Causal Inference for Health Data

(STATS C160/C260 — Winter 2026)

Lecture 18:

Unobserved Confounding — Part I

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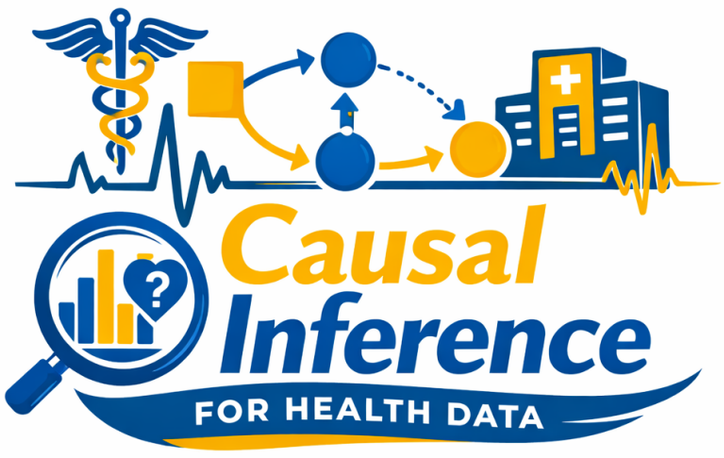
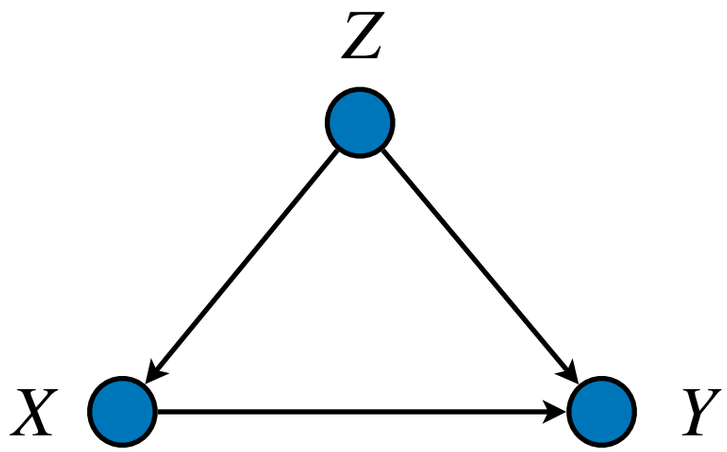


How well do causal estimates from observational data translate to RCTs?

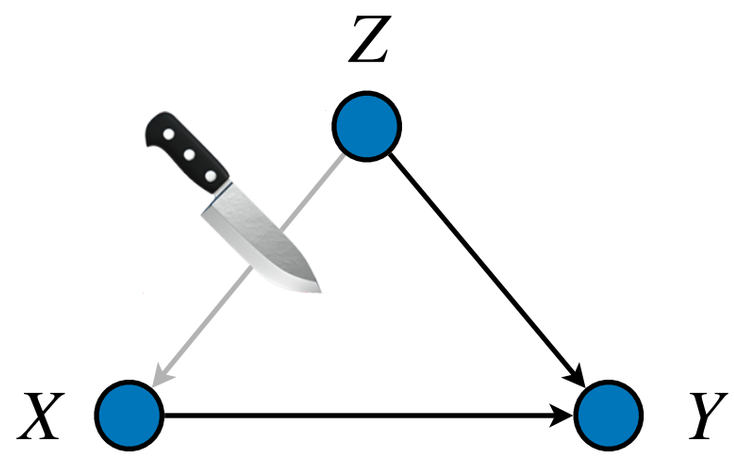
Observational Setting



- Z is back-door for (X, Y)
- $P(y \mid do(x))$ identified through adjustment on Z

$$\sum_{z} P(y \mid x, z)P(z)$$

Interventional Setting (RCT)

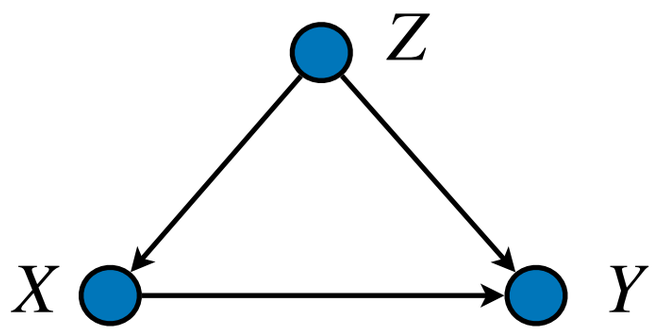


- We can obtain $P(y \mid do(x))$ directly,
- However, we already know the answer, and the RCT is not really needed!

What could go wrong?

- Most common culprit: unobserved confounding

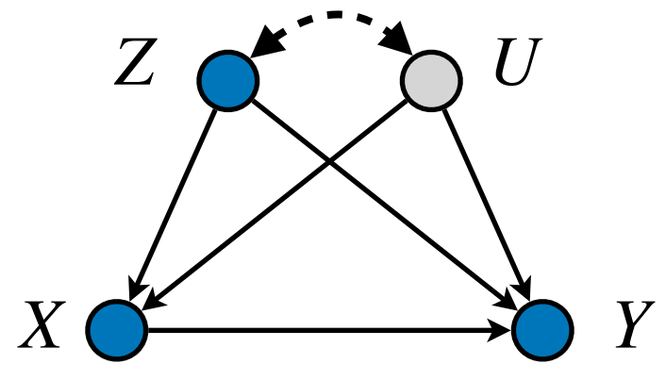
Our Analysis



- Z is back-door for (X, Y)
- $P(y \mid do(x))$ identified through adjustment on Z

$$\sum_z P(y \mid x, z)P(z)$$

Reality



- Z is **not** back-door for (X, Y)
- $P(y \mid do(x))$ **not** identified through adjustment on Z

$$P(y \mid do(x)) \neq \sum_z P(y \mid x, z)P(z)$$

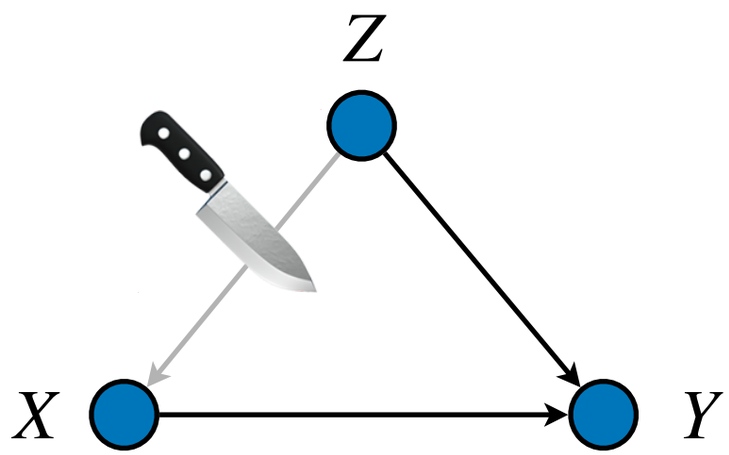
What could go wrong?

- Most common culprit: unobserved confounding

Our Analysis

Reality

In this case, our findings will not translate to the RCT setting



Does this happen in practice?
I: Menopausal HRT

- Post-menopause, hormone replacement therapy (HRT) may have benefits, such as vasodilation, lower inflammatroy activation, lower LDL cholesterol

> N Engl J Med. 1991 Sep 12;325(11):756-62. doi: 10.1056/NEJM199109123251102.

Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study

M J Stampfer [1], G A Colditz, W C Willett, J E Manson, B Rosner, F E Speizer, C H Hennekens

Affiliations + expand

PMID: 1870648 DOI: 10.1056/NEJM199109123251102

Free article

"Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease"

Does this happen in practice?
I: Menopausal HRT

- Post-menopause, hormone replacement therapy (HRT) may have benefits, such as vasodilation, lower inflammatroy activation, lower LDL cholesterol

HRT therapy seems like a good idea

Clinical Trial > JAMA. 2002 Jul 17;288(3):321-33. doi: 10.1001/jama.288.3.321.

Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial

Jacques E Rossouw [1], Garnet L Anderson, Ross L Prentice, Andrea Z LaCroix, Charles Kooperberg, Marcia L Stefanick, Rebecca D Jackson, Shirley A A Beresford, Barbara V Howard, Karen C Johnson, Jane Morley Kotchen, Judith Ockene; Writing Group for the Women's Health Initiative Investigators

Affiliations + expand

PMID: 12117397 DOI: 10.1001/jama.288.3.321

Does this happen in practice?
I: Menopausal HRT

- Post-menopause, hormone replacement therapy (HRT) may have benefits, such as vasodilation, lower inflammatroy act

"Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women"

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controlled trial

Issue: in observational data, patients on HRT were (i) healthier; (ii) had better healthcare utilization; (iii) had better socio-economic status.

HRT t
like

II: Vitamin E and coronary heart disease (CHD)

- Hypothesized benefits of vitamin E included reduced atheroscelrosis, reduced inflammation, and antithrombotic effects.

> N Engl J Med. 1993 May 20;328(20):1444-9. doi: 10.1056/NEJM199305203282003.

Vitamin E consumption and the risk of coronary disease in women

M J Stampfer [1], C H Hennekens, J E Manson, G A Colditz, B Rosner, W C Willett

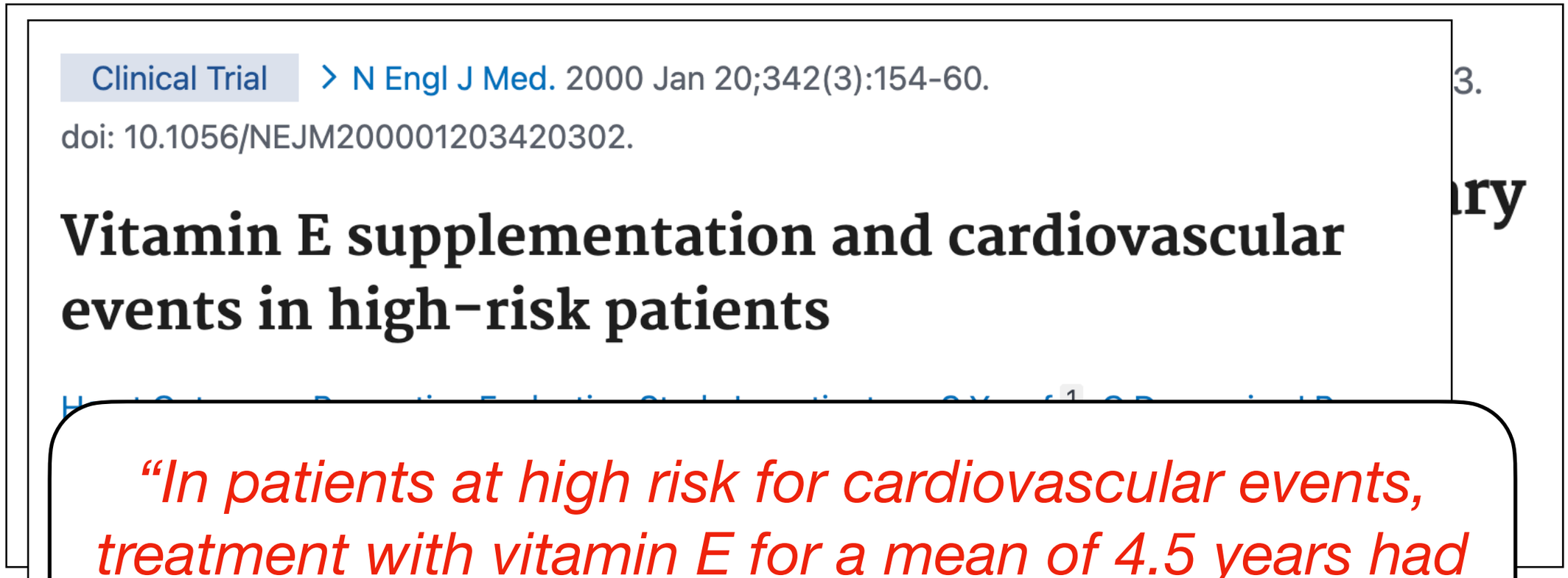
Affiliations + expand

PMID: 8479463 DOI: 10.1056/NEJM199305203282003

"Among middle-aged women the use of vitamin E supplements is associated with a reduced risk of coronary heart disease" **RCT makes sense?**

II: Vitamin E and coronary heart disease (CHD)

- Hypothesized benefits of vitamin E included reduced atheroscelrosis, reduced inflammation, and antithrombotic effects.



Clinical Trial > N Engl J Med. 2000 Jan 20;342(3):154-60.

doi: 10.1056/NEJM200001203420302.

Vitamin E supplementation and cardiovascular events in high-risk patients

"In patients at high risk for cardiovascular events, treatment with vitamin E for a mean of 4.5 years had no apparent effect on cardiovascular outcomes."

Supplement users exercised more, smoked less, and had healthier diets, and better SES.

III: Beta-carotene -> Lung Cancer

- Hypothesized benefits of beta-carotene included antioxidant protection against DNA damage, reduced lipid peroxidation, and enhanced immune surveillance, thereby lowering the risk of lung cancer.

› Br J Cancer. 1988 Apr;57(4):428-33. doi: 10.1038/bjc.1988.97.

Serum beta-carotene and subsequent risk of cancer: results from the BUPA Study

N J Wald [1], S G Thompson, J W Densem, J Boreham, A Bailey

Affiliations + expand

PMID: 3390380 PMCID: PMC2246576 DOI: 10.1038/bjc.1988.97

"Men in the top two quintiles of serum beta-carotene had only about 60% of the risk of developing cancer compared with men in the bottom quintile."

III: Beta-carotene -> Lung Cancer

- Hypothesized benefits of beta-carotene included antioxidant protection against DNA damage, reduced lipid peroxidation, and enhanced immune surveillance, thereby lowering the risk of lung cancer.

Clinical Trial > N Engl J Med. 1994 Apr 14;330(15):1029-35.

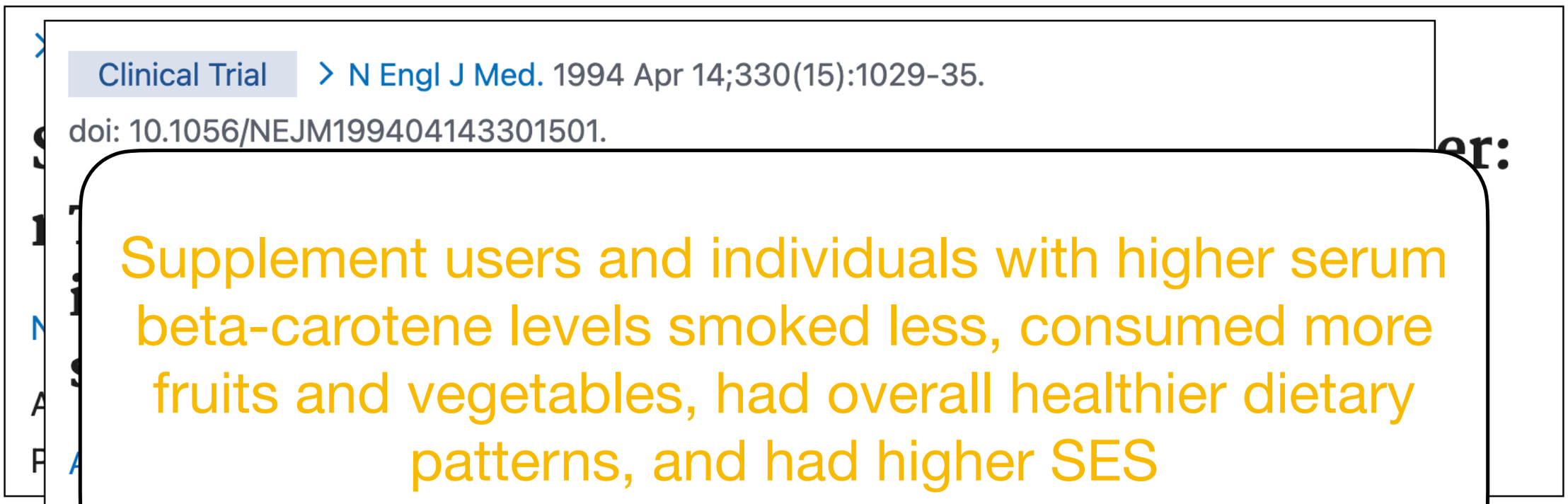
doi: 10.1056/NEJM199404143301501.

The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers

"We found no reduction in the incidence of lung cancer among male smokers after five to eight years of dietary supplementation with alpha-tocopherol or beta carotene."

III: Beta-carotene -> Lung Cancer

- Hypothesized benefits of beta-carotene included antioxidant protection against DNA damage, reduced lipid peroxidation, and enhanced immune surveillance, thereby lowering the risk of lung cancer.



Unobserved Confounding

- There are two components of protecting our findings against unobserved confounding:

Knowing what we didn't measure

- In all studies, it is important to report factors that may be relevant, but have not been included in the analysis,
- These factors can be measured in prospective studies.

Knowing what we don't know

- This is a lot more difficult — what if there is an unobserved confounder previously not hypothesized (discussion: what is treatment allocation),
- Performing sensitivity analysis.

Unobserved Confounding

- There are two components of protecting our findings against unobserved confounding:

Knowing what we didn't measure

- In all studies, it is im
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  studies.

Knowing what we don't know

- This is a lot more difficult
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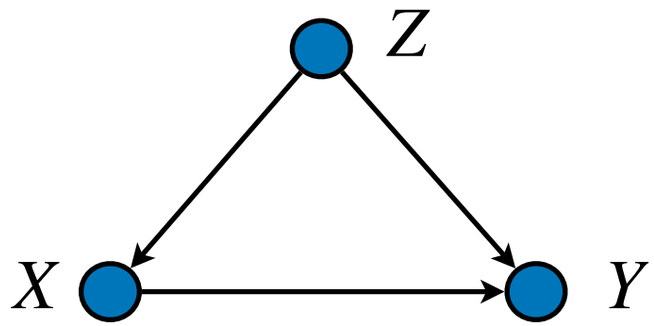
  analysis.

Key Question: How strong would an unobserved confounder have to be to change our study findings?

Sensitivity Analysis for Unobserved Confounding

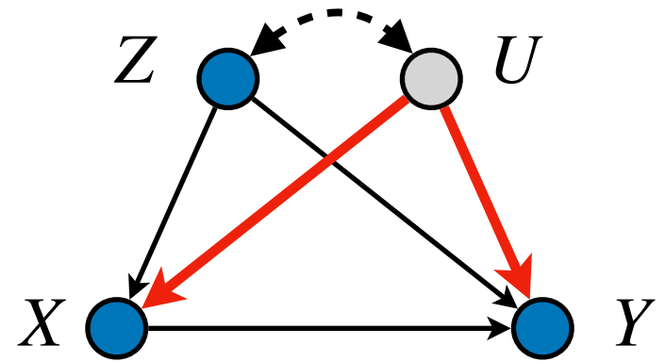
Run the Analysis



- Z is back-door for (X, Y)
- $P(y \mid do(x))$ identified and compute as

$$\sum_{z} P(y \mid x, z)P(z)$$

Key Question



- How strong would an unobserved confounder have to be to change our findings (red arrows)?
- How do we quantify this?

Quantifying UC Strength

- In the general, non-parametric setting, quantifying the strength of UCs is hard,
- Finding nice ways to do this is an open research area,
- Some useful tools for parametric settings exist:

Risk Ratio Scale: Total Risk Ratio (TRR) vs. Total Effect (TE)

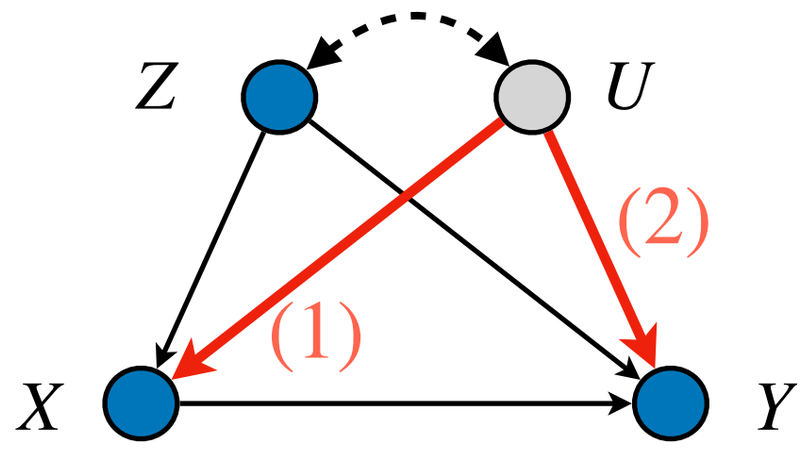
- So far, we considered the total effect (TE), given by $E[Y \mid do(x_1)] - E[Y \mid do(x_0)]$,
- For binary outcomes, another quantification is useful, through the total risk ratio (TRR)

$$\text{TRR}_{x_0,x_1}(y) = \frac{P(Y = 1 \mid do(x_1))}{P(Y = 1 \mid do(x_0))}$$

Note: TE > 0 $\iff$ TRR > 0

UC Sensitivity for TRR

- Let's assume the UC U is binary,
- Our analysis is z-specific,



- We start with the definitions of our sensitivity parameters:

$$\mathbf{RR}_{XU} \overset{(1)}{=} \max_{u} \frac{P(u \mid x_1, z)}{P(u \mid x_0, z)}$$

Captures the strength of X → U relationship: maximal risk-ratio from flipping $x_0 \to x_1$

$$\mathbf{RR}_{UY} \overset{(2)}{=} \max_{x} \frac{\max_u P(y \mid x, u, z)}{\min_u P(y \mid x, u, z)}$$

Captures the strength of U → Y relationship: maximal u-variation induced in $P(y \mid \cdot)$

UC Sensitivity for TRR

Theorem. Let $\text{RR}^{obs}(y \mid z)$ be the risk ratio $\dfrac{P(y \mid x_1, z)}{P(y \mid x_0, z)}$, and let $\text{RR}^{true}(y \mid z)$ be the true risk ratio obtained after adjusting for U,

$$\frac{\sum_u P(y \mid x_1, z, u)P(u)}{\sum_u P(y \mid x_0, z, u)P(u)}$$

Then, we have that

$$\frac{\text{RR}^{obs}(y \mid z)}{\text{RR}^{true}(y \mid z)} \leq \frac{\text{RR}_{XU}\text{RR}_{UY}}{\text{RR}_{XU} + \text{RR}_{UY} - 1}$$

Proof: Part I

We are assuming that $\text{RR}^{obs}(y \mid z) > 1$, WLOG.

We first note that

homework

$$\text{RR}^{true}(y \mid z) = \lambda \text{RR}^{true}(y \mid z, x_1) + (1 - \lambda)\text{RR}^{true}(y \mid z, x_0),\ \lambda \in [0,1]$$

meaning that the true RR is a convex combination of x -specific RRs.

Next, note that we have

whiteboard

$$\frac{\text{RR}^{obs}(y \mid z)}{\text{RR}^{true}(y \mid z, x_1)} = \frac{\sum_u P(y \mid x_0, z, u)P(u \mid z, x_1)}{\sum_u P(y \mid x_0, z, u)P(u \mid z, x_0)}$$

Proof: Part II

Our next step is to re-write both the numerator and the denominator as a convex combination of min/max over $P(y \mid x_0, z, u)$:

$$\frac{\mathrm{RR}^{obs}(y \mid z)}{\mathrm{RR}^{true}(y \mid z, x_1)} = \frac{w_1 \max_u P(y \mid x_0, z, u) + (1 - w_1) \min_u P(y \mid x_0, z, u)}{w_0 \max_u P(y \mid x_0, z, u) + (1 - w_0) \min_u P(y \mid x_0, z, u)}.$$

with

$$w_x = \frac{\sum_u [P(y \mid x_0, z, u) - \min'_u P(y \mid x_0, z, u')] P(u \mid x, z)}{\max_u P(y \mid x_0, z, u) - \min_u P(y \mid x_0, z, u)}.$$

Proof: Part III

Dividing through by $\min_u P(y \mid x_0, z, u)$, we get

$$\frac{\mathrm{RR}^{obs}(y \mid z)}{\mathrm{RR}^{true}(y \mid z, x_1)} = \frac{w_1\left(\frac{\max_u P(y \mid x_0, z, u)}{\min_u P(y \mid x_0, z, u)} - 1\right) + 1}{(\frac{w_1}{w_0})^{-1} w_1\left(\frac{\max_u P(y \mid x_0, z, u)}{\min_u P(y \mid x_0, z, u)} - 1\right) + 1}$$

$\mathbf{RR}_{UY|x_0}$

Note that we have

can be exchanged using RR_{XU}

$$\Gamma \triangleq \frac{w_1}{w_0} = \frac{\sum_u [P(y \mid x_0, z, u) - \min'_u P(y \mid x_0, z, u')] P(u \mid z, x_1)}{\sum_u [P(y \mid x_0, z, u) - \min'_u P(y \mid x_0, z, u')] P(u \mid z, x_0)}$$

$$\leq \frac{\sum_u [P(y \mid x_0, z, u) - \min'_u P(y \mid x_0, z, u')] \mathrm{RR}_{XU} P(u \mid z, x_0)}{\sum_u [P(y \mid x_0, z, u) - \min'_u P(y \mid x_0, z, u')] P(u \mid z, x_0)} = \mathrm{RR}_{XU}\,.$$

Proof: Part IV

Putting together, we can bound the ratio as

$$\frac{\text{RR}^{obs}(y \mid z)}{\text{RR}^{true}(y \mid z, x_1)} = \frac{w_1\left(\frac{\max_u P(y \mid x_0, z, u)}{\min_u P(y \mid x_0, z, u)} - 1\right) + 1}{\Gamma^{-1} w_1\left(\frac{\max_u P(y \mid x_0, z, u)}{\min_u P(y \mid x_0, z, u)} - 1\right) + 1}$$

$$f(x) = \frac{x+1}{\Gamma^{-1}x + 1}$$

increasing iff $\Gamma > 1$

$$\leq \frac{(\mathbf{RR}_{UY|x_0} - 1) + 1}{\Gamma^{-1}(\mathbf{RR}_{UY|x_0} - 1) + 1}$$

$$= \frac{\Gamma \mathbf{RR}_{UY|x_0}}{\mathbf{RR}_{UY|x_0} + \Gamma - 1}$$

$$\leq \frac{\mathbf{RR}_{XU}\mathbf{RR}_{UY}}{\mathbf{RR}_{UY} + \mathbf{RR}_{XU} - 1}$$

$$f(x, y) = \frac{xy}{x + y + 1}$$

increasing in x, y

Proof: Part V

Finally, we can combine the bounds treated and untreated groups:

$$\mathrm{RR}^{true}(y \mid z) = \lambda \mathrm{RR}^{true}(y \mid z, x_1) + (1-\lambda)\mathrm{RR}^{true}(y \mid z, x_0),\ \lambda \in [0,1]$$

$$\leq \lambda B \mathrm{RR}^{obs}(y \mid z) + (1-\lambda) B \mathrm{RR}^{obs}(y \mid z)$$

$$= B \cdot \mathrm{RR}^{obs}(y \mid z)$$

where $B \triangleq \dfrac{\mathrm{RR}_{XU}\mathrm{RR}_{UY}}{\mathrm{RR}_{UY} + \mathrm{RR}_{XU} - 1}$, completing the proof.

z-TRR to TRR

- Our obtained bound is for the *z-specific TRR,*
- For bounds on the population-level TRR, we have

$$\mathbf{RR}^{true}(y) = \frac{\sum_z P(y_{x_1} \mid z)P(z)}{\sum_z P(y_{x_0} \mid z)P(z)}$$

$$= \frac{\sum_z \mathbf{RR}^{true}_{x_0,x_1}(y \mid z)P(y_{x_0} \mid z)P(z)}{\sum_z P(y_{x_0} \mid z)P(z)}$$

$$\geq \frac{\sum_z \mathbf{RR}^{obs}_{x_0,x_1}(y \mid z)\dfrac{\mathbf{RR}_{UY} + \mathbf{RR}_{XU} - 1}{\mathbf{RR}_{XU}\mathbf{RR}_{UY}}P(y_{x_0} \mid z)P(z)}{\sum_z P(y_{x_0} \mid z)P(z)}$$

$$\geq \frac{\mathbf{RR}_{UY} + \mathbf{RR}_{XU} - 1}{\mathbf{RR}_{XU}\mathbf{RR}_{UY}} \min_z \mathbf{RR}^{obs}_{x_0,x_1}(y \mid z)\,.$$

Note: bound is based on the minimal z-specific TRR

E-value

- Now, in the very last step, we can further simplify the setting, and search for a minimum joint strength $\text{RR}_{XU}, \text{RR}_{UY}$ that explain aways the observed effect,
- Here, it is convenient to assume that $\text{RR}_{XU} = \text{RR}_{UY} = r$ so that we can say a confounder (i) for which $x_0 \rightarrow x_1$ causes an r-fold increase in risk-ratio for u_1 or u_0, and (ii) which causes an r-fold increase in risk-ratio for $Y = 1$ is capable of explaining away the effect under study.
- When $\text{RR}_{XU} = \text{RR}_{UY} = r$, we can find the minimal r capable of explaining away the effect.

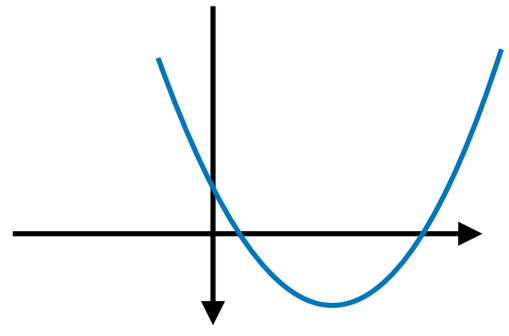
E-value

- Note that we can write

$$\mathrm{RR}^{true}(y \mid z) = \frac{\mathrm{RR}_{UY} + \mathrm{RR}_{XU} - 1}{\mathrm{RR}_{XU}\mathrm{RR}_{UY}}\mathrm{RR}^{obs}(y \mid z)$$

$$= \frac{2r - 1}{r^2}\mathrm{RR}^{obs}(y \mid z) \quad > 1$$

$$\iff \quad r^2 - (2r - 1)\mathbf{RR}^{obs}(y \mid z) < 0$$



searching for $r_{\min}$ so that this holds always $\Longrightarrow$ larger quadratic solution

$$r_{\min} = \mathbf{RR}^{obs}(y \mid z) + \sqrt{\mathbf{RR}^{obs}(y \mid z)(\mathbf{RR}^{obs}(y \mid z) - 1)}$$

E-value

- Note that we can write

$$\mathrm{RR}^{true}(y \mid z) = \frac{\mathrm{RR}_{UY} + \mathrm{RR}_{XU} - 1}{\mathrm{RR}_{UY}\,\mathrm{RR}_{XU}}\mathrm{RR}^{obs}(y \mid z)$$

This is known as the **E-value**:
minimal joint strength of the confounder that can explain away the estimated risk ratio!

searching for $r_{\min}$ so that this holds always $\Longrightarrow$ larger quadratic solution

$$r_{\min} = \mathrm{RR}^{obs}(y \mid z) + \sqrt{\mathrm{RR}^{obs}(y \mid z)(\mathrm{RR}^{obs}(y \mid z) - 1)}$$

Heuristics in Practice: Assume Away Heterogeneity

- In practice, often the $\min_z \text{RR}^{obs}(y \mid z)$ is not taken for obtaining bounds on $\text{RR}^{true}(y)$,
- Instead, practitioners are willing to assume away heterogeneity (i.e., that the risk ratio is constant across z),
- Upon doing so, a heuristic to understand how large (or small) the obtained E-value is, proceeds as follows: leave-out each of the observed confounders one by one, and compute how large the RR_{XU}, RR_{UY} would be for them!