UW}}$
  - W recovers bias up to a scale; Z recovers that scale

[13] Miao, Shi, and Tchetgen Tchetgen 2018; Miao, Geng, and Tchetgen Tchetgen 2018; Shi, Miao, and Tchetgen 2020; Shi, Miao, and Tchetgen Tchetgen 2020; Tchetgen et al. 2020.

From linear additive model to nonparametric identification

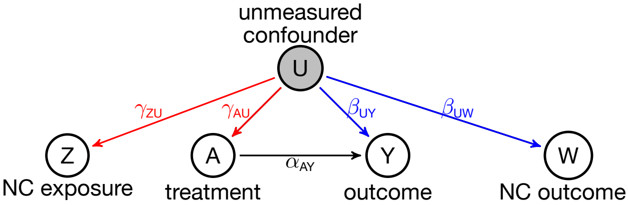
- For simplicity, consider the following two linear additive models
  - $E[Y \mid A, Z, U] = \beta_0 + \beta_A A + \beta_U U$
    $E[W \mid A, Z, U] = \gamma_0 + \gamma_U U$
  - The causal effect is $\beta_A = E[Y(1) - Y(0)] = E[Y(1) - Y(0) \mid U]$
- One can show that $\boxed{E[Y \mid A, Z] = \beta_0^* + \beta_A A + \beta_U^* E[W \mid A, Z]}$
  - Regress Y on A and $\widehat{W}$, where $\widehat{W}$ is predicted from $E[W \mid A, Z]$
- The ATE can be identified nonparametrically[14]
  - $E[Y(a)] = E[h(a, W)]$, $h()$ satisfies $\boxed{E[Y \mid A, Z] = E[h(A, W) \mid A, Z]}$
  - e.g., in the linear model above, $h(A, W) = \beta_0^* + \beta_A A + \beta_U^* W$
  - Requires Z and W to be sufficiently informative about U

[14] Miao, Shi, and Tchetgen Tchetgen 2018; Miao, Geng, and Tchetgen Tchetgen 2018; Shi, Miao, and Tchetgen Tchetgen 2020; Shi, Miao, and Tchetgen Tchetgen 2020; Tchetgen et al. 2020.

Double negative control in practice

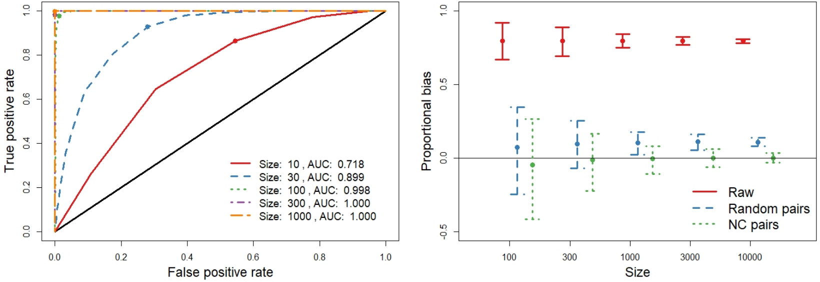
- Two stage least squares (TSLS) under linear models
  - Stage I: regress W on A and Z, and obtain fitted values $\widehat{W}$
  - Stage II: regress Y on A, adjusting for $\widehat{W}$ (as if it is U)
- Can use existing instrumental variable software packages
  - `SYSLIN` in SAS; `ivregress`, `ivreg`, `ivreg2` in Stata; `gmm`, `sem`, `ivpack`, `AER` in R
  - e.g., `gmm::gmm(g=Y~A+W+X,x=~A+Z+X)` in R

How to find a candidate negative control variable?



- Data-driven Automated Negative Control Estimation (DANCE)
  - Identifies triplets of negative control variables
  - Aggregates ATEs obtained from all pairs of negative controls
  - Limitation: can only detect a special type of negative control
- Rationale: all paths from $\{W, Z\}$ to $\{Y, A\}$ pass through U
  - Therefore $\Sigma_{\{W,Z\},\{Y,A\}} = \begin{pmatrix} cov(W,Y) & cov(W,A) \\ cov(Z,Y) & cov(Z,A) \end{pmatrix}$ is rank deficient
  - Such a rank constraint can be determined using statistical tests

Performance of the DANCE algorithm



- High AUC in negative control detection
- Low bias in effect estimation using the detected negative controls

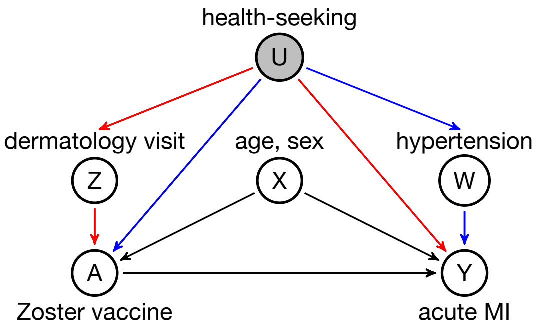
Proximal Causal Learning

Are two cheap, noisy measures better than one expensive, accurate measure?[15]

- Hard to eliminate measurement error
  - The "no unmeasured confounding" assumption depends on investigator's ability to accurately measure covariates capturing all potential sources of confounding
  - The most one can hope for is that covariate measurements are at best proxies of the true underlying confounding mechanism
- Easier to get to the right kind of measurement error
  - Acknowledge that covariates are imperfect proxies of confounders
  - Find proxies that satisfy certain assumptions
  - Allow the "no unmeasured confounding" to be violated

[15] Browning and Crossley 2009.

An example in vaccine safety study



- Adverse effect of a new Zoster vaccine on acute MI
- Plan to adjust for the following confounders:
  - age, sex (*X*)
  - dermatology visit (*Z*), hypertension (*W*)

Tchetgen et al. 2020

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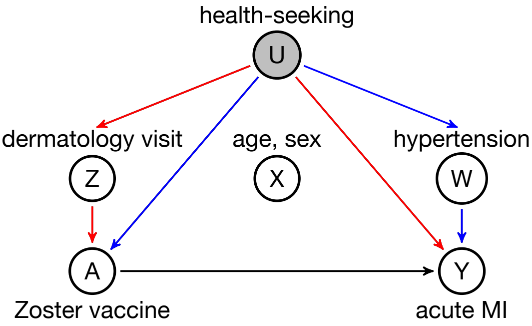

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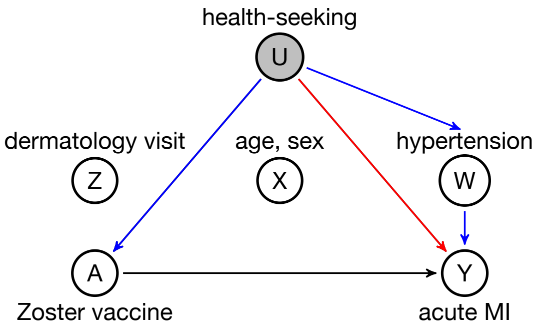
Tchetgen et al. 2020

An example in vaccine safety study



- Adverse effect of a new Zoster vaccine on acute MI
- Plan to adjust for the following confounders:
  - age, sex (*X*)
  - dermatology visit (*Z*), hypertension (*W*)

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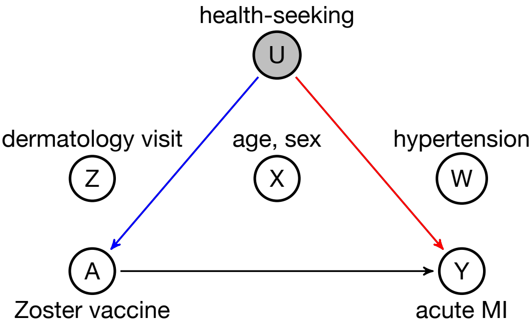

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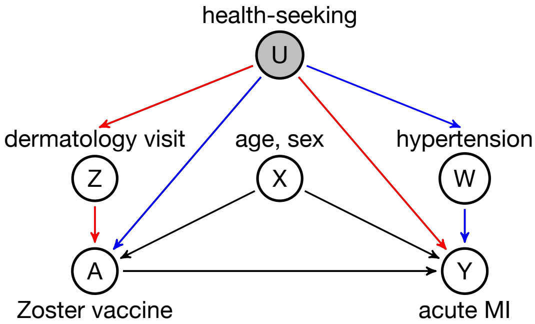

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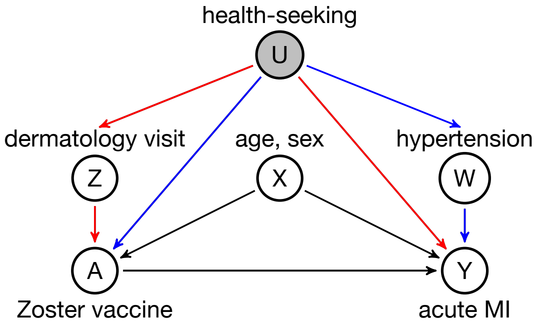

- Three types of confounding variables
  - Common causes of the treatment and outcome: age, sex (X)
  - Treatment-inducing confounding proxy: dermatology visit (Z)
  - Outcome-inducing confounding proxy: hypertension (W)

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Classical vs Proximal causal inference

- **Classical causal inference: fails when U exists**
  - Confounders $\{X, W, Z\}$: age, sex, dermatology visit, hypertension
  - Standard g-formula: $E[Y(a)] = E[m(a, X, W, Z)]$
  - $m(a, x, w, z)$ is the outcome model
    $m(a, x, w, z) = E[Y \mid A = a, X = x, W = w, Z = z]$
  - Estimation via g-computation

- **Proximal causal inference**
  - $X =$ age, sex; $W =$ hypertension; $Z =$ dermatology visit
  - Proximal g-formula: $E[Y(a)] = E[h(a, W, X)]$
  - $h(a, w, x)$ is the outcome bridge function
    $E[h(a, w, x) \mid A = a, Z = z, X = x] = E[Y \mid A = a, Z = z, X = x]$
  - Estimation via proximal g-computation or two-stage least squares

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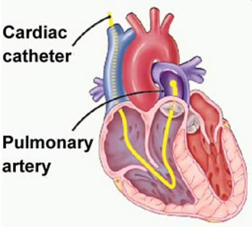
Greenland and Robins 1986; In slight abuse of notation let $\sum$ denote an integral in the case of a continuous variable

Application to the SUPPORT study



- Right heart catheterization (RHC) procedure
  - Performed to measure blood flow and pressures in the heart
  - Many physicians believed that measurements from the RHC can guide therapy and lead to better outcomes for critically ill patients
  - Due to the popularity and strong belief of the procedure, conducting a clinical trial was unethical

- The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT)[16]
  - Evaluate the effectiveness of RHC among adults admitted to the intensive care unit (ICU)
  - 2184 patient managed with RHC, 3551 without RHC

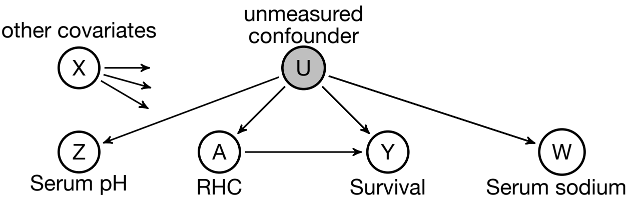
[16] Connors et al. 1996.

A controversial result

- The SUPPORT study found that RHC was harmful
- Potential confounding
  - Confounding bias might show harmful effect of RHC
  - Patients for whom RHC was performed might have been a lot sicker
- This data set has been analyzed by many researchers[17]
  - Majority relying on the no unmeasured confounding assumption

[17] Lin, Psaty, and Kronmal 1998; Tan 2006; Li, Morgan, and Zaslavsky 2018; Mao and Li 2020.

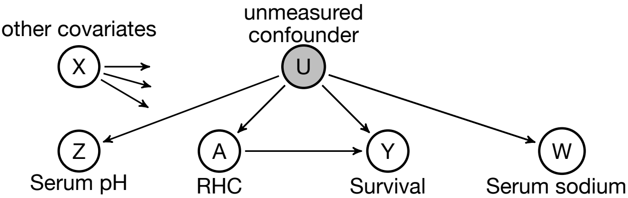
Candidate proxies in the SUPPORT study



- The SUPPORT study collected 72 covariates including
  - demographics, comorbidity, vital signs, functional status
  - physiological status measured from a blood test during the initial 24 hours in the ICU $\Rightarrow$ 10 candidate proxies

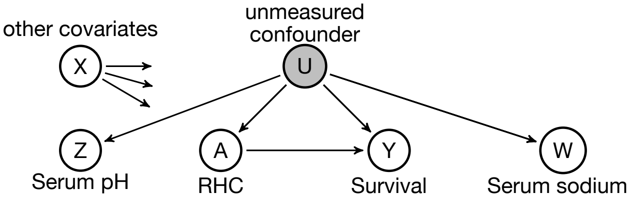
- We applied our DANCE algorithm to find valid proxies
  - Most frequently selected pair: ph and sod
  - ph = Serum pH; sod = Serum sodium

Methods



- We evaluate effect of RHC on survival time in days
    - Assumed a linear additive model
- Estimation
    - Proximal two stage least squares
    - Inverse probability weighting to adjust for the other covariates X

Results



Proxy variables	RHC effect (95% CI)
W = ph, Z = sod	-0.44 (-1.00, 0.11)
W = sod, Z = ph	-0.40 (-1.09, 0.30)
Average over all detected (W,Z) pairs	-0.71 (-1.50, 0.08)
Naive adjustment	-1.29 (-1.83, -0.75)

- RHC was not significantly associated with survival time
- Note that the role of Z and W are exchangeable
  - Our results remained invariant to the choice of *W* and *Z*
  - This verifies that the graph is correctly specified

Summary

- Negative controls and proxies can adjust for confounding bias
- Can directly use off-the-shelf software packages
- A data-driven pipeline of negative control detection and adjustment
- Current work by the proximal causal inference group

Review on negative controls	arXiv:2009.05641
Nonparametric identification	arXiv:1609.08816
Binary variable setting	arXiv:1808.04906
Outcome confounding bridge	arXiv:1808.04945
Proximal causal inference	arXiv:2009.10982
Outcome and treatment confounding bridge	arXiv:2011.08411
Longitudinal data setting	arXiv:2109.07030
Panel data setting	arXiv:2108.13935
Proximal mediation analysis	arXiv:2109.11904

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Questions?