Web Appendix for: "Sensitivity Analysis for Unmeasured Confounding in Meta-Analyses"

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Contents

1. Derivation of main results

1.1. $\widehat{p}(q)$

1.1.1 Causative case

Under the model described in the main text, we have (Ding & VanderWeele, 2016):

$$\begin{aligned} M^t + B^* &= M^c \\ \mu^t &= E\big[M^c - B^*\big] = \mu^c - \mu_{B^*} \\ \text{Var}\left(M^t + B^*\right) &= \text{Var}\left(M^c\right) \\ V^t + \sigma^2_{B^*} &= V^c && \text{(independence)} \\ V^t &= V^c - \sigma^2_{B^*} \end{aligned}$$

Then, $M^t = M^c - B^*$ is the difference of correlated normal random variables, so is itself normal. By Slutsky's Theorem, replace parameters with consistent estimators:

$$P\left(M^t > q\right) \approx 1 - \Phi\left(\frac{q + \mu_{B^*} - \widehat{y}^c_R}{\sqrt{\tau^2_c - \sigma^2_{B^*}}}\right), \ \tau^2_c > \sigma^2_{B^*}$$

1.1.2 Preventive case

The apparently preventive case is nearly identical.

1.2. Standard error for $\widehat{p}(q)$

We first establish a general result (Lemma 1.1) regarding conditions under which $\widehat{y}_R$ and τ^2 are asymptotically independent.

Lemma 1.1. *Let $\widehat{y}_R$ and τ^2 denote maximum likelihood estimates under a normal specification. Assume that $E[y_i \mid \sigma^2_i] = E[y_i]$. Then $\widehat{y}_R$ and τ^2 are asymptotically independent.*

Proof. The joint log-likelihood and partial derivatives are:

$$\log \mathcal{L}\left(\mu, V\right) = -\frac{1}{2}\sum_{i=1}^{k} \log\left(2\pi\left(\sigma_i^2 + V\right)\right) - \frac{1}{2}\sum_{i=1}^{k}\frac{(y_i-\mu)^2}{\sigma_i^2+V}$$

$$\frac{\partial \log \mathcal{L}}{\partial \mu} = -\frac{1}{2}\sum_{i=1}^{k}\left(\sigma_i^2+V\right)^{-1}\left(-2y_i+2\mu\right)$$

$$\frac{\partial^2 \log \mathcal{L}}{\partial \mu \partial V} = \frac{1}{2}\sum_{i=1}^{k}\left(\sigma_i^2+V\right)^{-2}\left(-2y_i+2\mu\right)$$

$$= -\frac{1}{2}\sum_{i=1}^{k}\frac{2y_i-2\mu}{\sigma_i^4+2\sigma_i^2V+V^2}$$

The off-diagonal element of the expected Fisher information matrix is therefore:

$$\mathcal{I}_{12} = -E\left[\frac{\partial^2 \log \mathcal{L}}{\partial \mu \partial V}\right]$$

$$= \frac{1}{2}kE\left[\frac{2y_i-2\mu}{\sigma_i^4+2\sigma_i^2V+V^2}\right]$$

By a second-order Taylor series expansion, we have, for general random variables X and Y:

$$E[X/Y] \approx \frac{E[X]}{E[Y]} - \frac{\mathrm{Cov}(X,Y)}{E[Y]^2} + \frac{\mathrm{Var}(Y)E[X]}{E[Y]^3} \tag{1.1}$$

We have $\mathrm{E}[2y_i - 2\mu] = 0$, so applying Equation (1.1) with the first and third terms equal to 0 yields:

$$\begin{aligned}
\mathcal{I}_{12} &\approx \frac{1}{2}k \; \frac{E\Big[\, (2\mu - 2y_i)\,(\sigma_i^4 + 2\sigma_i^2 V + V^2) \,\Big]}{E\Big[\sigma_i^4 + 2\sigma_i^2 V + V^2\Big]^2} \\
&= \frac{1}{2}k \; \frac{2\mu E\big[\sigma_i^4\big] + 4\mu V E\big[\sigma_i^2\big] + 2\mu V^2 - 2V^2 E\big[y_i\big] - 4V E\big[y_i \sigma_i^2\big] - 2E\big[y_i \sigma_i^4\big]}{E\Big[\sigma_i^4 + 2\sigma_i^2 V + V^2\Big]^2} \\
&= \frac{1}{2}k \; \frac{2\mu E\big[\sigma_i^4\big] + 4\mu V E\big[\sigma_i^2\big] + 2\mu V^2 - 2V^2 \mu - 4V^4 \mu E\big[\sigma_i^2\big] - 2\mu E\big[\sigma_i^4\big]}{E\Big[\sigma_i^4 + 2\sigma_i^2 V + V^2\Big]^2} \\
&= 0
\end{aligned}$$

The penultimate line follows from the assumption that $E[y_i \mid \sigma_i^2] = E[y_i]$. Since the maximum likelihood estimates are asymptotically bivariate normal, asymptotic independence is established. □

1.2.1 Causative case

We now derive an asymptotic confidence interval for $\widehat{p}(q)$ for an apparently causative relative risk via the delta method. We assume use of the standard random-effects estimator, $\widehat{y}_R^c$, and an arbitrary estimator τ_c^2 such that, asymptotically:

$$\begin{bmatrix} \widehat{y}_R^c - M^c \\ \tau_c^2 - V^c \end{bmatrix} \approx N \left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \underbrace{\begin{bmatrix} \text{Var}\left(\widehat{y}_R^c\right) & \text{Cov}\left(\widehat{y}_R^c, \tau_c^2\right) \\ \text{Cov}\left(\widehat{y}_R^c, \tau_c^2\right) & \text{Var}\left(\tau_c^2\right) \end{bmatrix}}_{\Sigma/k} \right)$$

(Asymptotic normality is theoretically justified for the maximum likelihood and restricted maximum likelihood estimators τ_c^2 and, in simulations, also appears to hold for those proposed by DerSimonian & Laird (1986), Paule & Mandel (1982), Sidik & Jonkman (2005), and

Hedges & Olkin (1985).) Apply the delta method:

$$
\begin{aligned}
h\left(x_1, x_2\right) &= \widehat{p}(q) = 1 - \Phi\left(\frac{q + \mu_{B^*} - x_1}{\sqrt{x_2 - \sigma^2_{B^*}}}\right) \\
\nabla = \begin{bmatrix} \frac{\partial h}{\partial x_1} \\ \frac{\partial h}{\partial x_2} \end{bmatrix} &= \begin{bmatrix} \frac{1}{\sqrt{x_2 - \sigma^2_{B^*}}} \cdot \phi\left(\frac{q+\mu_{B^*}-x_1}{\sqrt{x_2-\sigma^2_{B^*}}}\right) \\ \frac{1}{2}\left(x_2 - \sigma^2_{B^*}\right)^{-3/2} \cdot \left(q + \mu_{B^*} - x_1\right) \cdot \phi\left(\frac{q+\mu_{B^*}-x_1}{\sqrt{x_2-\sigma^2_{B^*}}}\right) \end{bmatrix} \\
&= \begin{bmatrix} \frac{1}{\sqrt{x_2 - \sigma^2_{B^*}}} \cdot \phi\left(\frac{q+\mu_{B^*}-x_1}{\sqrt{x_2-\sigma^2_{B^*}}}\right) \\ \frac{q+\mu_{B^*}-x_1}{2\left(x_2-\sigma^2_{B^*}\right)^{3/2}} \cdot \phi\left(\frac{q+\mu_{B^*}-x_1}{\sqrt{x_2-\sigma^2_{B^*}}}\right) \end{bmatrix}
\end{aligned}
$$

$$
\sqrt{k}\,\left[h\left(\widehat{y}^c_R, \tau^2\right) - h\left(M^c, V\right)\right] \to N\left(0, \nabla'\Sigma\nabla|_{M^c,V}\right)
$$

$$
\begin{aligned}
\nabla'\Sigma\nabla &= \nabla_1\left(\nabla_1\Sigma_{11} + \nabla_2\Sigma_{21}\right) + \nabla_2\left(\nabla_1\Sigma_{12} + \nabla_2\Sigma_{22}\right) \\
&= \frac{\partial h}{\partial x_1}\left(\frac{\partial h}{\partial x_1}\text{Var}\left(\widehat{y}^c_R\right) + \frac{\partial h}{\partial x_2}\text{Cov}\left(\widehat{y}^c_R, \tau^2_c\right)\right) \\
&\quad + \frac{\partial h}{\partial x_2}\left(\frac{\partial h}{\partial x_1}\text{Cov}\left(\widehat{y}^c_R, \tau^2_c\right) + \frac{\partial h}{\partial x_2}\text{Var}\left(\tau^2_c\right)\right)
\end{aligned}
$$

Denote consistent estimators with hats and apply Slutsky's Theorem:

$$\widehat{\text{Var}}\left(\widehat{p}(q)\right) = \nabla'\Sigma\nabla|_{M^c,V^c}$$

$$\approx \frac{\widehat{\text{Var}}\left(\widehat{y}_R^c\right)}{\tau_c^2 - \sigma_{B^*}^2} \cdot \left[\phi\left(\frac{q + \mu_{B^*} - \widehat{y}_R^c}{\sqrt{\tau_c^2 - \sigma_{B^*}^2}}\right)\right]^2 +$$

$$\left(\frac{1}{\sqrt{\tau_c^2 - \sigma_{B^*}^2}}\right) \frac{q + \mu_{B^*} - \widehat{y}_R^c}{2\left(\tau_c^2 - \sigma_{B^*}^2\right)^{3/2}} \cdot \widehat{\text{Cov}}\left(\widehat{y}_R^c, \tau_c^2\right) \cdot \left[\phi\left(\frac{q + \mu_{B^*} - \widehat{y}_R^c}{\sqrt{\tau^2 - \sigma_{B^*}^2}}\right)\right]^2 +$$

$$\frac{\widehat{\text{Var}}\left(\tau_c^2\right)\left(q + \mu_{B^*} - \widehat{y}_R^c\right)^2}{4\left(\tau_c^2 - \sigma_{B^*}^2\right)^3} \cdot \left[\phi\left(\frac{q + \mu_{B^*} - \widehat{y}_R^c}{\sqrt{\tau_c^2 - \sigma_{B^*}^2}}\right)\right]^2$$

$$= \left[\frac{\widehat{\text{Var}}\left(\widehat{y}_R^c\right)}{\tau_c^2 - \sigma_{B^*}^2} + \frac{\left(q + \mu_{B^*} - \widehat{y}_R^c\right)\widehat{\text{Cov}}\left(\widehat{y}_R^c, \tau_c^2\right)}{\left(\tau_c^2 - \sigma_{B^*}^2\right)^2} + \frac{\widehat{\text{Var}}\left(\tau_c^2\right)\left(q + \mu_{B^*} - \widehat{y}_R^c\right)^2}{4\left(\tau_c^2 - \sigma_{B^*}^2\right)^3}\right]$$

$$\cdot \left[\phi\left(\frac{q + \mu_{B^*} - \widehat{y}_R^c}{\sqrt{\tau_c^2 - \sigma_{B^*}^2}}\right)\right]^2$$

$$\widehat{\text{SE}}\left(\widehat{p}(q)\right) \approx \sqrt{\frac{\widehat{\text{Var}}\left(\widehat{y}_R^c\right)}{\tau_c^2 - \sigma_{B^*}^2} + \frac{\left(q + \mu_{B^*} - \widehat{y}_R^c\right)\widehat{\text{Cov}}\left(\widehat{y}_R^c, \tau_c^2\right)}{\left(\tau_c^2 - \sigma_{B^*}^2\right)^2} + \frac{\widehat{\text{Var}}\left(\tau_c^2\right)\left(q + \mu_{B^*} - \widehat{y}_R^c\right)^2}{4\left(\tau_c^2 - \sigma_{B^*}^2\right)^3}}$$

$$\cdot \phi\left(\frac{q + \mu_{B^*} - \widehat{y}_R^c}{\sqrt{\tau_c^2 - \sigma_{B^*}^2}}\right)$$

For choices of estimators τ_c^2 that are asymptotically independent of $\widehat{y}_R^c$ (which holds for the maximum likelihood estimates by Lemma 1.1 and also appears to hold for other common choices in simulations), this reduces to:

$$\widehat{\text{SE}}\left(\widehat{p}(q)\right) \approx \sqrt{\frac{\widehat{Var}\left(\widehat{y}_R^c\right)}{\tau_c^2 - \sigma_{B^*}^2} + \frac{\widehat{Var}\left(\tau_c^2\right)\left(q + \mu_{B^*} - \widehat{y}_R^c\right)^2}{4\left(\tau_c^2 - \sigma_{B^*}^2\right)^3}} \cdot \phi\left(\frac{q + \mu_{B^*} - \widehat{y}_R^c}{\sqrt{\tau_c^2 - \sigma_{B^*}^2}}\right)$$

1.2.2 Preventive case

For an apparently preventive relative risk, there is simply a sign change in the numerators:

$$\widehat{\text{SE}}\left(\widehat{p}(q)\right) \approx \sqrt{\frac{\widehat{\text{Var}}\left(\widehat{y}_R^c\right)}{\tau_c^2 - \sigma_{B^*}^2} + \frac{\widehat{\text{Var}}\left(\tau_c^2\right)\left(q - \mu_{B^*} - \widehat{y}_R^c\right)^2}{4\left(\tau_c^2 - \sigma_{B^*}^2\right)^3}} \cdot \phi\left(\frac{q - \mu_{B^*} - \widehat{y}_R^c}{\sqrt{\tau_c^2 - \sigma_{B^*}^2}}\right)$$

1.3. $\widehat{T}(r, q)$

1.3.1 Causative case

Simply solve $\widehat{p}(q)$ for μ_{B^*}, setting the latter equal to $\log \widehat{T}(r, q)$ and setting $\sigma^2_{B^*} = 0$:

$$
\begin{aligned}
r &= 1 - \Phi\left(\frac{q + \log \widehat{T}(r, q) - \widehat{y}^c_R}{\sqrt{\tau^2_c}}\right) \\
\Phi^{-1}(1 - r) &= \frac{q + \log \widehat{T}(r, q) - \widehat{y}^c_R}{\sqrt{\tau^2_c}} \\
\widehat{T}(r, q) &= \exp\left\{\Phi^{-1}(1 - r)\sqrt{\tau^2_c} - q + \widehat{y}^c_R\right\}
\end{aligned}
$$

1.3.2 Preventive case

$$
\begin{aligned}
r &= \Phi\left(\frac{q - \log \widehat{T}(r, q) - \widehat{y}^c_R}{\sqrt{\tau^2_c}}\right) \\
\Phi^{-1}(r) &= \frac{q - \log \widehat{T}(r, q) - \widehat{y}^c_R}{\sqrt{\tau^2_c}} \\
\widehat{T}(r, q) &= \exp\left\{q - \widehat{y}^c_R - \Phi^{-1}(r)\sqrt{\tau^2_c}\right\}
\end{aligned}
$$

1.4. Standard error for $\widehat{T}(r,q)$

1.4.1 Causative case

Apply the delta method:

$$
\begin{aligned}
h(x_1,x_2) &= \widehat{T}(r,q) = \exp\left\{x_2^{1/2}\left(\Phi^{-1}(1-r)\right) - q + x_1\right\} \\
\nabla = \begin{bmatrix} \frac{\partial h}{\partial x_1} \\ \frac{\partial h}{\partial x_2} \end{bmatrix} &= \begin{bmatrix} \exp\left\{x_2^{1/2}\left(\Phi^{-1}(1-r)\right) - q + x_1\right\} \\ \exp\left\{x_2^{1/2}\left(\Phi^{-1}(1-r)\right) - q + x_1\right\} \cdot \Phi^{-1}(1-r) \cdot \frac{1}{2} x_2^{-1/2} \end{bmatrix} \\
\widehat{\text{Var}}\left(\widehat{T}(r,q)\right) &= \nabla' \Sigma \nabla |_{M^c, V^c} \\
&\approx \left(\exp\left\{\sqrt{(\tau_c^2)}\left(\Phi^{-1}(1-r)\right) - q + \widehat{y}_R^c\right\}\right)^2 \\
&\left(\widehat{\text{Var}}\left(\widehat{y}_R^c\right) + \frac{\left(2\widehat{\text{Cov}}\left(\widehat{y}_R^c, \tau_c^2\right) + \widehat{\text{Var}}\left(\tau_c^2\right)\right)\left(\Phi^{-1}(1-r)\right)^2}{4\tau_c^2}\right) \\
\widehat{\text{SE}}\left(\widehat{T}(r,q)\right) &= \exp\left\{\sqrt{\tau_c^2}\left(\Phi^{-1}(1-r)\right) - q + \widehat{y}_R^c\right\} \\
&\sqrt{\widehat{\text{Var}}\left(\widehat{y}_R^c\right) + \frac{\left(2\widehat{\text{Cov}}\left(\widehat{y}_R^c, \tau_c^2\right) + \widehat{\text{Var}}\left(\tau_c^2\right)\right)\left(\Phi^{-1}(1-r)\right)^2}{4\tau_c^2}}
\end{aligned}
$$

For estimators such that $\widehat{y}_R^c$ is asymptotically independent of τ_c^2:

$$
\widehat{\text{SE}}\left(\widehat{T}(r,q)\right) = \exp\left\{\sqrt{\tau_c^2}\left(\Phi^{-1}(1-r)\right) - q + \widehat{y}_R^c\right\}\sqrt{\widehat{\text{Var}}\left(\widehat{y}_R^c\right) + \frac{\widehat{\text{Var}}\left(\tau_c^2\right)\left(\Phi^{-1}(1-r)\right)^2}{4\tau_c^2}} \tag{1.2}
$$

1.4.2 Preventive case

For the apparently preventive case under asymptotic independence, there is a sign change, and the cumulative distribution function is evaluated at r instead of $1-r$:

$$
\widehat{\text{SE}}\left(\widehat{T}(r,q)\right) = \exp\left\{q - \widehat{y}_R^c - \sqrt{\tau_c^2}\left(\Phi^{-1}(r)\right)\right\}\sqrt{\widehat{\text{Var}}\left(\widehat{y}_R^c\right) + \frac{\widehat{\text{Var}}\left(\tau_c^2\right)\left(\Phi^{-1}(r)\right)^2}{4\tau_c^2}} \tag{1.3}
$$

1.5. $\widehat{G}(r,q)$

Set $B^* = \log B^+$ and $\widehat{G}(r,q) = RR_{XU} = RR_{UY}$:

$$B^* = \log\left(\frac{\widehat{G}(r,q)^2}{2\widehat{G}(r,q)-1}\right)$$
$$0 = \widehat{G}(r,q)^2 - 2\exp\left(B^*\right)\widehat{G}(r,q) + \exp\left(B^*\right)$$

Apply the quadratic formula:

$$\widehat{G}(r,q) = \exp\left(B^*\right) + \sqrt{\left(\exp\left(B^*\right)\right)^2 - \exp\left(B^*\right)}$$

1.6. Standard error for $\widehat{G}(r,q)$

Apply the delta method to transform $\widehat{T}(r,q)$ into $\widehat{G}(r,q)$:

$$h(x) = x + \sqrt{x^2 - x}$$
$$\frac{dh}{dx} = 1 + \frac{2x-1}{2\sqrt{x^2-x}}$$

$$\widehat{\text{Var}}\left(\widehat{G}(r,q)\right) = \left(\frac{dh}{dx}\right)^2 \text{Var}(x)\Big|_{\widehat{T}(r,q)}$$
$$= \left(1 + \frac{2\widehat{T}(r,q)-1}{2\sqrt{\widehat{T}(r,q)^2 - \widehat{T}(r,q)}}\right)^2 \text{Var}\left(\widehat{T}(r,q)\right)$$

1.6.1 Causative case

Plug in variance estimator (1.2):

$$\widehat{\text{SE}}\left(\widehat{G}(r,q)\right) = \left(1 + \frac{2\widehat{T}(r,q)-1}{2\sqrt{\widehat{T}(r,q)^2 - \widehat{T}(r,q)}}\right) \cdot \exp\left\{\sqrt{\tau_c^2}\left(\Phi^{-1}(1-r)\right) - q + \widehat{y}_R^c\right\}$$
$$\cdot \sqrt{\widehat{\text{Var}}\left(\widehat{y}_R^c\right) + \frac{\widehat{\text{Var}}\left(\tau_c^2\right)\left(\Phi^{-1}(1-r)\right)^2}{4\tau_c^2}}$$

1.6.2 Preventive case

Plug in variance estimator (1.3):

$$\widehat{\text{SE}}\left(\widehat{G}(r,q)\right) = \left(1 + \frac{2\widehat{T}(r,q) - 1}{2\sqrt{\widehat{T}(r,q)^2 - \widehat{T}(r,q)}}\right) \cdot \exp\left\{\sqrt{\tau_c^2}\left(\Phi^{-1}(r)\right) - q - \widehat{y}_R^c\right\}$$
$$\cdot \sqrt{\widehat{\text{Var}}\left(\widehat{y}_R^c\right) + \frac{\widehat{\text{Var}}\left(\tau_c^2\right)\left(\Phi^{-1}(r)\right)^2}{4\tau_c^2}}$$

2. Fidelity of homogeneous-bias approximation

Table 1 in the main text provides upper or lower bounds on $\widehat{p}(q)$ that arise from assuming homogeneous bias (i.e., $\sigma^2_{B^*} = 0$). Here, we consider how closely these bounds approximate $\widehat{p}(q)$. Define $\delta = \frac{q + \mu_{B^*} - \widehat{y}_R^c}{\tau_c}$ for the apparently causative case and $\delta = \frac{q - \mu_{B^*} - \widehat{y}_R^c}{\tau_c}$ for the apparently preventive case. This quantity represents the difference between the threshold q and the bias-corrected mean estimate $\widehat{y}_R^t$ (i.e., $\widehat{y}_R^c - \mu_{B^*}$ for the causative case and $\widehat{y}_R^c + \mu_{B^*}$ for the preventive case), standardized by τ_c, the standard deviation of the confounded effect distribution. Let $w = \tau_c^2/\sigma^2_{B^*} > 1$, so that $1/w$ represents the proportion of variance in the confounded effects that is due to variability across studies in unmeasured confounding bias rather than to genuine effect heterogeneity. Let $\widetilde{p}(q)$ be the estimator $\widehat{p}(q)$ computed with $\sigma^2_{B^*} = 0$. Then, for the apparently causative case, the ratio relating the homogeneous-bias approximation to the unbiased estimate is:

$$\frac{\widetilde{p}(q)}{\widehat{p}(q)} = \frac{1 - \Phi\left(\delta\right)}{1 - \Phi\left(\delta \frac{1}{\sqrt{1 - \frac{1}{w}}}\right)}$$
$$= \frac{\Phi\left(-\delta\right)}{\Phi\left(-\delta \frac{1}{\sqrt{1 - \frac{1}{w}}}\right)}$$

The absolute difference is:

$$|\widetilde{p}(q) - \widehat{p}(q)| = \left| \Phi\left(-\delta\right) - \Phi\left(-\delta \frac{1}{\sqrt{1 - \frac{1}{w}}}\right) \right|$$

The apparently preventive case is symmetrical because, whereas $\delta > 0$ for an upper bound in the causative case, $\delta < 0$ for an upper bound in the preventive case (see Table 1 in the main text), and in the above expression, $-\delta$ is also replaced with δ for the apparently preventive case (see Section 4.1 in the main text). A comparable symmetry argument holds for lower bounds. Table S1 displays $\frac{\widetilde{p}(q)}{\widehat{p}(q)}$ as a function of $|\delta|$ and w and illustrates that, on the ratio scale, the homogeneous-bias approximation holds most closely for small $|\delta|$ and large w; that is, when q is chosen to be relatively close to the bias-corrected mean estimate and when $\sigma^2_{B^*}$ is small compared to τ^2_c. Table S2 displays $|\widetilde{p}(q) - \widehat{p}(q)|$ and illustrates that the large ratios in the lower left of Table S1 correspond to cases in which $\widehat{p}(q)$ and $\widetilde{p}(q)$ are both very small, such that a large ratio corresponds to a small absolute difference.

Table S1: *Ratio of homogeneous-bias approximation with* $\sigma^2_{B^*} = 0$ *to the unbiased estimate,* $\widehat{p}(q)$.

	$w = 1.5$	2	4	6	8	10
$\lvert\delta\rvert = 0.25$	1.21	1.11	1.04	1.02	1.02	1.01
0.5	1.60	1.29	1.09	1.06	1.04	1.03
1	3.81	2.02	1.28	1.16	1.11	1.09
1.5	14.25	3.94	1.60	1.33	1.23	1.17
2	85.53	9.73	2.17	1.60	1.40	1.30
2.5	833.38	30.52	3.19	2.01	1.65	1.48

Table S2: *Absolute difference of homogeneous-bias approximation with* $\sigma^2_{B^*} = 0$ *and the unbiased estimate,* $\widehat{p}(q)$.

	$w = 1.5$	2	4	6	8	10
$\lvert\delta\rvert = 0.25$	0.07	0.04	0.01	0.01	0.01	0.01
0.5	0.12	0.07	0.03	0.02	0.01	0.01
1	0.12	0.08	0.03	0.02	0.02	0.01
1.5	0.06	0.05	0.03	0.02	0.01	0.01
2	0.02	0.02	0.01	0.01	0.01	0.01
2.5	0.01	0.01	0.00	0.00	0.00	0.00

3. Sufficient conditions for approximate normality of bias factor

Lemma 3.1. *Let X and Y be iid $N(\mu, \sigma^2)$ with $\mu > 0$ and $\sigma^2 << \mu$. Then:*

$$\log\left(e^X + e^Y - 1\right) \approx N\left(\log\left(2e^\mu - 1\right), \frac{2e^{2\mu}}{\left(2e^\mu - 1\right)^2}\,\sigma^2\right)$$

Proof. Let $h(X, Y) = \log\left(e^X + e^Y - 1\right)$. Then, apply a first-order Taylor expansion around μ, dropping higher-order terms because $\sigma^2 << \mu$:

$$\begin{aligned}
\frac{\partial h}{\partial X} &= \frac{e^X}{(e^X + e^Y - 1)} \\
\frac{\partial h}{\partial Y} &= \frac{e^Y}{(e^X + e^Y - 1)} \\
h(X, Y) &\approx \log(2e^\mu - 1) + \frac{e^\mu}{2e^\mu - 1}(X - \mu) + \frac{e^\mu}{2e^\mu - 1}(Y - \mu) \\
&= \left[\log(2e^\mu - 1) - \frac{2\mu e^\mu}{2e^\mu - 1}\right] + \frac{e^\mu}{2e^\mu - 1}X + \frac{e^\mu}{2e^\mu - 1}Y \\
E\Big[h(X, Y)\Big] &\approx \left[\log(2e^\mu - 1) - \frac{2\mu e^\mu}{2e^\mu - 1}\right] + \frac{e^\mu}{2e^\mu - 1}E[X] + \frac{e^\mu}{2e^\mu - 1}E[Y] \\
&= \log(2e^\mu - 1) \\
\text{Var}\left(h(X, Y)\right) &\approx \frac{2e^{2\mu}}{\left(2e^\mu - 1\right)^2}\,\sigma^2
\end{aligned}$$

The result then follows from the fact that $h(X, Y)$ is approximately a linear combination of Normal random variables. □

Theorem 3.1. *Suppose* $\log RR_{XU}$ *and* $\log RR_{UY}$ *are iid* $N(\mu_U, \sigma_U^2)$. *Then* $\log B^+$ *is approximately normal.*

Proof. We have $\log B^+ = \log(RR_{XU}) + \log(RR_{UY}) - \log(RR_{XU} + RR_{UY} - 1)$; the result follows immediately from invoking Lemma 3.1 for the last term. □

4. Introduction to the package `EValue`

Here we briefly summarize the functions contained in the package `EValue`; details and examples are available in the standard `R` documentation.

The function `confounded_meta` computes point estimates, standard errors, and confidence interval bounds for (1) the proportion of studies with true effect sizes above q (or below q for an apparently preventive $\widehat{y}_R^c$) as a function of the bias parameters; (2) the minimum bias factor on the relative risk scale ($\widehat{T}(r, q)$) required to reduce to less than r the proportion of studies with true effect sizes more extreme than q; and (3) the counterpart to (2) in which bias is parameterized as the minimum relative risk for both confounding associations ($\widehat{G}(r, q)$).

The function `sens_table` produces several types of tables (returned as dataframes) at the user's specification. The `prop` option yields a table showing the proportion of true effect sizes more extreme than q across a grid of bias parameters μ_{B^*} and σ_{B^*}. Alternatively, the `Tmin` and `Gmin` options yield tables showing the minimum bias factor (as in Table 2) or confounding strength required to reduce to less than r the proportion of true effects more extreme than q (across a grid of r and q).

The function `sens_plot` produces two types of plots. With the `line` option, the plot shows the bias factor on the relative risk scale (with pointwise 95% confidence band) versus the proportion of studies with true relative risks more extreme than q (as in Figure 1). The plot includes a secondary, rescaled X-axis showing the minimum strength of confounding to produce the given bias factor. With the `dist` option, the plot overlays the estimated densities of the confounded effects and of the true effects for a user-provided range of μ_{B^*} and scalar σ_{B^*}.

The function `scrape_meta` is designed to facilitate sensitivity analyses of existing meta-analyses. Given relative risks and upper bounds of 95% confidence intervals from a forest plot or summary table, the function returns a dataframe ready for meta-analysis (e.g., via the `metafor` package) with the log-RRs and their variances. Optionally, the user may indicate studies for which the point estimates represent odds ratios of a common outcome rather than relative risks; for such studies, the function first applies a square-root transformation to convert the odds ratio to an approximate risk ratio (VanderWeele, 2017).

5. Code to reproduce applied example

The below code reproduces the applied example in Section 8. Extended code is also maintained at `https://osf.io/2r3gm/`.

```
# was run on R 3.3.3
# get data from Trock et al.'s Table 1
RRs = c(0.4, 1.8, 0.78, 0.96, 0.9, 1.4, 0.66, 0.76, 0.47,
        0.5, 2.0, 1.07, 0.66, 1.00, 0.83, 0.61, 1.0, 0.46,
        0.47, 1.16 )
UBs = c(0.8, 3.6, 1.0, 1.31, 1.3, 3.0, 0.88, 1.18, 1.33,
        1.1, 4.3, 1.47, 1.02, 1.30, 1.51, 0.97, 1.3, 0.84,
        0.74, 1.39 )

# compute point estimates and within-study variances
library(EValue)  # version 1.1.0
d = scrape_meta( type = "RR", est = RRs, hi = UBs )

# meta-analyze
library(metafor)  # version 2.0-0
m = rma.uni(yi=d$yi, vi=d$vyi, method="PM", measure="RR", test="knha")
yr = as.numeric(m$b)  # returned estimate is on log scale
vyr = as.numeric(m$vb)  # this is the KNHA-adjusted SE^2
t2 = m$tau2
```

```
vt2 = m$se.tau2^2

# reproduce Figure 1
library(ggplot2)
sens_plot( type="line",
                 q=log(0.9),
                 Bmin=log(1),
                 Bmax=log(2),
                 sigB=0.1,
                 yr=yr,
                 vyr=vyr,
                 t2=t2,
                 vt2=vt2,
                 breaks.x1=seq(1, 2, .25) )

# now for just one choice of sensitivity parameters
# represents a single cross-section of the plot (at muB = log(1.25))
confounded_meta( q = log(.90),
                muB = log(1.25),
                sigB = 0.10,
                yr=yr,
                vyr = vyr,
                t2 = t2,
                vt2 = vt2,
                CI.level = 0.95)

# reproduce Tmin in Table 2
sens_table( meas="Tmin",
                  q=c( log(0.70), log(0.80), log(0.90) ),
                        r=seq(0.1, 0.5, 0.1),
                        yr=yr,
                        t2=t2 )
```

```
# reproduce Gmin in Table 2
sens_table( meas="Gmin",
                   q=c( log(0.70), log(0.80), log(0.90) ),
                   r=seq(0.1, 0.5, 0.1),
                   yr=yr,
                   t2=t2 )
```

References

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