Sensitivity Analysis for Unmeasured Confounding in Studies and Meta-Analyses

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Goal

Assess the strength of evidence for causality in observational research that is potentially subject to unmeasured confounding.

Do so while avoiding assumptions on the structure or type of unmeasured confounder(s).

Questions of sensitivity analysis

Question #1: Given unmeasured confounding of specified strength, how large of a true causal e↵ect would remain?

Question #2: How severe would unmeasured confounding have to be to "explain away" the e↵ect?

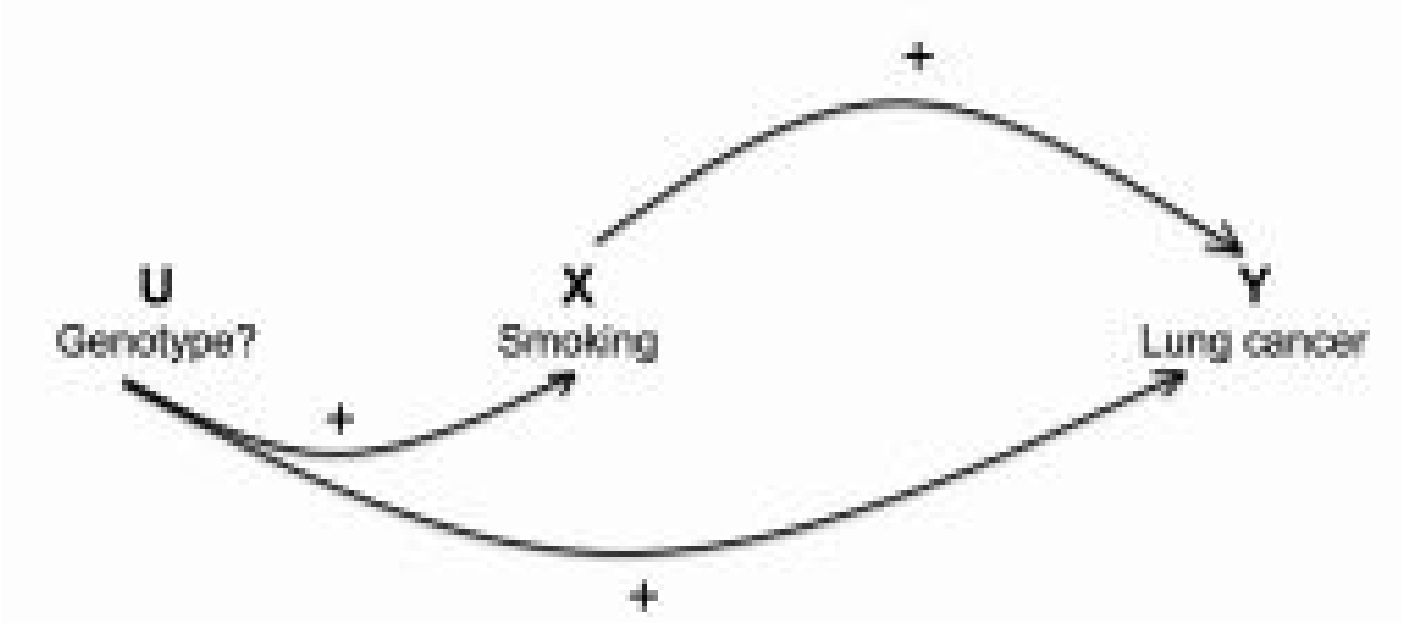
Sensitivity analysis for a single study

VanderWeele TJ & Ding P (2017). Sensitivity analysis in observational research: Introducing the E-value. *Annals of Internal Medicine*, 167(4), 268-274.

Example

An early debate about unmeasured confounding concerned the e↵ect of smoking on lung cancer.

Some (e.g., Fisher) disputed causal claims: Might confounding by genotype explain away the association?



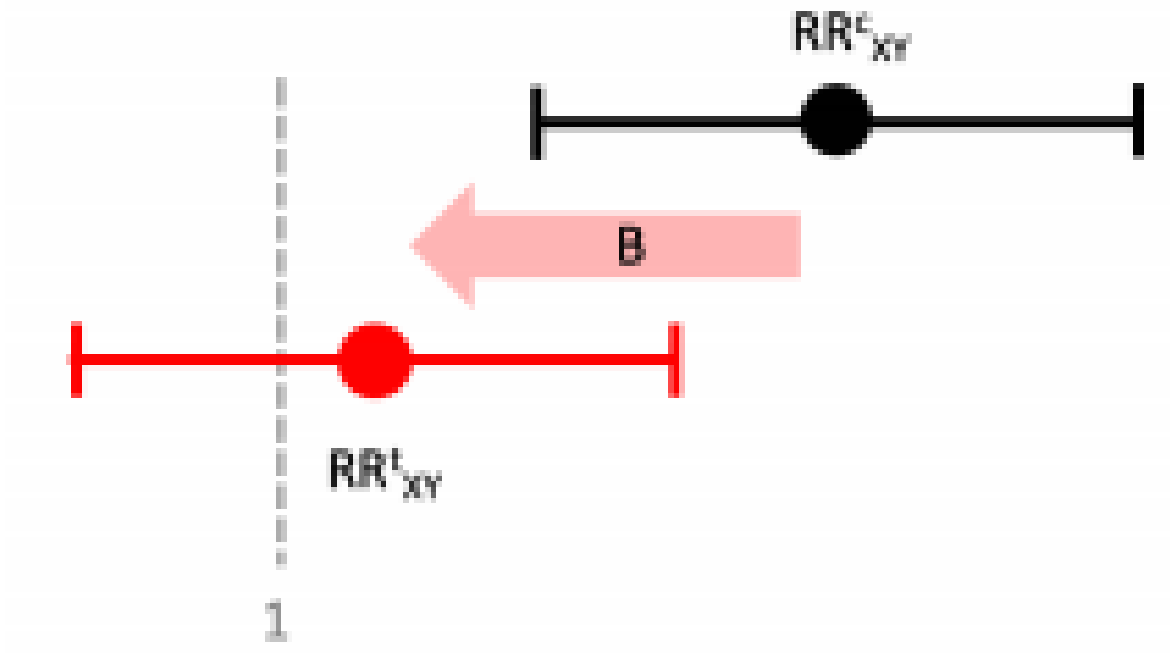
Question #1

Given unmeasured confounding of specified strength, how strong would the true causal e↵ect of smoking on lung cancer still be?

Bounds on confounding bias

RR^c_{XY}, RR^t_{XY}: confounded (observed) and true relative risks

Define the ratio of the confounded to true relative risk (for $RR^c_{XY} > 1$) as: $B = RR^c_{XY}/RR^t_{XY}$.



Bounds on confounding bias

For $RR^c_{XY} > 1$

RR^c_{XY}, RR^t_{XY}: confounded (observed) and true relative risks

✓ $RR_{XU} \cdot RR_{UY}$, $RR^{c}_{XY} > 1$

◆

RR^{t}_{XY} RR^{c}_{XY} $RR_{XU} + RR_{UY} - 1$

bound on B

RR_{XU} : Strongest RR_{XU} comparing any 2 categories of U

RR_{UY} : Strongest RR_{UY} comparing any 2 categories of U among $X = 0$ or $X = 1$

Bounds on confounding bias

For $RR^{c}_{XY} > 1$

RR^{c}_{XY}, RR^{t}_{XY} : confounded (observed) and true relative risks

✓ $RR_{XU} \cdot RR_{UY}$, $RR^{c}_{XY} > 1$

◆

RR^{t}_{XY} RR^{c}_{XY} $RR_{XU} + RR_{UY} - 1$

bound on B

Example

Smoking and lung cancer: $RR^{c}_{XY} = 10.73$.

Suppose $RR_{XU} = 2$ and $RR_{UY} = 3$.

Then bound on $B = \frac{2 \cdot 3}{2+3-1} = 1.5$, shifting the point estimate to 10.73/1.5=7.2 (still large!).

Bounds on confounding bias

For $RR^{c}_{XY} < 1$

RR^{c}_{XY}, RR^{t}_{XY}: confounded (observed) and true relative risks

RR^t_{XY} □ RR^c_{XY} ·

◆ ✓ $RR_{XU} \cdot RR_{UY}$, $RR^c_{XY} < 1$

$RR_{XU} + RR_{UY}$ 1

| {z }

bound on B

RR_{XU} : Strongest RR_{XU} for any category of confounder U

(inverse) RR_{UY} : Strongest RR_{UY} for any 2 categories of U among $X = 0$ or $X = 1$

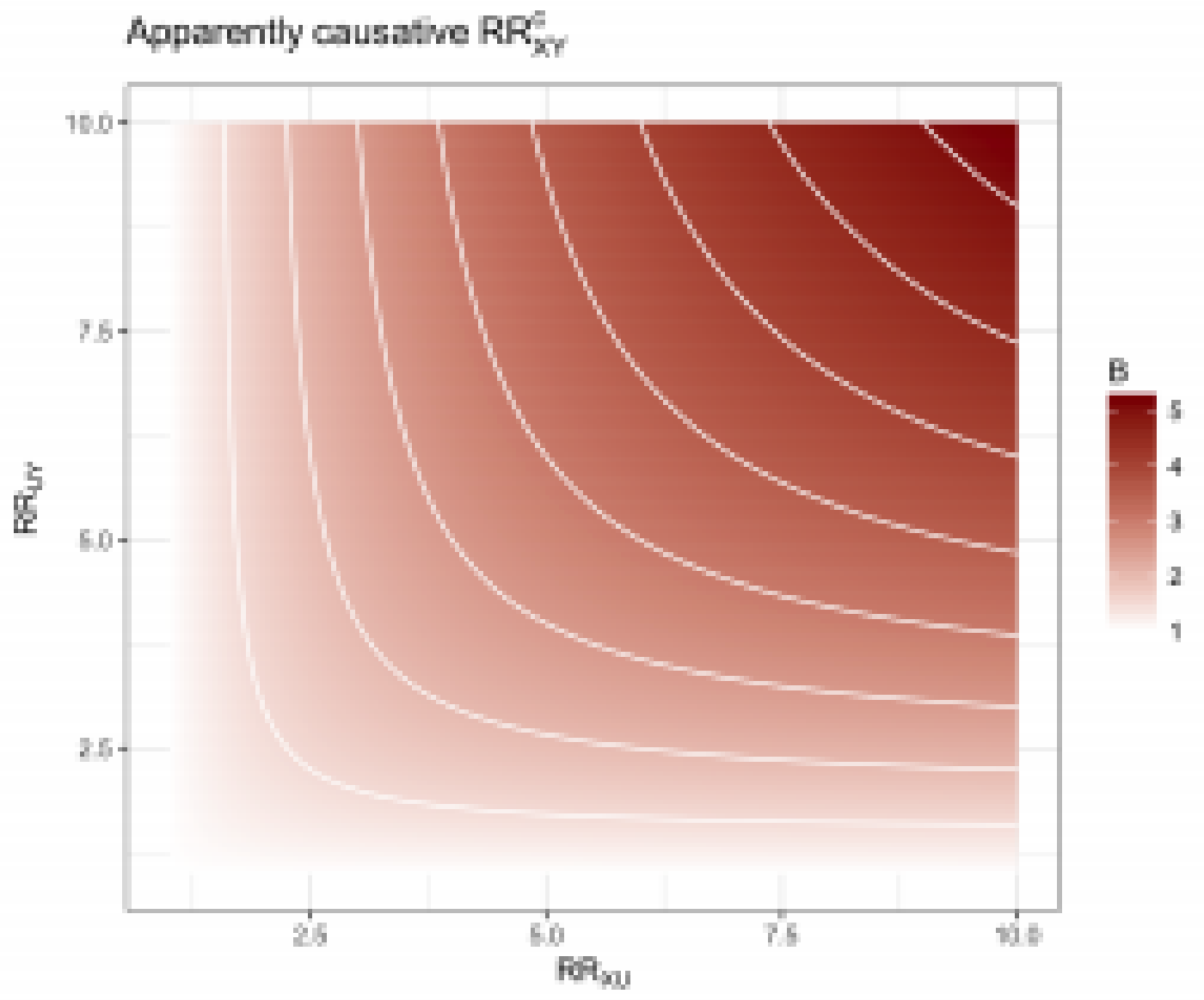
Fine print

Slight revisions to the definitions of RR_{XU} and RR_{UY} allow the same bound to apply for arbitrary type and number of U.

Can condition on any measured confounders throughout: then

B is the bias factor *above and beyond* measured confounders.

Visualizing the bias factor

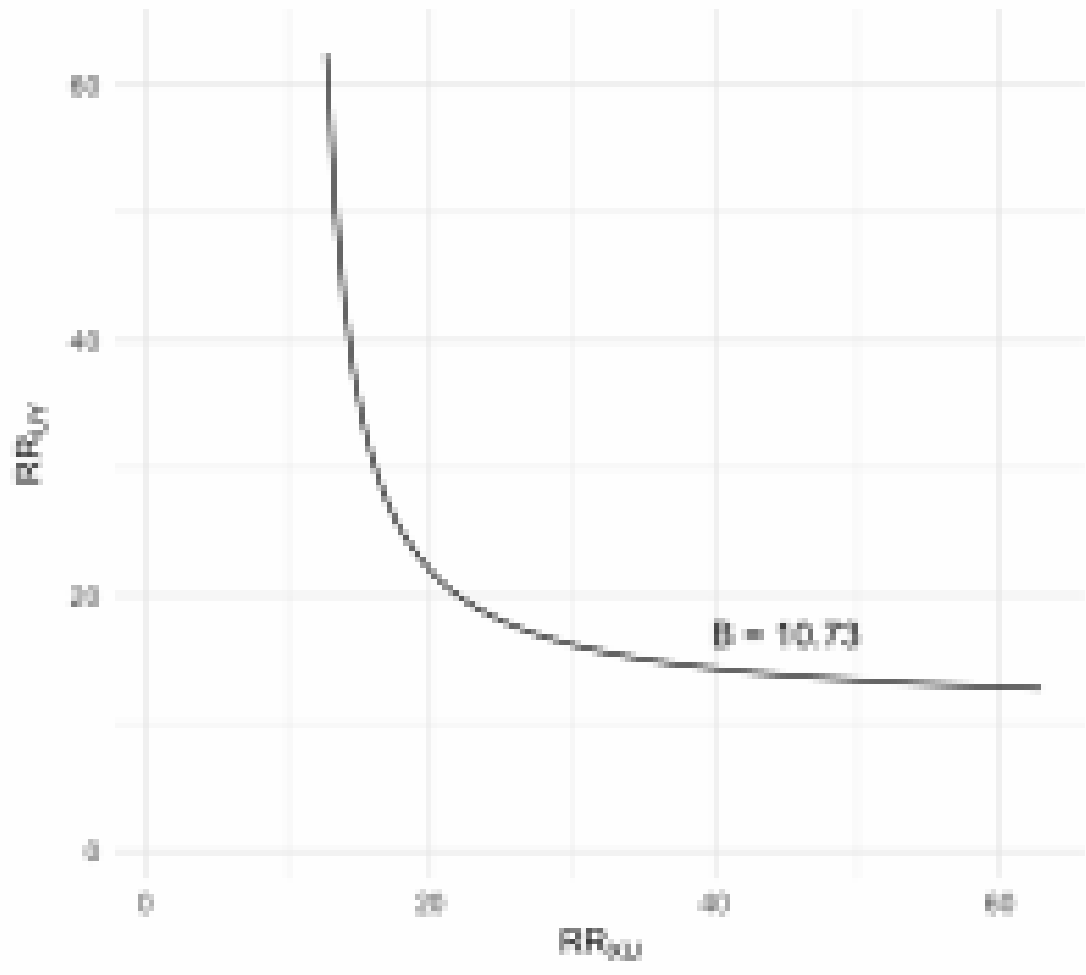

Apparently causative RR^{C}_{XY}
10.0
7.5
5.0
2.5
RR_{UY}
2.5
5.0
7.5
10.0
RR_{XU}
B
5
4
3
2
1

Question #2

How strong would unmeasured confounding have to be in order to completely explain away the e↵ect of smoking on lung cancer?

Example

Smoking and lung cancer: $RR^{c}_{XY} = 10.73$, 95% CI: [8.02,

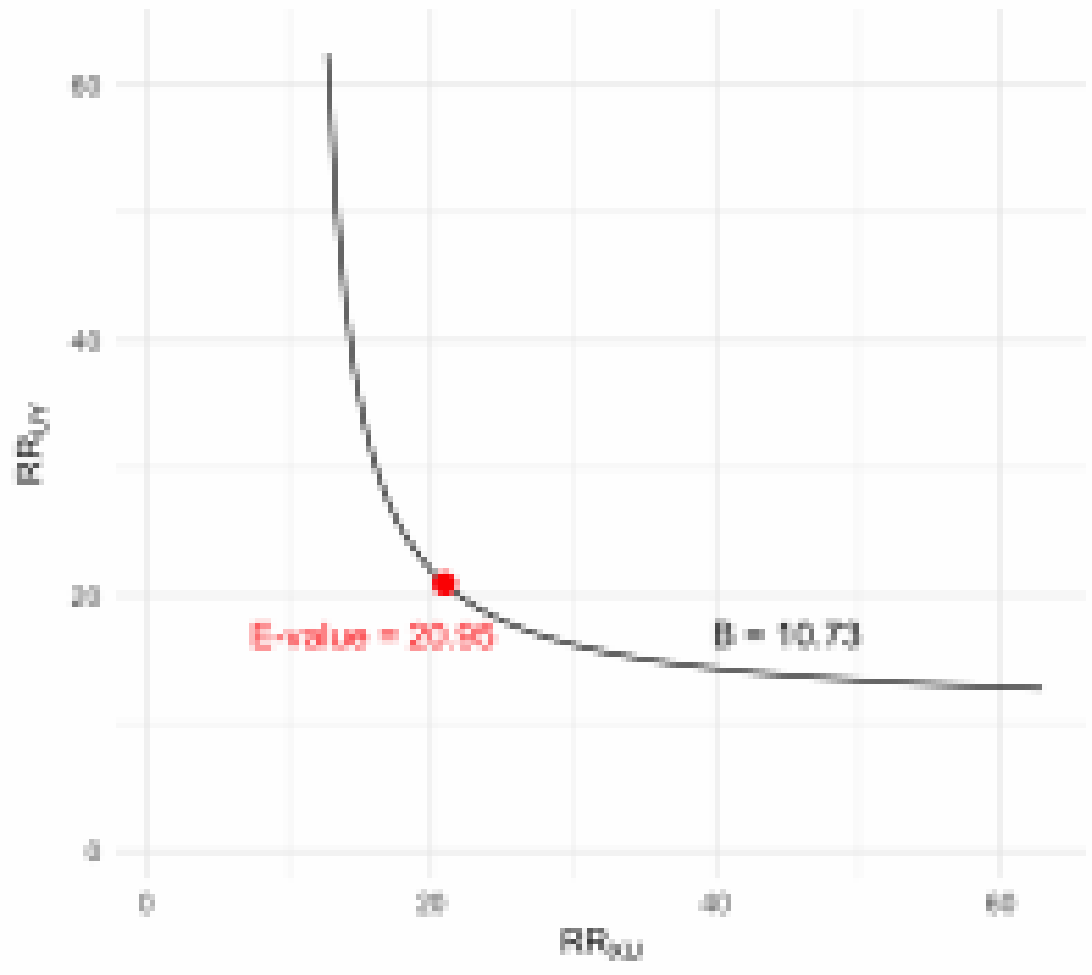


14.36].

Example

Smoking and lung cancer: $RR^{c}_{XY} = 10.73$, 95% CI: [8.02,

14.36]



The E-value

The minimum strength of association (*RR* scale) that *U* must have with both *X* and *Y* (conditional on measured covariates) to fully explain away RR^{c}_{XY} (i.e., to have $RR^{t}_{XY} = 1$).

$$\text{E-value} = RR^{c}_{XY} + \sqrt{RR^{c}_{XY} \cdot RR^{c}_{XY} - 1},\ RR^{c}_{XY} > 1$$

(For $RR^{c}_{XY} < 1$, first take its inverse.)

Could apply to point estimate and CI limit closer to null.
Smoking and lung cancer: E-value for lower CI limit of

$$8.08 \text{ is } 8.08 + \sqrt{8.08 \cdot (8.08 - 1)} = 15.64$$

.

Interpretation

For smoking and lung cancer (E-value for point estimate of 20.95 and for CI of 15.64):

“With an observed risk ratio of 10.73, an unmeasured

confounder that was associated with both the outcome and the exposure by a risk ratio of 21-fold each, above and beyond the measured confounders, could explain away the estimate, but weaker confounding could not. An unmeasured confounder that was associated with both the outcome and the exposure by a risk ratio of 16-fold each, above and beyond the measured confounders, could shift the CI to include the null, but weaker confounding could not."

Large E-value *)* Only severe unmeasured confounding could explain away the e↵ect *)* robust to unmeasured confounding

Small E-value *)* Weak unmeasured confounding could potentially explain away the e↵ect *)* not robust to unmeasured confounding

E-values vs. p-values

Associations of breast-feeding with health outcomes (AHRQ, 2007; Moorman, 2008):

Outcome	RR^{c}_{XY}	p-value	E_{est}	E_{CI}
Maternal ovarian cancer	0.50 [0.30, 0.80]	0.006	3.4	1.8
Childhood leukemia	0.81 [0.71, 0.91]	< 0.001	1.8	1.4

p-value is more extreme for leukemia than ovarian cancer, but opposite is true for E-values.

Other e↵ect size scales

Can apply E-value formula as-is:

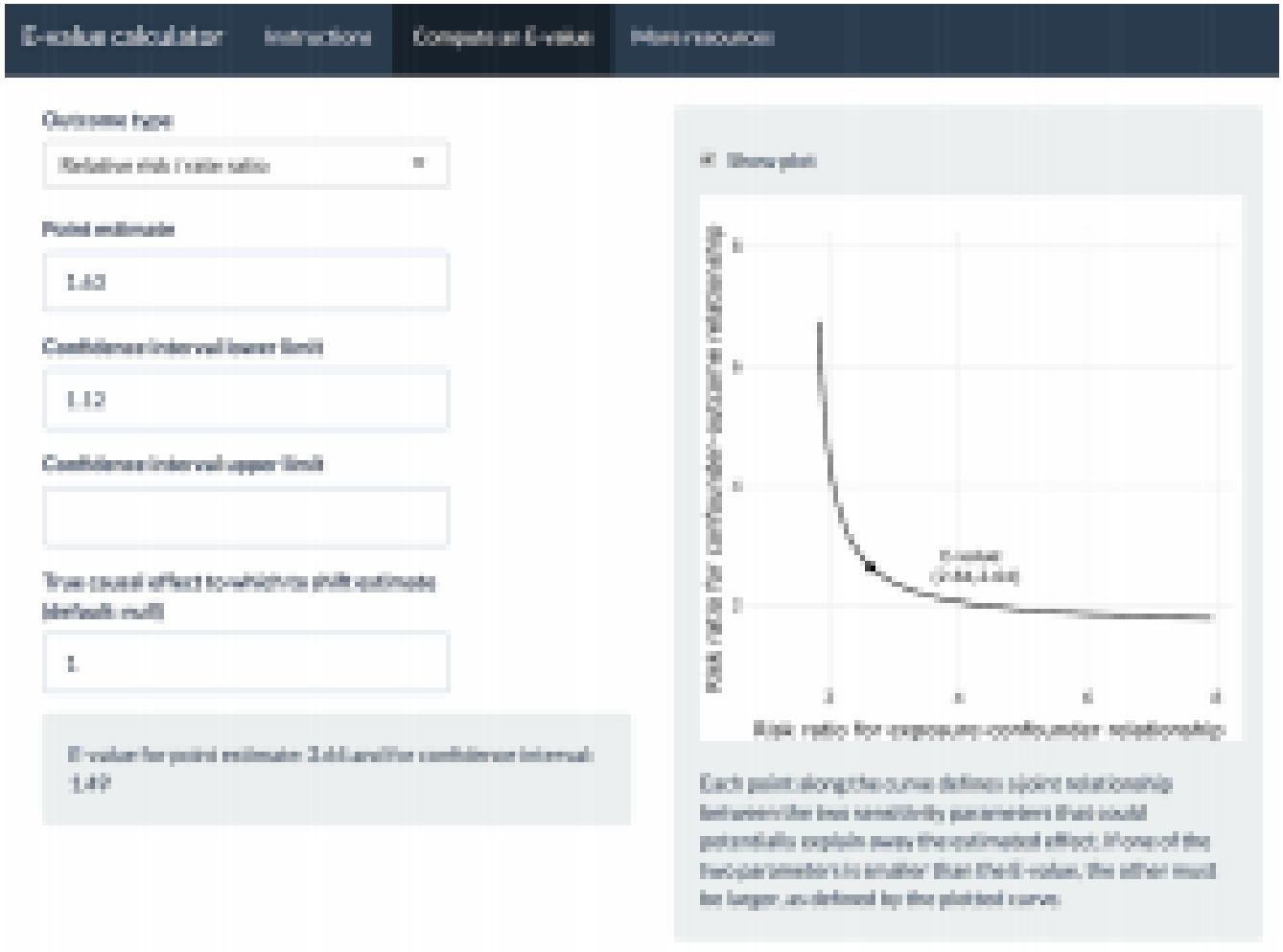
1. Rate ratio
2. *OR* with rare outcome
3. *HR* with rare outcome

Can approximately convert e↵ect size to *RR* and then apply E-value formula:

1. *OR* with common outcome
2. *HR* with common outcome
3. Risk di↵erence (inference more complicated) 4. Standardized mean di↵erence
5. Linear regression coecient

Software

Online calculator:
https://evalue.hmdc.harvard.edu (can Google “E-value calculator”)



R package EValue:

```
> library(EValue)
> evalues.RR( est = 1.63, lo = 1.12 )
```

	point	lower	upper
RR	1.630000	1.120000	NA
E-values	2.643361	1.486606	NA

Handles *OR*, *HR*, rate ratio, risk di↵erence, standardized mean di↵erence, linear regression coecient.

Also does analogous sensitivity analyses for meta-analysis (tomorrow) or for selection bias.

Summary

The E-value is a tool to characterize robustness to unmeasured confounding. It is easy to calculate manually or using our software.

It does not require specifying sensitivity parameters, so removes “researcher degrees of freedom”.

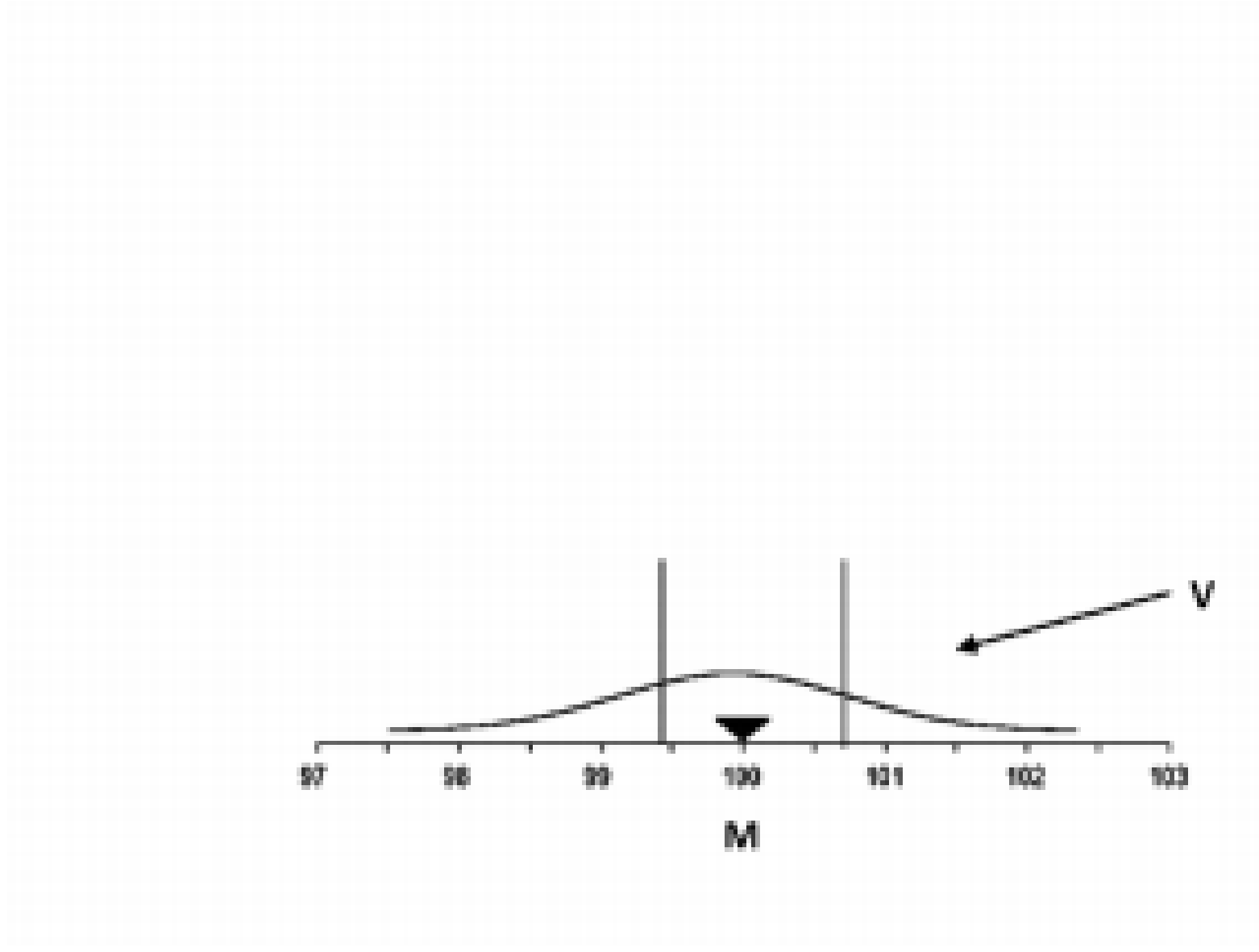
It can be reported in just 1-2 sentences in a paper.

We think its widespread use would better calibrate confidence in observational research.

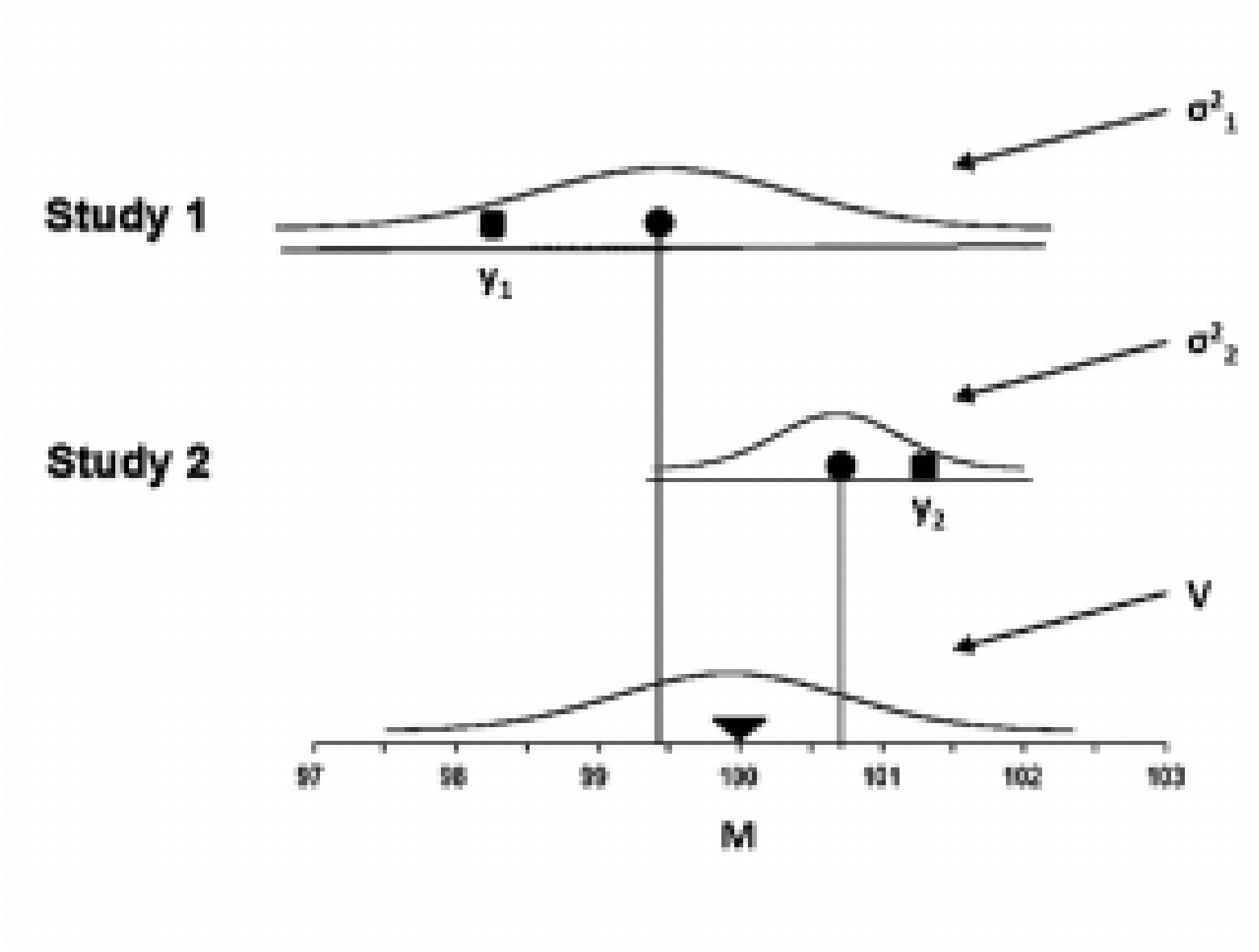
Sensitivity analysis for a meta-analysis

Mathur MB & VanderWeele TJ (2019). Sensitivity analysis for unmeasured confounding in meta-analyses. *JASA.*

Meta-analysis basics



Meta-analysis basics



Applied example

Meta-Analysis of Soy Intake and Breast Cancer Risk

Bruce J. Trock, Leena Hilakivi-Clarke, Robert Clarke

Background: High intake of soy foods has been proposed to contribute to the low breast cancer risk in Asian countries. However, results of epidemiologic studies of this association are highly variable, and experimental data suggest that soy constituents can be estrogenic and potentially risk enhancing. Thus, rigorous evaluation of available epidemiologic data is necessary before appropriate recommendations can be made, especially for women at high risk of breast cancer or those who have survived the disease. *Methods:* We performed a meta-analysis of 18 epidemiologic studies (12 case–control and six cohort or nested case–control) published from 1978 through 2004 that examined soy exposure and breast cancer risk. Pooled relative risk estimates were based on either the original soy exposure measure defined in each study or on an estimate of daily soy protein intake. *Results:* Risk estimates, levels and measures of soy exposure, and control for confounding factors varied considerably across studies. In a pooled analysis, among all women, high soy intake was modestly associated with reduced breast cancer risk (odds ratio [OR] = 0.86, 95% confidence interval [CI] = 0.75 to 0.99); the association was not statistically significant among women in Asian countries (OR = 0.89, 95% CI = 0.71 to 1.12). Among the 10 studies that stratified by menopausal status, the inverse association between soy exposure and breast cancer risk was somewhat stronger in premenopausal women (OR = 0.70, 95% CI = 0.58 to 0.85) than in postmenopausal women (OR = 0.77, 95% CI = 0.60 to 0.98); however, eight studies did not provide menopause-specific results, six of which did not support an association. When exposure was analyzed by soy protein intake in grams per day, a statistically significant association with breast cancer risk was seen only among premenopausal women (OR = 0.94, 95% CI = 0.92 to 0.97). *Conclusions:* Soy intake may be associated with a small reduction in breast cancer risk. However, this result should be interpreted with caution due to potential exposure misclassification, confounding, and lack of a dose response. Given these caveats and results of some experimental studies that suggest adverse effects from soy constituents, recommendations for high-dose isoflavone supplementation to prevent breast cancer or prevent its recurrence are premature. [J Natl Cancer Inst 2006;98:459–71]

Breast cancer rates among women in Asian countries have long been noted to be substantially lower than those among women in Western nations (1) but rapidly increase in Asian women following emigration to the United States (2). Because changes in cancer risk following emigration are thought to reflect lifestyle changes, particularly in dietary patterns, these observations have led to a search for protective factors in the Asian diet. Soy-based foods have long been a staple of Asian diets; before 1990 these foods were consumed regularly by only approximately 5% of women in the United States (3,4). However, this figure is

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See "Notes" following "References."

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Question #1

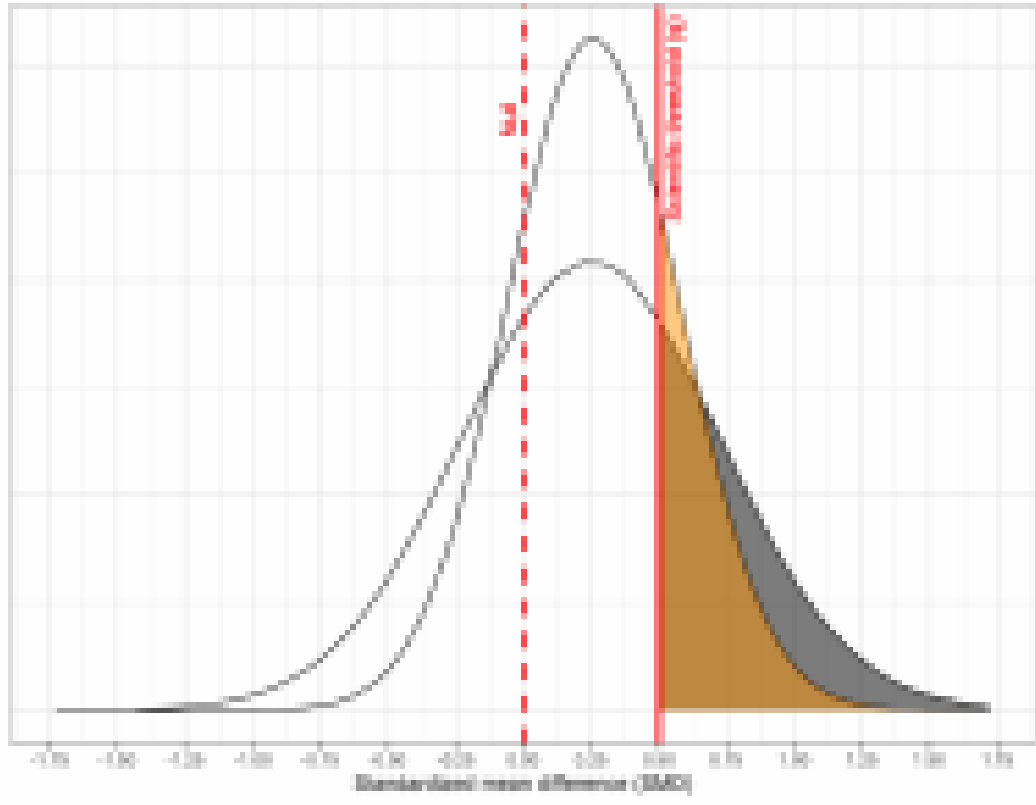
For a meta-analysis

Soy consumption is not very interesting unless its true, unconfounded RR is < 0.90.

Given unmeasured confounding of specific strength, what proportion of the (heterogeneous) true e↵ects of soy on breast cancer would still be more protective than *RR* = 0.90?

Why characterize evidence strength this way?

Figure 1: Estimated proportion of standardized mean differences (shaded) stronger than threshold of scientific importance at $SMD = 0.50$ (solid red line) in two meta-analyses with differing "statistical significance". Dashed red line: reference null value ($SMD = 0$).



Orange: $SMD^{\setminus} = 0.26$, 95% CI: (0.12, 0.39), $pb(q)=0.22$, CI: (0.06, 0.38) Gray: $SMD^{\setminus} = 0.25$, 95% CI: (0.07, 0.56), $pb(q)=0.30$, CI: (0.04, 0.56)

Bounds on confounding bias

For a meta-analysis

$B^{\leftarrow} = \log(B)$

y^{t}_{i} = true log-RR in study i

y^{c}_{i} = confounded (observed) log-RR in study i Assume $y^{t}_{i} \leftarrow N\, M^{t},\ V^{t}$.

Also assume $B^{\leftarrow}_{i} \leftarrow N\, \mu_{B^{\leftarrow}},\ {}^{2}B^{\leftarrow}\, q\, y^{t}_{i}$.

Then:

$$pb(q) = P^{b}\ y^{t} < q$$

$$= \quad @^{q\ \ \mu_{B^{\leftarrow}}}\ \ 1$$

$$0 \quad yb^{c} \quad A\ ,\ \boxtimes^{2}{}_{c} >$$

$$\text{q}\frac{R}{\boxtimes^{2}{}_{c}\ {}^{2}B^{\leftarrow}\ {}^{2}B^{\leftarrow}}$$

(apparently preventive RR)

Bounds on confounding bias

For a meta-analysis

Applying the delta method,

asymptotically: $\sqrt{\mathrm{Var}\left(\hat{\beta}_{RR}\right)}$

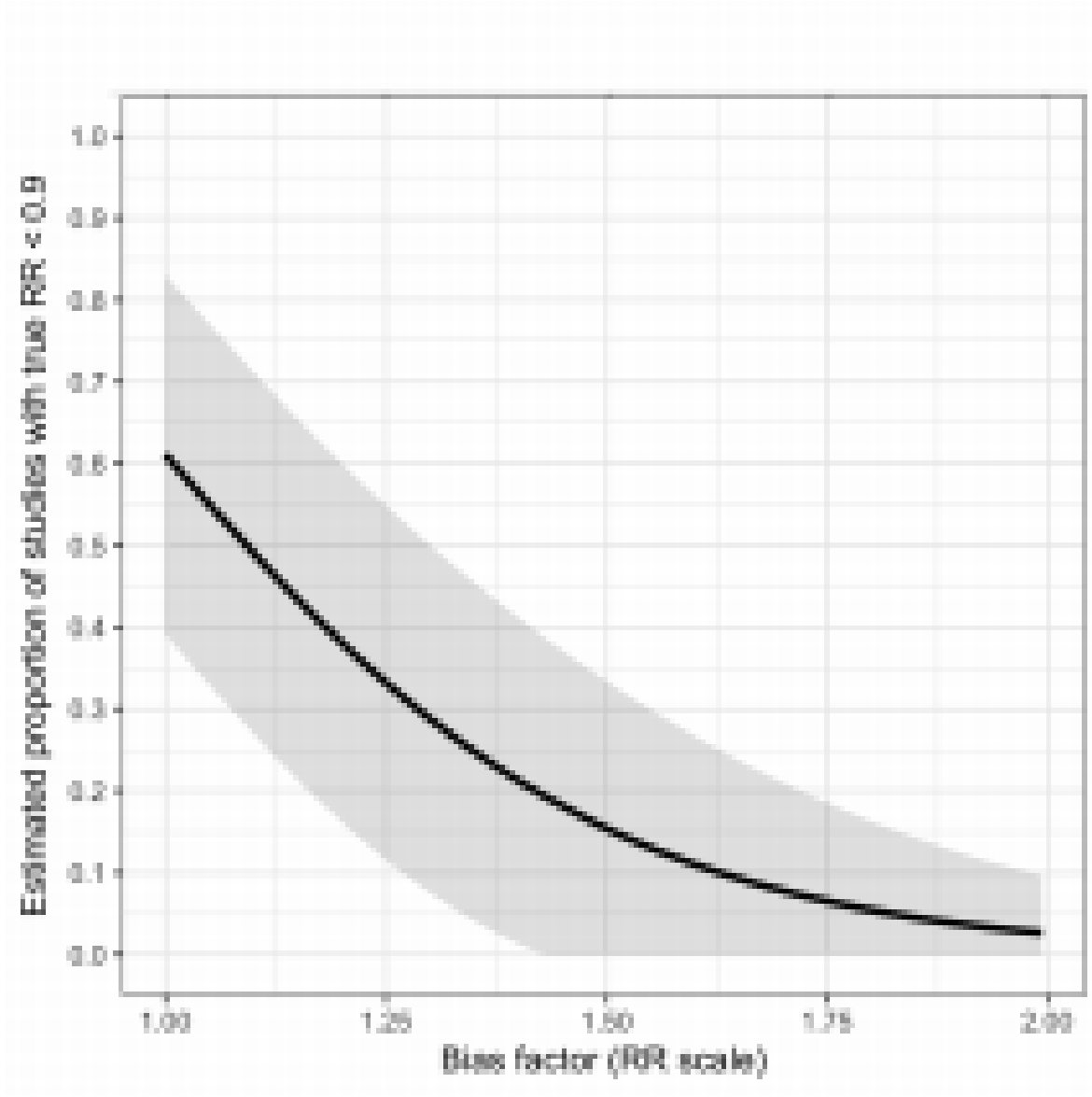
$$SE\left(\hat{p}\left(\hat{q}\right)\right) = \sqrt{\sigma^2_{\beta_{RR}}\left(\hat{\beta}_{RR}\right)^2 + \mathrm{Var}\left(\sigma^2_{\beta_{RR}}\right)\hat{q}^4\left(\sigma^2_{\beta_{RR}}\right)^3 - 4\sigma^2_{\beta_{RR}}\left(\hat{\beta}_{RR}\right)^3 \hat{q}\left(\hat{\beta}_{RR}\right)}$$

$$\hat{q}^R \cdot 0$$

$$\sigma^2_{\beta_{RR}}\left(\hat{\beta}_{RR}\right)$$

Works for any *asymptotically independent* estimators $\hat{y}_R$, $\hat{\sigma}^2$.

Applied example


Estimated proportion of studies with true RR < 0.9
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
1.00
1.25
1.50
1.75
2.00
Bias factor (RR scale)

Question #2

For a meta-analysis

Soy consumption is not very interesting unless its true, unconfounded RR is < 0.90. If < 10% of true e↵ects meet this criterion, the soy-cancer relationship is too weak to care about.

How severe would unmeasured confounding have to be to reduce to < 10% the proportion of true e↵ects more protective than *RR* = 0.90?

Minimum bias factor to yield few strong e↵ects

For a meta-analysis

$T^{b}(r, q)$: The minimum common bias factor (RR scale) required

to lower to less than *r* the proportion of studies with true e↵ect stronger than *q*

Small $T^{b}(r, q)$ *)* Slight bias could explain away e↵ect *)* Sensitive to unmeasured confounding

Large $T^{b}(r, q)$ *)* Only large bias could explain away *)* Robust to unmeasured confounding

Minimum bias factor to yield few strong e↵ects

For a meta-analysis

$T^{b}(r, q)$: The minimum common bias factor (RR scale) required to lower to less than *r* the proportion of studies with true e↵ect stronger than *q*

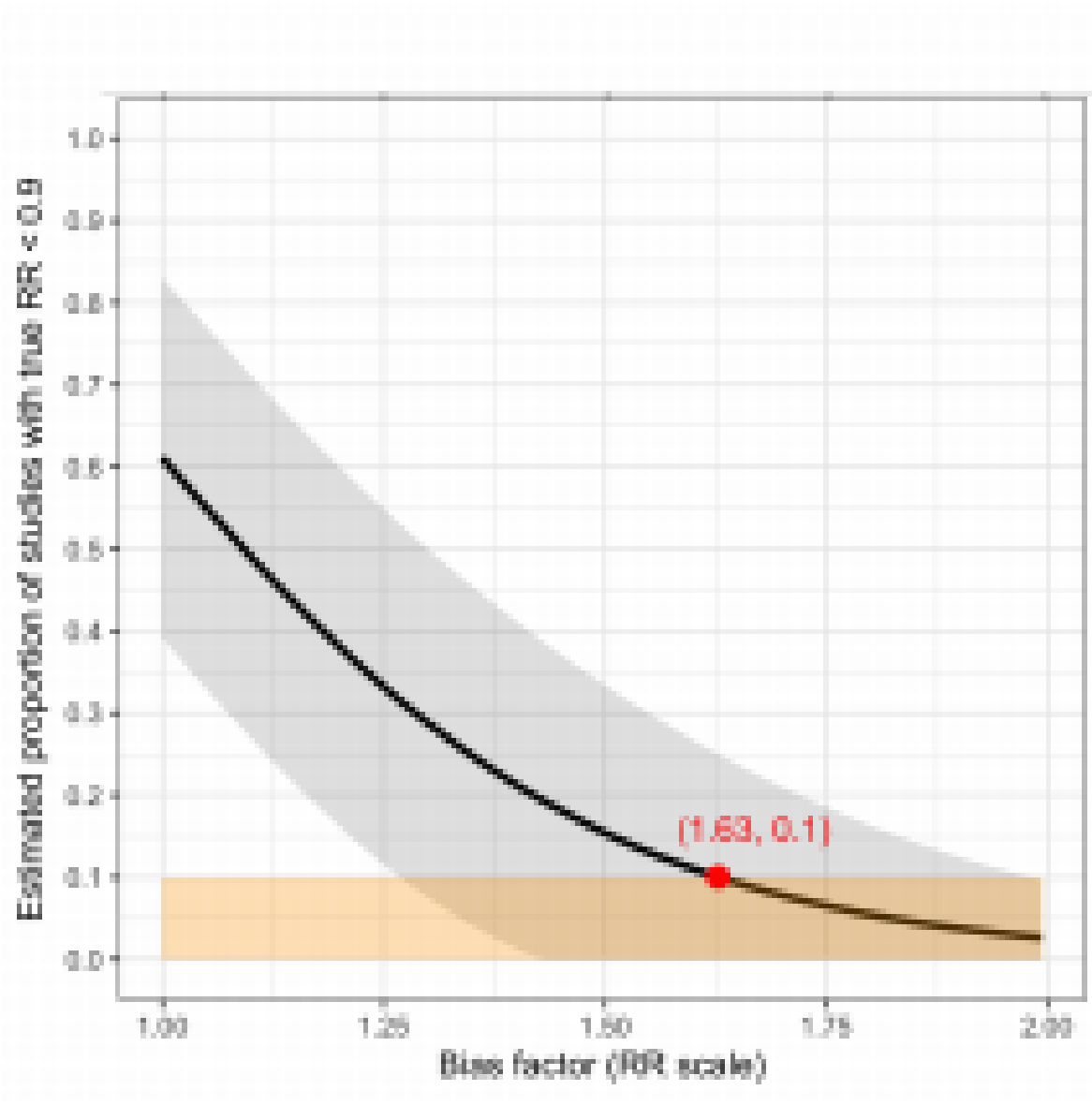
$$\hat{T}(r, q) = \exp\left[(1 - r)^{-1}\left(\sigma_c^2 q + y\bar{b}_R\right)\right]$$

with approximate standard error:

$$\widehat{SE}\left[\hat{T}(r, q)\right] = \exp\left[(1 - r)^{-1}\left(\sigma_c^2 q + y\bar{b}_R\right)\right] \sqrt{\mathrm{Var}(y\bar{b}_R) + \mathrm{Var}(\sigma_c^2)\left(\frac{q}{4\sigma_c^2}\right)(1 - r)^{-2}}$$

Applied example

$$\hat{T}(r = .10, q = \log 0.90) = 1.63$$



Minimum confounding strength

to yield few strong e↵ects

For a meta-analysis

$G^{b}(r,\ q)$: The minimum common confounding strength of association (RR scale) required to lower to less than r the proportion of studies with true e↵ect stronger than q

$$G^{b}(r,\ q) = \frac{r}{T^{b}(r,\ q)} + \sqrt{T^{b}(r,\ q)\left(T^{b}(r,\ q) - 1\right)}$$

with approximate standard error:

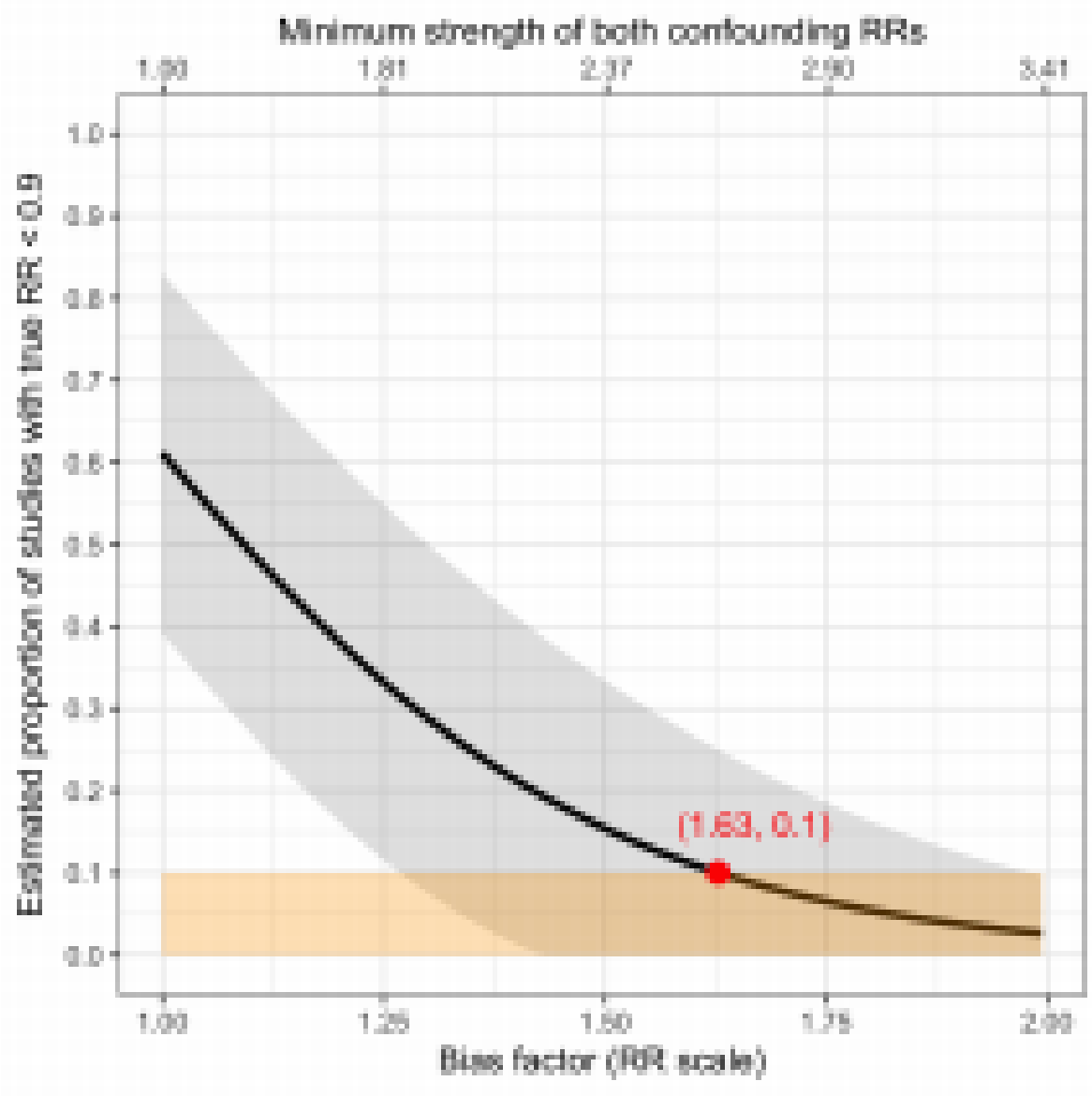
$$SEc\left[G^{b}(r,\ q)\right] = SEc\left[T^{b}(r,\ q)\right] \cdot \sqrt{1 + \frac{2}{T^{b}(r,\ q)} - 1}$$

A

$$\frac{2}{T^{b}(r, q)^{2}} \frac{q}{T^{b}(r, q)}$$

Applied example

$T^{b}(r = .10, q = \log 0.90) = 1.63$, $G^{b}(r = .10, q = \log 0.90) = 2.64$


Minimum strength of both confounding RRs
1.00
1.81
2.37
2.90
3.41
Estimated proportion of studies with true RR < 0.9
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
(1.63, 0.1)
1.00
1.25
1.50
1.75
2.00
Bias factor (RR scale)

Software

R: Function confounded meta in package

EValue Online calculator:

https://mmathur.shinyapps.io/meta_gui_2/

	Meta-analysis	(Ding & VanderWeele, 2017)
	Summary	*p*b(*q*) (Mathur & VanderWeele, in press)
Single study	True e↵ect strength with confounding of specific strength	Min confounding needed to explain away e↵ect
	RR^{c}_{XY}/B (causative case)	

2017)

(Mathur &
VanderWeele, in press)

E-value

(VanderWeele & Ding, $G^{b}(r, q)$

References

For single studies

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2. VanderWeele TJ & Ding P (2017). Sensitivity analysis in observational research: Introducing the E-value. *Annals of Internal Medicine*, 167(4), 268-274.

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For meta-analyses

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To download slides:
https://osf.io/2r3gm/

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APPENDIX

Appendix

Conservative choices for $^{2}B^{\nleftarrow}$

Table: Bounds on $p\mathrm{b}(q)$ provided by homogeneous bias with an apparently causative or preventive pooled e↵ect. $\mu\mathrm{b}^{t}$ estimates μ^{t} and is equal to $y\mathrm{b}^{c}_{R}\ \mu_{B^{\nleftarrow}}$ for $y\mathrm{b}^{c}_{R} > 0$ or $y\mathrm{b}^{c}_{R} + \mu_{B^{\nleftarrow}}$ for $y\mathrm{b}^{c}_{R} < 0$.

$$q > \mu\mathrm{b}^{t}\ q < \mu\mathrm{b}^{t}$$

$y\mathrm{b}^{c}_{R} > 0$ Upper bound Lower bound

$y\mathrm{b}^{c}_{R} < 0$ Lower bound Upper bound