STA 640 — Causal Inference

Chapter 4 – Sensitivity Analysis

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Assessing Assumptions

- Two key assumptions in causal inference with observational data: overlap (a.k.a. positivity) and unconfoundedness
- Overlap is on the observed data, testable
- Unconfoundedness is inherently untestable, but can be sometimes indirectly assessed
- Prudent to perform some sensitivity analysis to assess how sensitive the causal analysis if unconfoundedness is violated
- Balance is not an assumption, but closed related to both overlap and unconfoundedness, should always be checked

Assessing Overlap

- To detect lack of overlap, plot distributions of covariates by treatment groups. In the case with one or two covariates one can do this directly
- In high dimensional cases, inspecting pairs of marginal distributions by treatment status is not necessarily informative about lack of overlap. Possible that for each covariate the distribution for the treatment and control groups are identical, even though there are areas where the PS is zero or one
- Instead inspect the distribution of the propensity score in both groups (overlapping histograms), which can reveal lack of overlap in the multivariate covariate distributions
- Drop units fall out of the common support between groups

Unconfoundedness and Balance

- Unconfoundedness: $\{Y(1), Y(0)\} \perp Z|X$.
- Unconfoundedness is an assumption on unmeasured data, and hence inherently untestable: the data are uninformative about the distribution of $Y(0)$ for treated units and $Y(1)$ for control units
- But unconfoundedness can be sometimes indirectly assessed
- Unconfoundedness implies, within strata of observed covariates, potential outcomes corresponding to both treatment conditions would be balanced between groups
- Re-think balance: randomization balance both covariates and potential outcomes

Unconfoundedness and Balance

- Re-think balance: randomization balance both covariates and potential outcomes
- What we really want to balance in observational studies: potential outcomes between groups
- Specifically, we want to balance:
  $\Pr(Y(0)|Z = 1)$ vs. $\Pr(Y(0)|Z = 0)$, and
  $\Pr(Y(1)|Z = 1)$ vs. $\Pr(Y(1)|Z = 0)$
- In practice, we use balance in covariates as a proxy to balance in potential outcomes
- Check unconfoundedness: how about balancing more direct proxies to potential outcomes?

Assessing Unconfoundedness: Multiple Control Groups

- Assessing unconfoundedness indirectly is possible with additional data
- Method 1: using multiple control groups
- Suppose we have a three-valued indicator $T_i \in \{-1, 0, 1\}$ for the groups (e.g., ineligibles, eligible nonnonparticipants and participants), with the treatment indicator equal to $Z_i = 1\{T_i = 1\}$, so that

$$Y_i = \begin{cases} Y_i(0) & \text{if } T_i \in \{-1, 0\} \\ Y_i(1) & \text{if } T_i = 1 \end{cases}$$

Assessing Unconfoundedness: Multiple Control Groups

- Suppose we extend the unconfoundedness assumption to independence of the potential outcomes and the three-valued group indicator given covariates

$$\{Y_i(0), Y_i(1)\} \perp T_i | X_i$$

- Now a testable implication is

$$Y_i(0) \perp 1\{T_i = 0\} | X_i, T_i \in \{-1, 0\}$$

and thus

$$Y_i^{obs} \perp 1\{T_i = 0\} | X_i, T_i \in \{-1, 0\}$$

- Whether this test has much bearing on the unconfoundedness assumption depends on whether the extension of the assumption is plausible given unconfoundedness itself (requires another untestable assumption)

Assessing Unconfoundedness: Using Lagged Outcomes

- Method 2: using lagged outcomes (e.g. Crump et al., 2008)
- The idea: the lagged outcome Y_{lag}, can be considered a proxy for $Y(0)$ and, given it is observed before the treatment, it is unaffected by the treatment
- Consequently, if the ATE on the lagged outcome is zero for all subpopulations defined by the rest of the covariates, $\mathbf{V} = (\mathbf{X} \backslash Y_{lag})$, then unconfoundedness is plausible
- Formally, testing

$$H_0 : \mathbb{E}(Y_{lag,z=1} - Y_{lag,z=0} | \mathbf{V} = \mathbf{v}) = 0 \quad \forall \mathbf{v}$$

$$\text{vs.} \qquad H_1 : \exists \mathbf{v} \; s.t. \; \mathbb{E}(Y_{lag,z=1} - Y_{lag,z=0} | \mathbf{V} = \mathbf{v}) \neq 0,$$

Lagged Outcomes

- Examples: Mercatanti and Li (2014, AOAS); evaluation of traffic safety countermeasures – selection of reference (control) groups (Li and Li, 2019 Obs Studies)
- Panel data or repeated cross-sectional data provide richer information than cross-sectional data
- In these data, lagged outcomes are often the most important covariates (pre-treatment variable)
- Balancing lagged outcomes between groups is important
- Have close connections to difference-in-differences (DID) methods

Assessing Unconfoundedness: Negative Controls

- Method 3: using negative control outcomes (NCO) (e.g., Sofer et al. 2016 Stat Sci)
- The idea: select another outcome variable known not be causally affected by the treatment of interest (requires substantive knowledge)
- can view lagged outcome as a special case of NCO
- Define $W = ZW(1) + (1 - Z)W(0)$ as NCO, then unconfoundedness implies $\{W(1), W(0)\} \perp Z|X$, which can be tested, because $\mathbb{E}[W(1) - W(0)|X] = 0$
- An example: flu shot (Z), influenza hospitalization (Y), injury hospitalization (W) (Shi et al. 2020+)

Falsification tests

- All three methods are also known as falsification analyses/tests
  - Falsification test using data from alternative control group (method 1)
  - Falsification test using data from prior periods (method 2)
  - Falsification test using alternative placebo outcome that is not supposed to be affected by the treatment (method 3)
- One can also use negative control exposure (NCE): a variable known not to causally affect the outcome of interest
  - Double negative control (NCO, NCE) allows nonparametric identification of ATE (Wang et al. 2018; Shi et al. 2020+)
  - Better design of observational studies?

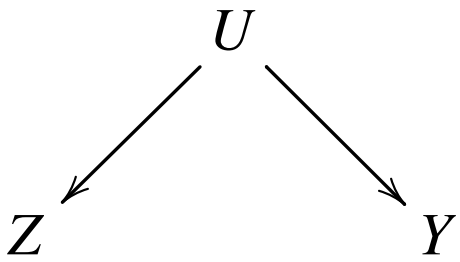
Sensitivity analysis

- Most often, validity of unconfoundedness can not be easily checked. Alternatively, one should check sensitivity of a causal analysis to unconfoundedness
- Sensitivity analysis aims at assessing the bias of causal effect estimates when the unconfoundedness assumption is assumed to fail in some specific and meaningful ways
- Sensitivity is different from testing – unconfoundedness is intrinsically non-testable, more of a "insurance" check
- Sensitivity analysis in causal inference dates back to the Hill-Fisher debate on causation between smoking and lung cancer, and first formalized in Cornfield (1959, JNCI)

Smoking and Lung Cancer: Revisited

Cornfield et al. (1959 JNCI)

Common cause hypothesis



- Smoking Z
- Lung cancer Y
- Genetic factor U

- Fisher argued the association between smoking and lung cancer may be due to a common gene that causes both
- Cornfield showed: assuming Fisher is right, the smoking-gene association must satisfy:

$$\mathrm{RR}_{ZU} \geq \mathrm{RR}_{ZY}^{\mathrm{obs}} \approx 9$$

- Such a genetic confounder is too strong to be realistic
- Thus, here association must be due

Sensitivity Analysis since Cornfield et al. (1959)

An incomplete review

Epidemiology

- Bross (1966, 1967)
- Schlesselman (1978)
- Flanders and Khoury (1990)
- Poole (2010)
- Lee (2011)
- MacLehose et al. (2005, bounds)
- Ding and VanderWeele (2014, 2016, 2016)

Statistics and Econometrics

- Rosenbaum and Rubin (1983, JRSSB)
- Yanagawa (1984)
- Lin et al. (1998)
- Rosenbaum (2002, book)
- Imbens (2003 AER)
- Ichino et al. (2008, JAE)
- Manski (1990 AER, bounds)

Sensitivity analysis

Rosenbaum and Rubin (1983, JRSS-B)

- Fundamental idea: check what would happen had there was one unmeasured confounder?
- Central assumption: the assignment to treatment is not unconfounded given the set of observed covariates X, i.e.,

$$P(Z|Y(0), Y(1), X) \neq P(Z|X)$$

but uncounfoundedness holds given X and an unobserved binary covariate U (latent unconfoundedness)

$$P(Z|Y(0), Y(1), X, U) = P(Z|X, U)$$

- Draw DAG

Sensitivity analysis

Rosenbaum and Rubin (1983, JRSS-B)

- Given these assumptions, specify a set of parameters characterizing the distribution of U and the association of U with Z, $Y(1)$ and $Y(0)$ given observed covariates
- Binary outcome Y, binary treatment Z, and one binary unmeasured confounder U
- One categorical covariate X ($x = 1, \ldots, k$) - think of subclass of propensity score
- Decompose the joint distribution:

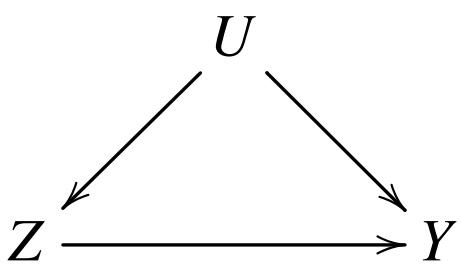
$$P(Y(1), Y(0), Z, X, U) = P(Y(1), Y(0)|X, U)P(Z|X, U)P(U|X)P(X)$$

Sensitivity analysis

Rosenbaum and Rubin (1983, JRSS-B)

Within strata of

- covariates
- propensity scores



- Confounder $U \sim \text{Bern}(\pi)$
- Assignment mechanism model:

$$\text{logit}\, P(Z = 1 \mid u) = \gamma + \alpha u$$

- Outcome model:

$$\text{logit}\, P\{Y(z) = 1 \mid u\} = \beta_z + \delta_z u$$

- Sensitivity parameters:

$$(\pi, \alpha, \delta_1, \delta_0)$$

Sensitivity analysis

Rosenbaum and Rubin (1983, JRSS-B)

- Interpret the parameters:
  - $\alpha = \log\left[\frac{P(Z=1|U=1)/P(Z=0|U=1)}{P(Z=1|U=0/P(Z=0|U=0)}\right]$: log odds ratio between Z and U
  - $\delta_z = \log\left[\frac{P(Y(z)=1|U=1)/P(Y(z)=0|U=1)}{P(Y(z)=1|U=1)/P(Y(z)=0|U=1)}\right]$: log odds ratio between $Y(z)$ and U
- In practice, the the parameters is all conditioning on X or propensity scores
- For parsimony, often assume the parameters α, δ are constant across strata of X or PS

Sensitivity analysis

Rosenbaum and Rubin (1983, JRSS-B)

Sensitivity parameters

- U is not observed, the above models are not identifiable
- The parameters $\pi, \alpha, \delta_0, \delta_1$ can be viewed as sensitivity parameters
- Treatment effects can still be estimated by fixing the values of $\tau, \alpha, \delta_0, \delta_1$
- Rosenbaum and Rubin maximized the full likelihood of the two logistic models given the fixed sensitivity parameters (integration bridges observed likelihood and likelihood of full data)

Sensitivity analysis: Procedure

Rosenbaum and Rubin (1983, JRSS-B)

1. Set $\tau, \alpha, \delta_0, \delta_1$ to a grid of possible values (boundary are the most extreme values deemed plausible substantively)
2. Estimate treatment effect for each grid point
3. Assess the variability of these values: If conclusions are relatively insensitive over a range of plausible assumptions about U, causal inference is more defensible

One can also identify the boundary of the sensitivity parameters where the treatment effect reduces to null (explained away)

Sensitivity analysis: Limitations

Rosenbaum and Rubin (1983, JRSS-B)

- In order to conduct sensitivity analysis, one needs additional un-testable assumptions about confounding!
- One binary confounder, otherwise we have a large number of sensitivity parameters
- One confounder: can consider all unmeasured confounders are summarized into one dimension, similar to propensity scores
- Binary confounder: causal conclusions are more sensitive to unobserved binary covariates than (normal) continuous unobservables (Wang and Krieger, 2005)
- Parametric models
- Much literature assumes homogeneity $\delta_1 = \delta_0$, i.e., no interaction in outcome regression (Lin et al. 1998; Imbens 2003)

Sensitivity analysis: later advancements

- Rosenbaum (1987, Biometrika) assesses the sensitivity of significance levels and confidence intervals, rather than of point estimates, involves only one sensitivity parameter – the association between Z and U (design sensitivity)
- Imbens (2003) uses the same method as Rosenbaum and Rubin (1983) but expresses the sensitivity parameters in terms of partial R^2 for interpretation
- Ichino, Mealli, Nanncini (2008, J App Econometrics): nonparametrically specifies the distribution of U given Z and Y, then simulate U for each units, re-do the analysis with simulated U and original data
- Bayesian version is straightforward, and better accounts for uncertainty of SA (e.g. Schwartz, Li, Reiter, 2012, SIM)

Sensitivity analysis: later advancements

- To summarize, many sensitivity analysis (SA) techniques often require additional untestable assumptions
  - a single binary confounder U
  - no interaction between treatment and confounders on outcome
  - SA only for null hypothesis of no causal effect (focus on "explaining away" the observed effect)

- Ding and VanderWeele (2014, 2016, Biometrika; 2016 Epidemiology): sharpen the original Cornfield inequality, free of assumptions on the unmeasured confounder, only two sensitivity parameters, clean interpretation

- Further simplifications

Sensitivity Analysis Without Assumptions

(Ding and VanderWeele, 2014, 2016, Biometrika; 2016 Epidemiology)

- Assume binary outcome
- Observed relative risk (RR):

$$\begin{aligned} \mathrm{RR}^{\mathrm{obs}}_{ZY|x} &= \frac{P(Y=1 \mid Z=1,x)}{P(Y=1 \mid Z=0,x)} \\ &= \frac{\sum_u P(Y=1 \mid Z=1,x,u)P(u \mid Z=1,x)}{\sum_u P(Y=1 \mid Z=0,x,u)P(u \mid Z=0,x)} \end{aligned}$$

- Causal RR:

$$\begin{aligned} \mathrm{RR}^{\mathrm{true}}_{ZY|x} &= \frac{P\{Y(1)=1 \mid x\}}{P\{Y(0)=1 \mid x\}} \\ &= \frac{\int P\{Y(1)=1 \mid x,u\}F(du \mid x)}{\int P\{Y(0)=1 \mid x,u\}F(du \mid x)} \\ &= \frac{\sum_u P(Y=1 \mid Z=1,x,u)P(u \mid x)}{\sum_u P(Y=1 \mid Z=0,x,u)P(u \mid x)} \end{aligned}$$

- Not the same because $Z \not\perp\!\!\!\perp (Y(1), Y(0)) \mid X$

Exposure-Confounder Association

- We will use "exposure" and "treatment" interchangeably
- RR of level $U = u$:

$$\mathrm{RR}_{ZU|x}(u) = \frac{P(u \mid Z = 1, x)}{P(u \mid Z = 0, x)}$$

- Maximal RR of Z on U:

$$\mathrm{RR}_{ZU|x} = \max_{u} \mathrm{RR}_{ZU|x}(u)$$

- When U is binary, the RR of level $U = 1$ becomes the traditional RR:

$$\mathrm{RR}_{ZU|x}(1) = \frac{P(U = 1 \mid Z = 1, x)}{P(U = 1 \mid Z = 0, x)} = \mathrm{RR}_{ZU|x}$$

Confounder-Outcome Association

- Maximal RR among unexposed:

$$\mathrm{RR}_{UY(0)|x} = \frac{\max_u P\{Y(0) = 1 \mid x, u\}}{\min_u P\{Y(0) = 1 \mid x, u\}}$$

- Maximal RR among exposed:

$$\mathrm{RR}_{UY(1)|x} = \frac{\max_u P\{Y(1) = 1 \mid x, u\}}{\min_u P\{Y(1) = 1 \mid x, u\}}$$

- Maximal RR of U on Y:

$$\mathrm{RR}_{UY|x} = \max\left\{\mathrm{RR}_{UY(0)|x}, \mathrm{RR}_{UY(1)|x}\right\}$$

- When U is binary, the maximal RRs reduce to traditional RRs

Simplicity, Interpretation and Goal

- From now on, we drop the condition "$X = x$" for simplicity
- Conduct analysis within strata of covariates or propensity scores
- Measures of the strength of confounding:

$$(\mathrm{RR}_{ZU}, \mathrm{RR}_{UY})$$

- Goal of sensitivity analysis:

  (Partially) recover the causal risk ratio (RR_{ZY}^{true}) *from the observed risk ratio* (RR_{ZY}^{obs}) *and the measures of the strength of unobserved confounding* (RR_{ZU}, RR_{UY})

Main Result: Sensitivity Analysis Without Assumptions

$$\mathrm{RR}_{ZY}^{\text{true}} \geq \mathrm{RR}_{ZY}^{\text{obs}} \Big/ \frac{\mathrm{RR}_{ZU} \times \mathrm{RR}_{UY}}{\mathrm{RR}_{ZU} + \mathrm{RR}_{UY} - 1}$$

- allows for obtaining a lower bound of the causal risk ratio
- holds without any assumptions about the (nature of) unmeasured confounder(s)
- requires only two sensitivity parameters that are easy to interpret

Bounding Factor

$$\mathrm{BF}_U = \frac{\mathrm{RR}_{ZU} \times \mathrm{RR}_{UY}}{\mathrm{RR}_{ZU} + \mathrm{RR}_{UY} - 1}$$

- With (assumed) values of RR_{ZU}, RR_{UY}, dividing the $\mathrm{RR}_{ZY}^{\mathrm{obs}}$ by BF_U gives a lower bound of causal RR (do the same for CI)
- Not merely assessing a binary confounder (U can be a vector, as long as RR_{ZU}, RR_{UY} are appropriately defined as the maximum of RR comparing any two categories of multivariate U)
- No assumptions on no-interaction (homogeneity of association)
- Not restricted to how much confounding can explain away an effect

Bounding Factor

- Recall that

$$\mathrm{BF}_U = \frac{\mathrm{RR}_{ZU} \times \mathrm{RR}_{UY}}{\mathrm{RR}_{ZU} + \mathrm{RR}_{UY} - 1}$$

  is the maximum relative amount by which unmeasured confounding can reduce an observed RR

- May divide the point estimate and the CI limits by BF_U to obtain the maximum the unmeasured confounder could move the CI toward the null.

- The formula applies when the observed RR is greater than 1. If less than 1, then one multiplies BF_U rather than dividing by it

Bounding Factor

$$\mathrm{BF}_U = \frac{\mathrm{RR}_{ZU} \times \mathrm{RR}_{UY}}{\mathrm{RR}_{ZU} + \mathrm{RR}_{UY} - 1}$$

- a measure of confounding induced by U
- symmetric and monotone in RR_{ZU} and RR_{UY}
- smaller than $\min(\mathrm{RR}_{ZU}, \mathrm{RR}_{UY})$
- if one of RR_{ZU} and RR_{UY} is one, then BF_U is one
- $\approx$ half of $\max(\mathrm{RR}_{ZU}, \mathrm{RR}_{UY})$ for strong confounding

Values of the Bounding Factor

		RR_{UY}								
bounding factor		1.3	1.5	1.8	2	2.5	3	3.5	4	5
	1.3	1.06	1.08	1.11	1.13	1.16	1.18	1.20	1.21	1.23
	1.5	1.08	1.12	1.17	1.20	1.25	1.29	1.31	1.33	1.36
	1.8	1.11	1.17	1.25	1.29	1.36	1.42	1.47	1.50	1.55
	2	1.13	1.20	1.29	1.33	1.43	1.50	1.56	1.60	1.67
RR_{ZU}	2.5	1.16	1.25	1.36	1.43	1.56	1.67	1.75	1.82	1.92
	3	1.18	1.29	1.42	1.50	1.67	1.80	1.91	2.00	2.14
	3.5	1.20	1.31	1.47	1.56	1.75	1.91	2.04	2.15	2.33
	4	1.21	1.33	1.50	1.60	1.82	2.00	2.15	2.29	2.50
	5	1.23	1.36	1.55	1.67	1.92	2.14	2.33	2.50	2.78

Simple Numerical Examples

- Observed risk ratio 2.1 with a 95% CI $[1.4, 3.1]$
- Example One:
  - unmeasured confounding with $(\mathrm{RR}_{ZU}, \mathrm{RR}_{UY}) = (2, 2)$
  - bounding factor is $2 \times 2/(2 + 2 - 1) = 1.33$
  - causal risk ratio is larger than $2.1/1.33 = 1.58 > 1$
  - with lower confidence limit larger than $1.4/1.33 = 1.05 > 1$
  - cannot explain away the observed RR or its lower limit
- Example Two:
  - unmeasured confounding with $(\mathrm{RR}_{ZU}, \mathrm{RR}_{UY}) = (2.5, 3.5)$
  - bounding factor is $2.5 \times 3.5/(2.5 + 3.5 - 1) = 1.75$
  - causal risk ratio is larger than $2.1/1.75 = 1.20 > 1$
  - with lower confidence limit larger than $1.4/1.75 = 0.8 < 1$
  - cannot explain away the observed RR, but the lower limit < 1

Relation with the Cornfield Conditions

- Assuming binary U and $Z \perp Y|U$, Cornfield showed

$$\text{RR}_{ZU} \geq \text{RR}_{ZY}^{\text{obs}}$$

- Schlesselman further showed that confounder-outcome relative risk must also be at least as large as the observed exposure-outcome relative risk

$$\text{RR}_{UY} \geq \text{RR}_{ZY}^{\text{obs}}$$

- In fact, can show that these two classical Cornfield conditions are just special cases of the general results with the bounding function

Generalizing Cornfield Conditions

$$\frac{\mathrm{RR}_{ZU} \times \mathrm{RR}_{UY}}{\mathrm{RR}_{ZU} + \mathrm{RR}_{UY} - 1} \geq \frac{\mathrm{RR}_{ZY}^{\mathrm{obs}}}{\mathrm{RR}_{ZY}^{\mathrm{true}}}$$

Interpretation:

To reduce the "observed" risk ratio to the "true" risk ratio,

BF_U must exceed $\mathrm{RR}_{ZY}^{\mathrm{obs}}/\mathrm{RR}_{ZY}^{\mathrm{true}}$

- Cornfield inequality allowing for nonzero effect
- To explain away $\mathrm{RR}_{ZY}^{\mathrm{obs}}$, BF_U must exceed $\mathrm{RR}_{ZY}^{\mathrm{obs}}$
- Cornfield inequalities are special cases by letting one of RR_{ZU} or $\mathrm{RR}_{UY} \to \infty$

General Cornfield Inequalities

- Bounding factor:

$$\mathrm{BF}_U \geq \mathrm{RR}_{ZY}^{\mathrm{obs}} / \mathrm{RR}_{ZY}^{\mathrm{true}}$$

- Exposure-confounder association:

$$\mathrm{RR}_{ZU} \geq \mathrm{RR}_{ZY}^{\mathrm{obs}} / \mathrm{RR}_{ZY}^{\mathrm{true}}$$

- Confounder-outcome association:

$$\mathrm{RR}_{UY} \geq \mathrm{RR}_{ZY}^{\mathrm{obs}} / \mathrm{RR}_{ZY}^{\mathrm{true}}$$

- Cornfield inequalities were derived under stronger assumptions
  - binary confounder
  - strong null: $Z \perp\!\!\!\perp Y \mid U \implies \mathrm{RR}_{ZY}^{\mathrm{true}} = 1$ (again special case)

Stronger Cornfield Inequalities—High Thresholds

- General results can lead to – maximum of the two associations:

$$\max(\mathrm{RR}_{ZU}, \mathrm{RR}_{UY}) \geq \left\{\mathrm{RR}_{ZY}^{\mathrm{obs}} + \sqrt{\mathrm{RR}_{ZY}^{\mathrm{obs}}(\mathrm{RR}_{ZY}^{\mathrm{obs}} - \mathrm{RR}_{ZY}^{\mathrm{true}})}\right\} \Big/ \mathrm{RR}_{ZY}^{\mathrm{true}}$$

- To explain away the observed RR ($\mathrm{RR}_{ZY}^{\mathrm{true}} = 1$), the maximum must exceed:

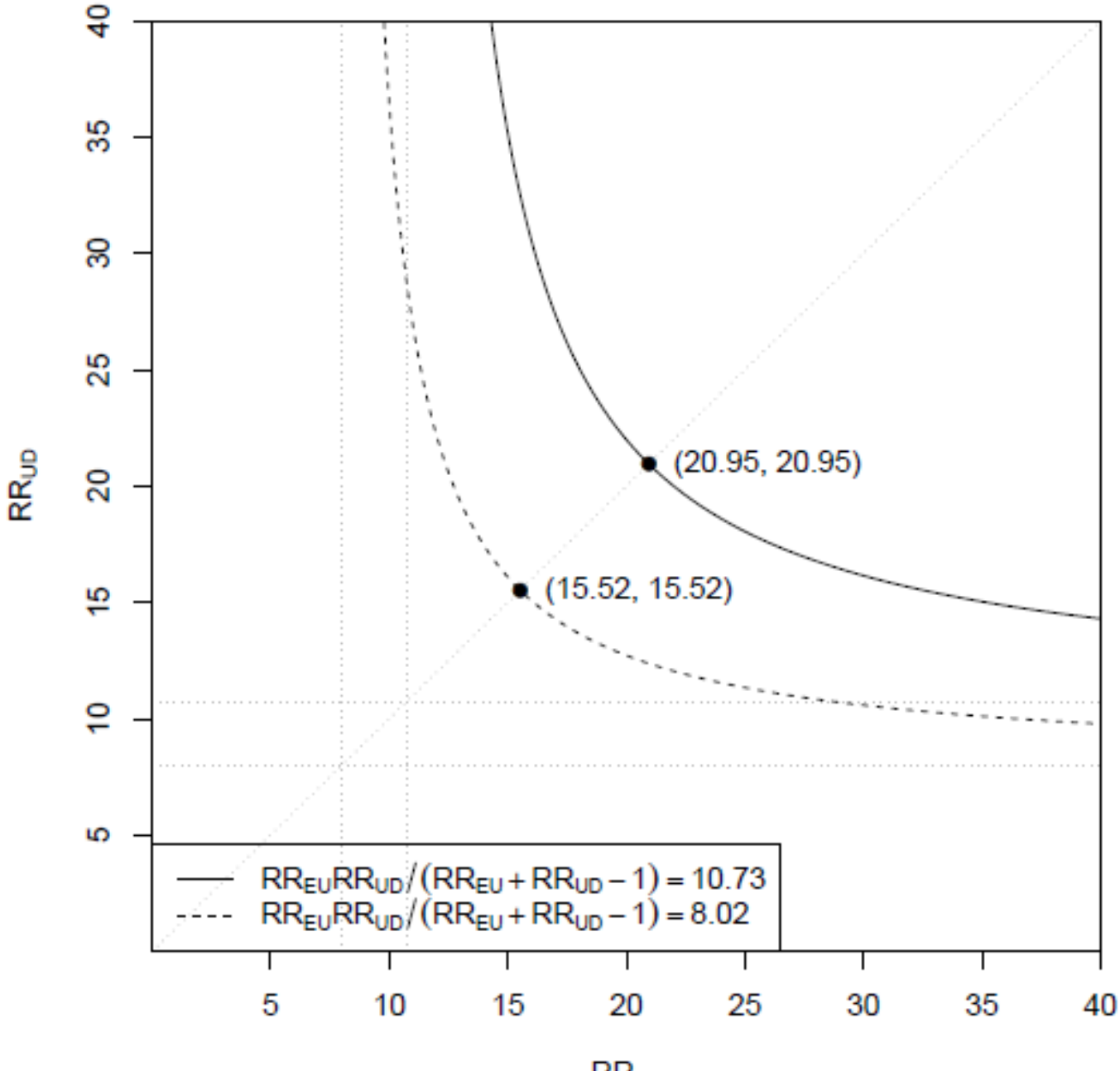
$$\max(\mathrm{RR}_{ZU}, \mathrm{RR}_{UY}) \geq \mathrm{RR}_{ZY}^{\mathrm{obs}} + \sqrt{\mathrm{RR}_{ZY}^{\mathrm{obs}}(\mathrm{RR}_{ZY}^{\mathrm{obs}} - 1)}$$

- High threshold is harder to satisfy to explain away observed RR

Back to Smoking and Lung Cancer Example

- Hammond and Horn (1958) case-cohort study in the United States
- Observed RR estimate 10.73 with a 95% CI [8.02, 14.36]
- Assume relatively strong confounding:
  - confounding measures: $(\text{RR}_{ZU}, \text{RR}_{UY}) = (10.73, 10.73)$
  - bounding factor:
    $\text{BF}_U = 10.73 \times 10.73/(10.73 + 10.73 - 1) = 5.63$
  - point estimate of causal RR $\geq 10.73/\text{BF}_U = 1.91 > 1$
  - low confidence limit of causal RR $\geq 8.02/\text{BF}_U = 1.42 > 1$

(RR_{ZU}, RR_{UY}) to explain away RR and Lower Conf. Limit



Introducing the E-Value

VanderWeele and Ding (2017; Annals of Internal Medicine)

- The bounding factor condition motivates the E-value (published in 2017, already 817 citations and up)
- Definition: *The E-value represents the minimum strength of association, on the RR scale, that an unmeasured confounder would need to have with both the treatment and outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates*

E-value

- Unlike BF_U, the E-value focuses on the magnitude of the confounder associations that could produce confounding bias equal to the observed treatment-outcome association
- Simple calculation

$$\text{E-value} = \mathrm{RR} + \sqrt{\mathrm{RR} \times (\mathrm{RR} - 1)},$$

  where $\mathrm{RR} = \mathrm{RR}_{ZY}^{\mathrm{obs}}$, i.e. the observed RR
- No need to choose the variables but merely reports how strongly an unmeasured confounder must be related to the treatment and outcome to explain away an effect estimate
- leave the readers or other researchers to assess whether the confounder associations of that magnitude are plausible

Motivation

- Obtained under high threshold with causal null

$$\max(\mathrm{RR}_{ZU}, \mathrm{RR}_{UY}) \geq \mathrm{RR}_{ZY}^{\mathrm{obs}} + \sqrt{\mathrm{RR}_{ZY}^{\mathrm{obs}}(\mathrm{RR}_{ZY}^{\mathrm{obs}} - 1)}$$

- Essentially sets the two sensitivity parameters, $\mathrm{RR}_{ZU} = \mathrm{RR}_{UY}$, equal to each other to determine the required minimum for both
- Simple calculation and minimum assumptions

What the statements should be like?

- Just like the statements for p-value, interpreting E-value is made easier with a "template"
- *"The observed risk ratio of (**put your point estimate here**) could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of (**put your E-value here**)-fold each, above and beyond the measured confounders, but weaker confounding could not do so."*

Another Simple Example

- For a observed $\text{RR}_{ZY}^{obs} = 3.9$, one may calculate the E-value as

$$\text{E-value} = 3.9 + \sqrt{3.9 \times (3.9 - 1)} = 7.26$$

- Relatively strong confounding associations would be needed to completely explain away the observed treatment-outcome association

- Further, If 1 of the 2 parameters, RR_{ZU} and RR_{UY}, is smaller than the E-value, then the other must be larger (to explain away the results)

Operationalize the reporting of E-values

VanderWeele and Ding (2017; Annals of Internal Medicine)

Table 1. Calculating the E-Value for Risk Ratios

Estimate or CI, by Direction of Risk Ratio	Computation of the E-Value
***RR* >1**	
Estimate	E-value = $RR + \text{sqrt}\{RR \times (RR - 1)\}$
CI	If $LL \leq 1$, then E-value = 1 If $LL > 1$, then E-value = $LL + \text{sqrt}\{LL \times (LL - 1)\}$
***RR* <1**	
Estimate	Let $RR^* = 1/RR$ E-value = $RR^* + \text{sqrt}\{RR^* \times (RR^* - 1)\}$
CI	If $UL \geq 1$, then E-value = 1 If $UL < 1$, then let $UL^* = 1/UL$ and E-value = $UL^* + \text{sqrt}\{UL^* \times (UL^* - 1)\}$

LL = lower limit of the CI; *RR* = risk ratio; *RR** = inverse of *RR*; *UL* = upper limit of the CI; *UL** = inverse of *UL*.

Remarks of E-value

- The E-value is a continuous measure of an association's robustness to potential uncontrolled confounders
- The lowest possible E-value is 1 (that is, no unmeasured confounding is needed to explain away the observed association)
- The higher the E-value, the stronger the confounder associations must be to explain away the effect
- Again, the E-value essentially sets the 2 parameters, RR_{ZU} and RR_{UY}, in the high threshold, equal to each other to determine the required minimum for both

Remarks of E-value

- What about E-values for other effect measures (OR, HR or mean differences for continuous outcomes)
  - E-values can be computed based on conversion formulas (e.g. transform OR, HR to RR)
- E-value depends on the magnitude of the association, and cannot be made arbitrarily large by simply increasing N (p-value will)
- The E-value for the CI depends on the sample size, but bounded by the strength of the association
- In the context of biomedical studies, effect sizes $\geq$ 2- or 3-fold occasionally occur but are not particularly common; a variable that affects both treatment and outcome each by 2- or 3-fold would likely be even less common

Back to Sir Austin Bradford Hill's 1965 Paper

famous for "Bradford Hill's criteria" for determining causation

> *What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation? (1) Strength. First upon my list I would put the strength of the association... (2) ...(9)...*

- To explain away larger effects, we need larger bounding factors.
- To explain away larger effects, we need stronger confounding.
- Another view: Rosenbaum (2004)'s "design sensitivity" for testing

Extension—Other Standardization Populations

- Treatment effect on the treated

$$\begin{aligned} \mathrm{RR}_{ZY+}^{\text{true}} &= \frac{P\{Y(1)=1 \mid Z=1, c\}}{P\{Y(0)=1 \mid Z=1, c\}} \\ &= \frac{\sum_u P(Y=1 \mid Z=1, u) P(u \mid Z=1)}{\sum_u P(Y=1 \mid Z=0, u) P(u \mid Z=1)} \end{aligned}$$

- The same result hold:

$$\mathrm{RR}_{ZY+}^{\text{true}} \geq \mathrm{RR}_{ZY}^{\text{obs}} \Big/ \frac{\mathrm{RR}_{ZU} \times \mathrm{RR}_{UY}}{\mathrm{RR}_{ZU} + \mathrm{RR}_{UY} - 1}$$

- Analogous for treatment effect on the control

Extension—Preventive Exposures

- Observed risk ratio: $\mathrm{RR}_{ZY}^{\mathrm{obs}} < 1$
- Relabel the levels of the exposure
- Or modify exposure-confounder association as

$$\mathrm{RR}_{ZU} = \max_{u} \mathrm{RR}_{ZU}^{-1}(u)$$

- Analogous result for upper bound:

$$\mathrm{RR}_{ZY}^{\mathrm{true}} \leq \mathrm{RR}_{ZY}^{\mathrm{obs}} \times \frac{\mathrm{RR}_{ZU} \times \mathrm{RR}_{UY}}{\mathrm{RR}_{ZU} + \mathrm{RR}_{UY} - 1}$$

Extension—Average Over Observed Covariates

Previous results are about conditional causal risk ratio:

$$\mathrm{RR}^{\text{true}}_{ZY|x} = \frac{P\{Y(1) = 1 \mid x\}}{P\{Y(0) = 1 \mid x\}}$$

We may be more interested in marginal causal risk ratio:

$$\mathrm{RR}^{\text{true}}_{ZY} = \frac{P\{Y(1) = 1\}}{P\{Y(0) = 1\}}$$

- Worse case without assumptions:

$$\mathrm{RR}^{\text{true}}_{ZY} \geq \min_{x} \left(\mathrm{RR}^{\text{obs}}_{ZY|x} / \mathrm{BF}_{U|x} \right)$$

- Common risk ratio as in log-linear model:

$$\mathrm{RR}^{\text{true}}_{ZY} \geq \max_{x} \left(\mathrm{RR}^{\text{obs}}_{ZY|x} / \mathrm{BF}_{U|x} \right)$$

Risk Difference Scale—Average Treatment Effect

Again within strata of covariates or propensity scores

- Treatment effect on the exposed:

$$\begin{aligned} \mathrm{RD}^{\mathrm{true}}_{ZY+} &= P\{Y(1)=1 \mid Z=1\} - P\{Y(0)=1 \mid Z=1\} \\ &= P(Y=1 \mid Z=1) - P\{Y(0)=1 \mid Z=1\} \end{aligned}$$

- Treatment effect on the unexposed:

$$\begin{aligned} \mathrm{RD}^{\mathrm{true}}_{ZY-} &= P\{Y(1)=1 \mid Z=0\} - P\{Y(0)=1 \mid Z=0\} \\ &= P\{Y(1)=1 \mid Z=0\} - P(Y=1 \mid Z=0) \end{aligned}$$

- Observed: $\mathrm{RD}^{\mathrm{obs}}_{ZY} = P(Y=1 \mid Z=1) - P(Y=1 \mid Z=0) \equiv p_1 - p_0$

Bounding the Causal RDs for Exposed and Unexposed

- Same bounding factor:

$$\mathrm{BF}_U = \frac{\mathrm{RR}_{ZU} \times \mathrm{RR}_{UY}}{\mathrm{RR}_{ZU} + \mathrm{RR}_{UY} - 1}$$

- Treatment effect on the exposed:

$$\mathrm{RD}^{\mathrm{true}}_{ZY+} \geq p_1 - p_0 \times \mathrm{BF}_U$$

- Treatment effect on the unexposed:

$$\mathrm{RD}^{\mathrm{true}}_{ZY-} \geq p_1/\mathrm{BF}_U - p_0$$

- Observed: $\mathrm{RD}^{\mathrm{obs}}_{ZY} = p_1 - p_0$

Bounding the Causal RDs for the Whole Population

- Prevalence of exposure $f = P(Z = 1)$
- ATE for the whole population:

$$\begin{aligned} \mathrm{RD}_{ZY}^{\mathrm{true}} &= P\{Y(1) = 1\} - P\{Y(0) = 1\} \\ &= f\mathrm{RD}_{ZY+}^{\mathrm{true}} + (1 - f)\mathrm{RD}_{ZY-}^{\mathrm{true}} \end{aligned}$$

- If we specify f, then

$$\mathrm{RD}_{ZY}^{\mathrm{true}} \geq (p_1 - p_0 \times \mathrm{BF}_U)\left(f + \frac{1 - f}{\mathrm{BF}_U}\right)$$

- Otherwise we still have

$$\mathrm{RD}_{ZY}^{\mathrm{true}} \geq \min\left(\mathrm{RD}_{ZY+}^{\mathrm{true}}, \mathrm{RD}_{ZY-}^{\mathrm{true}}\right)$$

Cornfield-type Inequalities for RD—Equivalent Forms

- For exposed:

$$BF_U \geq (p_1 - \mathrm{RD}^{\mathrm{true}}_{ZY+})/p_0$$

- For unexposed:

$$BF_U \geq p_1/(p_0 + \mathrm{RD}^{\mathrm{true}}_{ZY-})$$

- For the whole population:

$$\mathrm{BF}_U \geq \frac{\sqrt{\{\mathrm{RD}^{\mathrm{true}}_{ZY}+p_0(1-f)-p_1 f\}^2+4p_1p_0f(1-f)}-\{\mathrm{RD}^{\mathrm{true}}_{ZY}+p_0(1-f)-p_1 f\}}{2p_0 f}$$

- Low and high thresholds for RR_{ZU} and RR_{UY}

- $\mathrm{RD}^{\mathrm{true}}_{ZY+} = \mathrm{RD}^{\mathrm{true}}_{ZY-} = 0$: all reduce to the same as on the RR scale.

Average Over Observed Covariates

- Previous results are about conditional causal RD:

$$\mathrm{RD}^{\mathrm{true}}_{ZY|x} = \Pr\{Y(1) = 1 \mid x\} - \Pr\{Y(0) = 1 \mid x\}$$

- We may be more interested in marginal causal RD:

$$\mathrm{RD}^{\mathrm{true}}_{ZY} = \Pr\{Y(1) = 1\} - \Pr\{Y(0) = 1\}$$

- Simply by linearity:

$$\mathrm{RD}^{\mathrm{true}}_{ZY} = \sum_{x} \mathrm{RD}^{\mathrm{true}}_{ZY|x} P(x)$$

Discussion—Binary Confounder Assumption

- Cornfield et al. (1959) assumed this to refute Fisher.
- Bross (1966, 1967), Schlesselman (1978), Rosenbaum and Rubin (1983), and Imbens (2003) all imposed this assumption.
- Without it, sensitivity analysis involves lots of sensitivity parameters (Flanders and Khoury 1990; VanderWeele and Arah 2011).
- Wang and Krieger (2006): "Causal conclusions are most sensitive to unobserved binary covariates" for matched pairs.
- Ichino et al. (2008): extreme binary confounder recovers bounds
- This assumption is not crucial in the Ding-VanderWeele framework.

Discussion—Scale of Sensitivity Parameters

- For RR and RD: sensitivity parameters on RR scale
- Sensitivity parameters on RD scale (Ding and VanderWeele 2014)
  - results depend on the number of categories of U
  - become weaker with more categories of U
  - not appropriate for sensitivity analysis

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