Sensitivity Analysis

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Definition

- A method to determine the robustness of an assessment by examining the extent to which **results are affected by changes** in **methods, models, values of unmeasured variables, or assumptions** (Thabane et al, 2013)
- A series of analyses of a data set to assess whether **altering any of the assumptions** made leads to **different final interpretations or conclusions** (Thabane et al, 2013)
- "Sensitivity analysis" is also referred to as "**bias analysis**" (Rothman et al., 2008; lash et al., 2009; Ding and VanderWeele, 2016)

Importance

- Epidemiological studies, regardless of study design, often **rely on some assumptions**. If those assumptions are violated, results or conclusions might be affected.
- For instance, Ignorability assumption for general causal inference (no unmeasured confounder); Missing Completely At Random/At Random for Complete-Case Analysis
- Researchers in Epi are interested in higher causal strength, better reliability and better validity
- To determine the robustness of our results
- To strengthen our conclusions and credibility of results

Types

- **Basic idea is same:** to assess the effects of altering underlying assumptions by conducting sensitivity analysis
- **Observational Studies (Delaney and Seeger, 2013):**
- 1) study definitions (exposure, outcome, covariate, confounder, selection bias)
- 2) study design (data source, subpopulations, measurements)
- 3) modelling (distributions and functional forms)
- Something more: missing data

Types

- **RCTs (Thabane et al, 2013):**
- Outliers, missing data, definition of outcome, distributional assumptions, non-compliance and protocol deviation, clustering or correlation and multisite, competing risks, baseline imbalance
- Not the focus of this presentation

Limitations

- **Subjectivity**: researchers could choose the sensitivity parameters that make the result seem robust
- **Assumptions of assessing assumptions**: conducting sensitivity analysis needs new assumptions to test old assumptions
- **Complexity**: most of sensitivity analysis approaches are not easy to use or interpret (for instance, using propensity score, instrumental variable analysis or multiple imputation)
- **Difficulty to publish**: sensitivity analysis takes much space

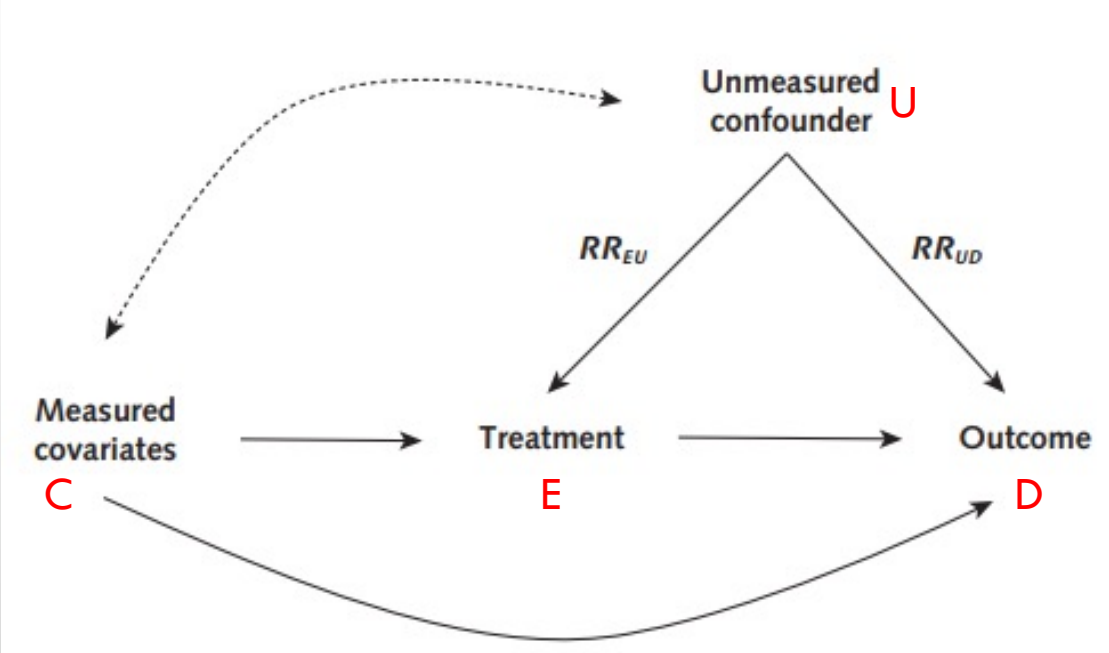
E-Value

- **Definition**: the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have **with both the treatment and the outcome** to fully explain away a specific treatment-outcome association, **conditional on the measured confounding**.
- Developed by Peng Ding and Tyler J. VanderWeele (2016, 2017)
- To assess the potential effect of unmeasured confounders on causal conclusions in observational studies

Assumptions

- Luckily, NONE

Notations



E: Exposure
D: Binary Outcome
C: Measured Confounders
U: One or More Unmeasured Confounders (with K categories)
RR: risk ratio

Parameters

$$RR_{ED|c}^{obs} = \frac{P(D=1|E=1,C=c)}{P(D=1|E=0,C=c)}$$

Observed RR of Exposure on Outcome in stratum of Measured Confounders C=c

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$$RR_{EU,k|c} = \frac{P(U=k|E=1,C=c)}{P(U=k|E=0,C=c)} \rightarrow RR_{EU|c} = max_k RR_{EU,k|c}$$

Maximal RR between Exposure and Unmeasured Confounders in stratum C=c

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$$RR_{UD|E=0,c} = \frac{max_k P(D=1|E=0,C=c,U=k)}{min_k P(D=1|E=0,C=c,U=k)}$$

$$RR_{UD|E=1,c} = \frac{max_k P(D=1|E=1,C=c,U=k)}{min_k P(D=1|E=1,C=c,U=k)}$$

$$RR_{UD|c} = \max(RR_{UD|E=1,c}, RR_{UD|E=0,c})$$

Maximal RR of Unmeasured Confounders on Outcome in stratum C=c

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$$RR_{ED|c}^{true} = \frac{\sum_{k=0}^{K-1} P(D=1|E=1,C=c,U=k)P(U=k|C=c)}{\sum_{k=0}^{K-1} P(D=1|E=0,C=c,U=k)\,P(U=k|C=c)}$$

True causal RR of Exposure on Outcome in stratum C=c

Bounding Factor and E Value

If $RR^{obs}_{ED|c} > 1$, $RR^{true}_{ED|c} \geq RR^{obs}_{ED|c} \Big/ \frac{RR_{EU|c} \times RR_{UD|c}}{RR_{EU|c} + RR_{UD|c} - 1}$ → Bounding Factor (B)

The largest factor by which U could reduce an observed RR

If $RR^{obs}_{ED|c} < 1$, $RR^{true}_{ED|c} \leq RR^{obs}_{ED|c} \times \frac{RR_{EU|c} \times RR_{UD|c}}{RR_{EU|c} + RR_{UD|c} - 1}$

If $RR^{obs}_{ED|c} > 1$, $\max(RR_{EU|c}, RR_{UD|c}) \geq E\ Value$

$$= RR^{obs}_{ED|c} + \sqrt{RR^{obs}_{ED|c} \times (RR^{obs}_{ED|c} - 1)}$$

$E\ Value \geq 1$

Estimate or CI, by Direction of Risk Ratio	Computation of the E-Value
***RR* >1**	
Estimate	E-value = *RR* + sqrt{*RR* × (*RR* − 1)}
CI	If *LL* ≤ 1, then E-value = 1 If *LL* > 1, then E-value = *LL* + sqrt{*LL* × (*LL* − 1)}
***RR* <1**	
Estimate	Let *RR** = 1/*RR* E-value = *RR** + sqrt{*RR** × (*RR** − 1)}
CI	If *UL* ≥ 1, then E-value = 1 If *UL* < 1, then let *UL** = 1/*UL* and E-value = *UL** + sqrt{*UL** × (*UL** − 1)}

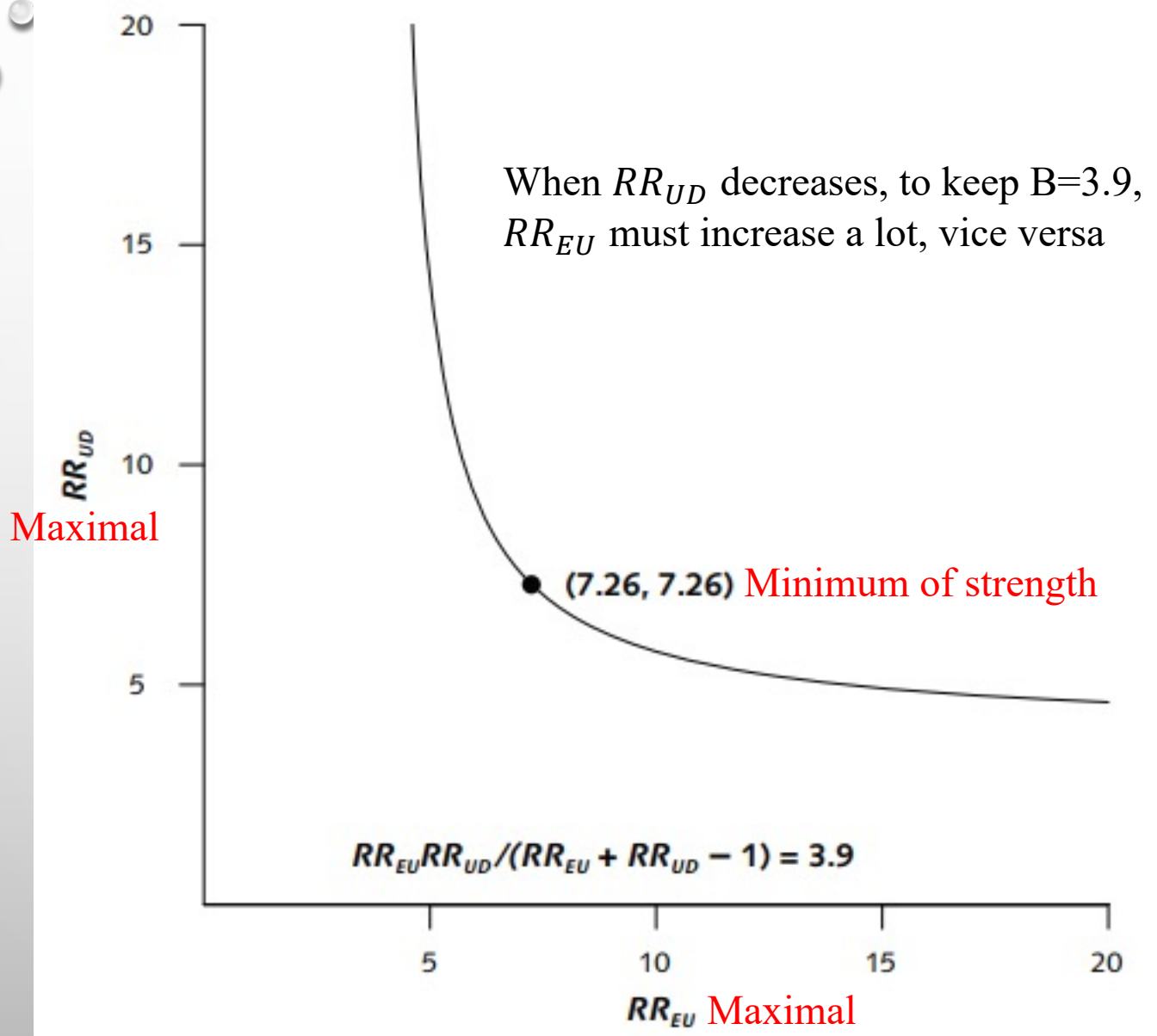
LL = lower limit of the CI; *RR* = risk ratio; *RR** = inverse of *RR*; *UL* = upper limit of the CI; *UL** = inverse of *UL*.

Example (VanderWeele and Ding, 2017)

- Association between maternal breastfeeding (E) and respiratory death (D) (Victora et al, 1987)
- RR^{obs} =3.9 (CI, 1.8 to 8.7) for infants formula-fed rather than breastfed
- Unmeasured confounder (U): maternal smoking status
- Adjusted measured confounders

- Suppose maximal $RR_{UD} = 4$ and $RR_{EU} = 2$
- $B = 4 \times \frac{2}{4+2-1} = 1.6$
- $RR^{true} \geq 3.9/1.6 = 2.43$ (CI, 1.1 to 5.4)
- U would not suffice to explain away the effect estimate of E on D

- E-value $= 3.9 + \sqrt{3.9 \times (3.9 - 1)} = 7.26$
- The observed RR of 3.9 could be explained away by an unmeasured confounder that was associated with both exposure and outcome by a RR of 7.26-fold each, above and beyond the measured confounders, but weaker confounding could not do so



- Large E-value: considerable unmeasured confounding would be needed to explain away an effect estimate
- Small E-value: little unmeasured confounding would be needed to explain away an effect estimate
- "Large or small" is relative to the outcome and exposure

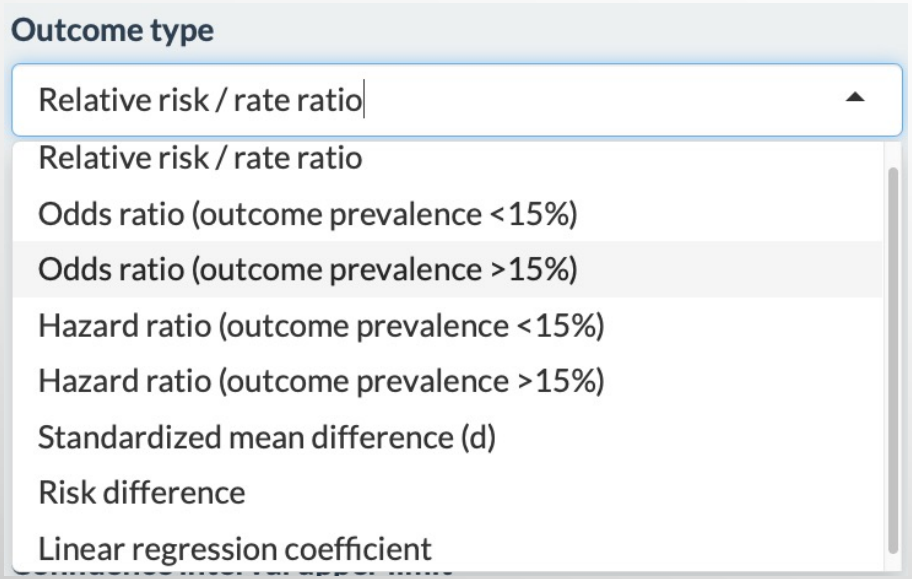
Strengths and Limitations

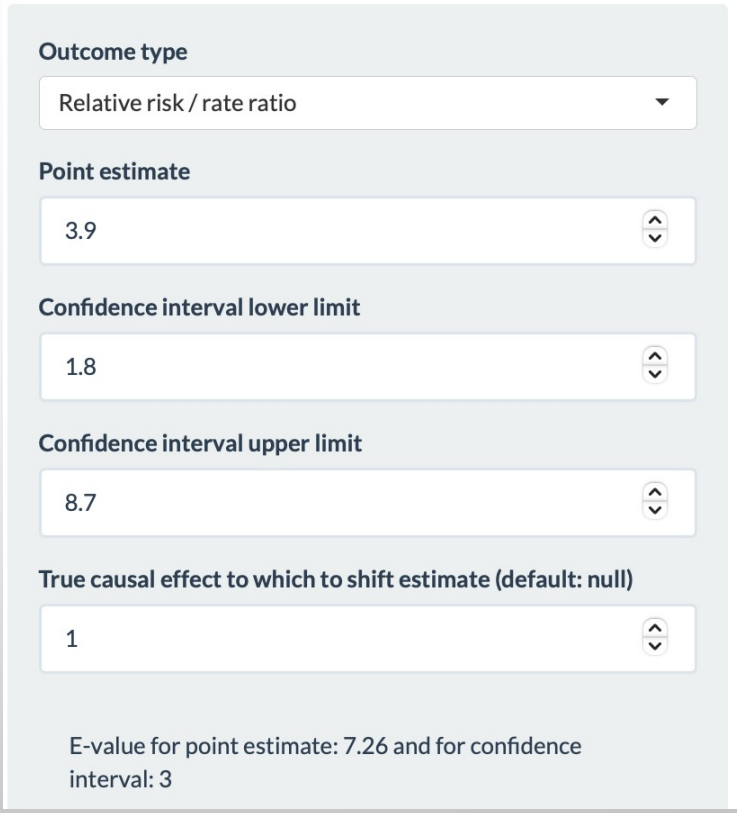
- **Strengths:**
- Without assumptions (Conservative)
- Easy to calculate, report and interpret
- Standardized across different scales (OR, HR, count, continuous outcome)
- Reducing subjectivity
- **Limitations:**
- Avoid to be used: unmeasured confounder is known and rare
- E-value cannot be used to provide evidence for no effect
- Hard to interpret when unmeasured confounders have more than 2 categories or are continuous
- Bias other than confounding, such as selection bias, measurement error or publication bias can undermine causal effects

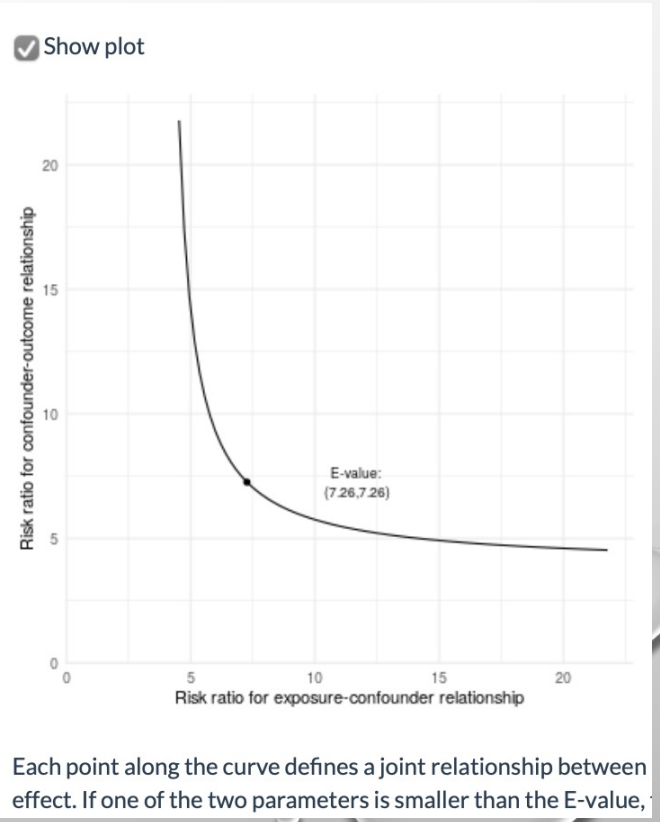
Applications

- R Package: EValue
- Stata Module: EVALUE
- Website: https://www.evalue-calculator.com

More Resources: selection bias; measurement error; a combination of unmeasured confounding, selection bias, and measurement error; unmeasured confounding and publication bias in meta-analyses







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