

APPENDIX A

Complete derivation of new estimator based on the Delta method: RR^Δ

The multivariate Delta method is a useful way to approximate the mean and variance of RR by relying on a (truncated) Taylor series expansion. Typically for meta-analysis, effect size metrics like RR, Hedges' d , and the Odds ratio use only first-order expansions to approximate asymptotic sampling distributions (Hedges 1981; Lajeunesse 2011). However, higher-order expansions are also useful given that they can be used to adjust or correct bias in the “naïve” effect size estimator (such as RR). Here, I begin with how the mean (Eq. 1) and variance (Eq. 2) of the original RR described in the main text can be approximated with the Delta method. I then extend this approach to obtain the higher-order terms necessary for deriving a correction.

Given the challenges of determining the moments of ratios and log-ratios (see below *Sampling distribution of the ratio of two means*), the Delta method provides a compromise to approximate the asymptotic sampling distribution for λ . Following Stuart and Ord (1994), the expectation of the simplest estimator of λ based on the first-order Taylor expansion around the population means μ_T and μ_C of $\lambda = \ln(\mu_T/\mu_C)$ is approximately:

$$\mathbb{E}(\text{RR}) \approx \lambda + \mathbf{J}^T(\mathbf{x} - \boldsymbol{\mu}) + \varepsilon_{\text{RR}}, \quad (\text{A.1})$$

where the superscript T indicates the transposition of a matrix, ε_{RR} the remainder (i.e., the ignored higher-order Taylor expansions), $\boldsymbol{\mu}$ a column vector of the population means μ_T and μ_C (e.g., $\boldsymbol{\mu}^T = [\mu_T, \mu_C]$), and \mathbf{x} a vector of the sample means $\mathbf{x}^T = [\bar{X}_T, \bar{X}_C]$. Also included is a Jacobian vector (\mathbf{J}) containing all the first-order partial derivatives (∂) of each variable in λ :

$$\mathbf{J}^T = \left[\frac{\partial \lambda}{\partial \mu_T}, \frac{\partial \lambda}{\partial \mu_C} \right] = \left[\frac{1}{\mu_T}, \frac{-1}{\mu_C} \right].$$

Solving Eq. A.1, and noting that the expectation of $\bar{X} - \mu$ is zero at large sample sizes (e.g., when sampling error becomes negligible as assumed by the Law of Large Numbers; Stuart and Ord 1994), we get the original formulation of the response ratio:

$$\mathbb{E}(\text{RR}) \approx \log \left[\frac{\mu_T}{\mu_C} \right] + \frac{\bar{X}_T - \mu_T}{\mu_T} - \frac{\bar{X}_C - \mu_C}{\mu_C} \approx \log \left[\frac{\mu_T}{\mu_C} \right] \approx \lambda.$$

In a parallel way, we can also apply the multivariate Delta method to approximate the variance of RR using the Law of Propagation of Variances equation:

$$\text{var}(\text{RR}) \approx \mathbf{J}^T \mathbf{V} \mathbf{J} + \varepsilon_{\text{var}(\text{RR})}, \quad (\text{A.2})$$

where \mathbf{V} is the variance–covariance matrix of μ_T and μ_C containing their large-sample variances and zero covariances as follows:

$$\mathbf{V} = \begin{bmatrix} \sigma_T^2/N_T & 0 \\ 0 & \sigma_C^2/N_C \end{bmatrix}.$$

Examples of when study parameters are dependent and have non-zero covariances are covered elsewhere (Lajeunesse 2011). Solving Eq. A.2 we get the variance:

$$\text{var}(\text{RR}) \approx \frac{\sigma_T^2}{N_T \mu_T^2} + \frac{\sigma_C^2}{N_C \mu_C^2}.$$

When replacing the population parameters μ and σ^2 with their respective sample statistics, \bar{X} and $(SD)^2$, we get the original response ratio and variance of Eqs. 1 and 2 of the main text. Based on this approach, RR and $\text{var}(\text{RR})$ can be described as first-order approximations of the log ratio of two means.

However, for both the expected mean and variance of the log ratio (Eqs. A.1 and A.2, respectively), the remainder portion ε of Taylor expansions were ignored. Here we will add the second-order portion of ε to improve these estimators. The expectation of λ with a second-order Taylor expansion is:

$$\mathbb{E}(\text{RR}) \approx \lambda + \mathbf{J}^T(\mathbf{x} - \boldsymbol{\mu}) + \underbrace{\frac{1}{2}(\mathbf{x} - \boldsymbol{\mu})^T \mathbf{H}(\mathbf{x} - \boldsymbol{\mu})}_{\text{second-order term}} + \varepsilon_{\text{RR}}, \quad (\text{A.3})$$

where \mathbf{H} is a Hessian matrix containing all the second partial derivatives (∂^2) of λ :

$$\mathbf{H} = \begin{bmatrix} \frac{\partial^2 \lambda}{\partial^2 \mu_T^2} & \frac{\partial^2 \lambda}{\partial \mu_C \mu_T} \\ \frac{\partial^2 \lambda}{\partial \mu_T \mu_C} & \frac{\partial^2 \lambda}{\partial^2 \mu_C^2} \end{bmatrix} = \begin{bmatrix} -1/\mu_T^2 & 0 \\ 0 & 1/\mu_C^2 \end{bmatrix}.$$

Solving for Eq. A.3, again assuming that the expectation of $\bar{X} - \mu$ will equal zero, but also that the square of this expectation equals its variance ($\bar{X} - \mu$)² = σ^2/N , we get:

$$\mathbb{E}(\text{RR}) \approx \log \left[\frac{\mu_T}{\mu_C} \right] + \frac{1}{2} \left[\frac{(\bar{X}_C - \mu_C)^2}{\mu_C^2} - \frac{(\bar{X}_T - \mu_T)^2}{\mu_T^2} \right] \approx \log \left[\frac{\mu_T}{\mu_C} \right] + \frac{1}{2} \left[\frac{\sigma_C^2}{N_C \mu_C^2} - \frac{\sigma_T^2}{N_T \mu_T^2} \right]. \quad (\text{A.4})$$

Note that because this second-order approximation did not reduce to λ , this corroborates the Monte Carlo results that RR is biased (Fig. 1 of the main text).

Finally, using the compact matrix notation of Preacher et al. (2007), the approximation of the variance with a second-order term is:

$$\text{var}(\text{RR}) \approx \mathbf{J}^T \mathbf{V} \mathbf{J} + \underbrace{\frac{1}{2} \text{tr}[\mathbf{H}(\mathbf{V}\mathbf{V})\mathbf{H}]}_{\text{second-order term}} + \varepsilon_{\text{var}(\text{RR})}, \quad (\text{A.5})$$

with tr indicating the trace of a matrix. Solving Eq. A.5 gives the second-order approximation:

$$\text{var}(\text{RR}) \approx \frac{\sigma_T^2}{N_T \mu_T^2} + \frac{\sigma_C^2}{N_C \mu_C^2} + \frac{1}{2} \left[\frac{(\sigma_T^2)^2}{N_T^2 \mu_T^4} + \frac{(\sigma_C^2)^2}{N_C^2 \mu_C^4} \right]. \quad (\text{A.6})$$

Equations A.4 and A.6 both contain the original response ratio and its variance but now also include an additional (2nd order) term meant to improve the approximation of the expected log ratio.

The predicted bias of the RR estimator can be used to adjust the original RR as follows:

$$\text{RR}^{\text{adj}} = \text{RR} - \text{bias}(\text{RR}) = \text{RR} - [\mathbb{E}(\text{RR}) - \lambda]. \quad (\text{A.7})$$

However, given that we do not know what λ will be, or the population parameters μ and σ^2 , we can substitute the study sample statistics \bar{X} and $(SD)^2$ to approximate these parameters. Using the expected mean of Eq. A.4, substituting the original RR as an estimate of λ , and consolidating terms, the small-sample bias corrected estimator for λ based on the Delta method (Δ) becomes:

$$RR^\Delta = RR + \frac{1}{2} \left[\frac{(SD_T)^2}{N_T \bar{X}_T^2} - \frac{(SD_C)^2}{N_C \bar{X}_C^2} \right]. \quad (\text{A.8})$$

Likewise, applying Eq. A.5 with the general form of Eq. A.7 to adjust the variance we get:

$$var(RR^\Delta) = var(RR) + \frac{1}{2} \left[\frac{(SD_T)^4}{N_T^2 \bar{X}_T^4} + \frac{(SD_C)^4}{N_C^2 \bar{X}_C^4} \right]. \quad (\text{A.9})$$

Complete derivation of new estimator based on the Linearity of Expectation rule: RR^Σ

The expected value of $\mathbb{E}(RR)$ can also be calculated using the Linearity of Expectation rule which states that the expected value of a sum of random variables, such as A and B, will equal the sum of their individual expectations (Stuart and Ord 1994), or more formally: $\mathbb{E}(A + B) = \mathbb{E}(A) + \mathbb{E}(B)$. Applying this rule to our case, and by using a convenient expression of RR based the quotient rule of logarithms, the expected mean of RR is:

$$\mathbb{E}(RR) = \mathbb{E}(\ln[\mu_T]) - \mathbb{E}(\ln[\mu_C]). \quad (\text{A.10})$$

According to Stuart and Ord (1994), the individual expected values of μ_T and μ_C in terms of $\ln[\mu_T]$ and $\ln[\mu_C]$ will have a mean of:

$$\mathbb{E}(\ln[\mu]) = \ln[\mu] - \frac{1}{2} \ln \left[1 + \frac{\sigma^2}{N\mu^2} \right].$$

For the purposes of developing an effect size estimator, this expected mean assumes the large-sample approximation of the variance of a mean (i.e., σ^2/N). Substituting these expected means of $\ln[\mu_T]$ and $\ln[\mu_C]$ into Eq. A.10, and simplifying terms, we get the expected mean of RR as:

$$\mathbb{E}(\text{RR}) = 2 \ln \left[\frac{\mu_T}{\mu_C} \right] - \frac{1}{2} \ln \left[\frac{\mu_T^2 + N_T^{-1} \sigma_T^2}{\mu_C^2 + N_C^{-1} \sigma_C^2} \right]. \quad (\text{A.11})$$

The Linearity of Expectation rule also applies to variances, but now we must assume that $\ln[\mu_T]$ and $\ln[\mu_C]$ are independent from one another. This assumption of independence was not needed to derive RR^Δ from Eq. A.4 (Stuart and Ord 1994). Here, the variance of $\mathbb{E}(\text{RR})$ from Eq. A.10 is:

$$\text{var}(\text{RR}) = \text{var}(\ln[\mu_T]) + \text{var}(\ln[\mu_C]). \quad (\text{A.12})$$

Again following Stuart and Ord (1994), the variance of the log of a normally distributed variable will be:

$$\text{var}(\ln[\mu]) = \ln \left[1 + \frac{\sigma^2}{N\mu^2} \right],$$

and therefore the sum of the variances of $\ln[\mu_T]$ and $\ln[\mu_C]$ will yield the variance of $\mathbb{E}(\text{RR})$ as:

$$\text{var}(\text{RR}) = \ln \left[1 + \frac{\sigma_T^2}{N_T \mu_T^2} \right] + \ln \left[1 + \frac{\sigma_C^2}{N_C \mu_C^2} \right]. \quad (\text{A.13})$$

Finally, much like the RR^Δ estimator, we apply the $\mathbb{E}(\text{RR})$ of Eq. A.11 and variance of Eq. A.13 to estimate an adjustment to the original response ratio, and following Eq. A.7 we get a new small-sample bias corrected estimator based on the Linearity of Expectation rule:

$$\text{RR}^\Sigma = \text{RR} + \frac{1}{2} \ln \left[\frac{1 + (N_T \bar{X}_T^2)^{-1} (\text{SD}_T)^2}{1 + (N_C \bar{X}_C^2)^{-1} (\text{SD}_C)^2} \right] = \frac{1}{2} \ln \left[\frac{\bar{X}_T^2 + N_T^{-1} (\text{SD}_T)^2}{\bar{X}_C^2 + N_C^{-1} (\text{SD}_C)^2} \right], \quad (\text{A.14})$$

which has a variance of:

$$\text{var}(\text{RR}^\Sigma) = 2 \cdot \text{var}(\text{RR}) - \ln \left[1 + \text{var}(\text{RR}) + \frac{(\text{SD}_T)^2 (\text{SD}_C)^2}{N_T N_C \bar{X}_T^2 \bar{X}_C^2} \right]. \quad (\text{A.15})$$

A few tips on up-keeping the accuracy of response ratio estimators

Diagnostics like Eqs. 12 and 13 of the main text are important given that they can help identify when effect sizes provide accurate estimates of study outcomes (Appendix: Fig. A.3). However, there are other simple ways to uphold the accuracy of RR , RR^Δ , and RR^Σ . One is to make sure that the means used to estimate effect sizes are in units with a natural zero point (e.g., converting data expressed in degrees Celsius to degrees Kelvin), and are not adjusted/corrected relative to other variables (i.e. least square or marginal means). These types of means can yield negative values for either the control or treatment outcomes, and effect sizes cannot be computed in these cases because the log of a negative ratio is undefined. Although note that RR^Σ is capable of computing effect sizes under these situations; but this should still be avoided because the magnitude of effect will be underestimated with these data. Again, the predicted sampling distribution of RR , RR^Δ , and RR^Σ will no longer be approximately normal when negative values are possible for the denominator or numerator of the ratio (see Hinkley 1969; see also below section: *Sampling distribution of ratio and log ratio of two means*). It is also important to avoid using percentages, proportions and counts when estimating effect sizes. These are inappropriate types of data for RR (as well as the corrected estimators) since its derivation assumes that \bar{X}_C and \bar{X}_T are from independent and normally distributed populations (Hedges et al. 1999). The odds ratio family of effect size estimators is more appropriate for these data (Fleiss 1994). Finally, effect sizes calculated from experiments with unbalanced designs should also be treated with caution—such as when sample sizes (N) differ considerably between the control and treatment groups (see Friedrich et al. 2008). However, this is not an issue unique to RR , RR^Δ , and RR^Σ ; most effect size estimators will perform poorly under such conditions.

Sampling distribution of the ratio of two means

If the denominator of a ratio like $R = X/Y$ is always positive, and X and Y are independent random variables where $i = 1, \dots, n$ and $j = 1, \dots, m$ for $X_i \sim \mathcal{N}(\mu, \sigma_X^2)$ and $Y_j \sim \mathcal{N}(\eta, \sigma_Y^2)$, then Geary (1930) and Fieller (1932) defined the probability density function $f(x)$ of this ratio to be:

$$f(R) = \frac{1}{\sqrt{2\pi}} \frac{R\mu\sigma_Y^2 + \eta\sigma_X^2}{(R^2\sigma_Y^2 + \sigma_X^2)^{3/2}} \times \exp\left[-0.5 \left(\frac{[R\eta - \mu]^2}{R^2\sigma_Y^2 + \sigma_X^2}\right)\right]. \quad (\text{A.16})$$

For the purposes of developing an effect size metric (estimator) using the ratio of two independent but normally distributed (\mathcal{N}) means, with now $R = \bar{X}/\bar{Y}$, we can replace the variances of X and Y in Eq. A.16 with their large sample approximations, $\sigma_X^2 n^{-1}$ and $\sigma_Y^2 m^{-1}$ respectively, to get:

$$f(R) = \frac{1}{\sqrt{2\pi}} \frac{R\mu\sigma_Y^2 m^{-1} + \eta\sigma_X^2 n^{-1}}{(R^2\sigma_Y^2 m^{-1} + \sigma_X^2 n^{-1})^{3/2}} \times \exp\left[-0.5 \left(\frac{[R\eta - \mu]^2}{R^2\sigma_Y^2 m^{-1} + \sigma_X^2 n^{-1}}\right)\right]. \quad (\text{A.17})$$

This probability distribution function is the same as the one reported in the Appendix A of Hedges et al. (1999). However, they opted to re-arrange Eq. A.17 to simplify the way sample sizes m and n were presented (i.e., not using their inversed form). Given these differences and the several typos in Hedges et al. (1999) equation, below is a corrected version of their probability function:

$$f(R) = \frac{1}{\sqrt{2\pi}} \frac{\sqrt{mn}(nR\mu\sigma_Y^2 + m\eta\sigma_X^2)}{(nR^2\sigma_Y^2 + m\sigma_X^2)^{3/2}} \times \exp\left[-0.5 \left(\frac{mn[\mu - R\eta]^2}{nR^2\sigma_Y^2 + m\sigma_X^2}\right)\right]. \quad (\text{A.18})$$

The Appendix Figure A4 illustrates the broad variability of the probability distribution of the unlogged ratio of two means when the denominator is allowed to take on negative values; unfortunately when this is the case, the predicted probability distribution will not have a clean closed-form expression (Fenton 1960), and therefore the sampling variance for this distribution (for all ranges of μ and η) remains undefined.

FIG. A1. Results from a Monte Carlo simulation exploring bias in the variance estimators of the log ratio of two means: $var(RR)$, $var(RR^\Delta)$, and $var(RR^\Sigma)$. Interpretation, color coding, and contour lines are the same as Fig. 1 of the main text.

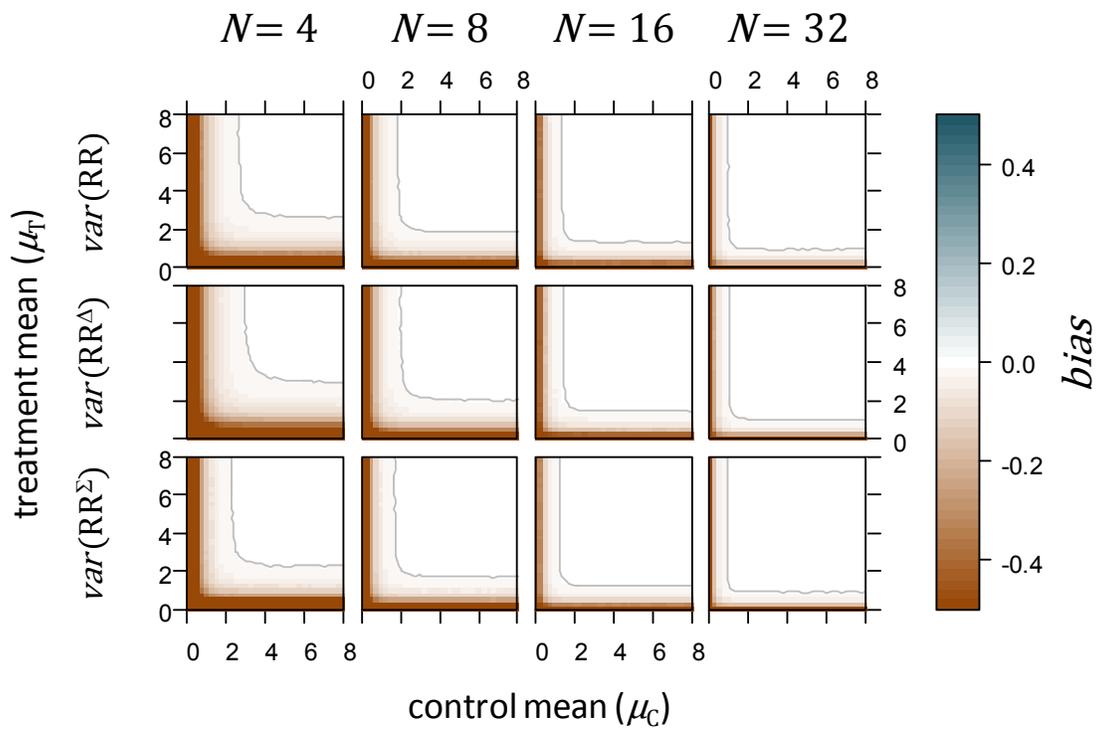


FIG. A2. A Monte Carlo simulation comparing the skewness (deviation from Normality) of randomly simulated log ratio estimators: RR , RR^Δ , and RR^Σ . A positive skew, emphasized in green, indicates a distribution with a longer right-tail; whereas a negative skew, emphasized in brown, indicates a longer left-tail. Following Tabachnick and Fidell (1996), the threshold where skewness is deemed non-zero was estimated as: ± 0.01549 . The contour line in light grey emphasizes this threshold.

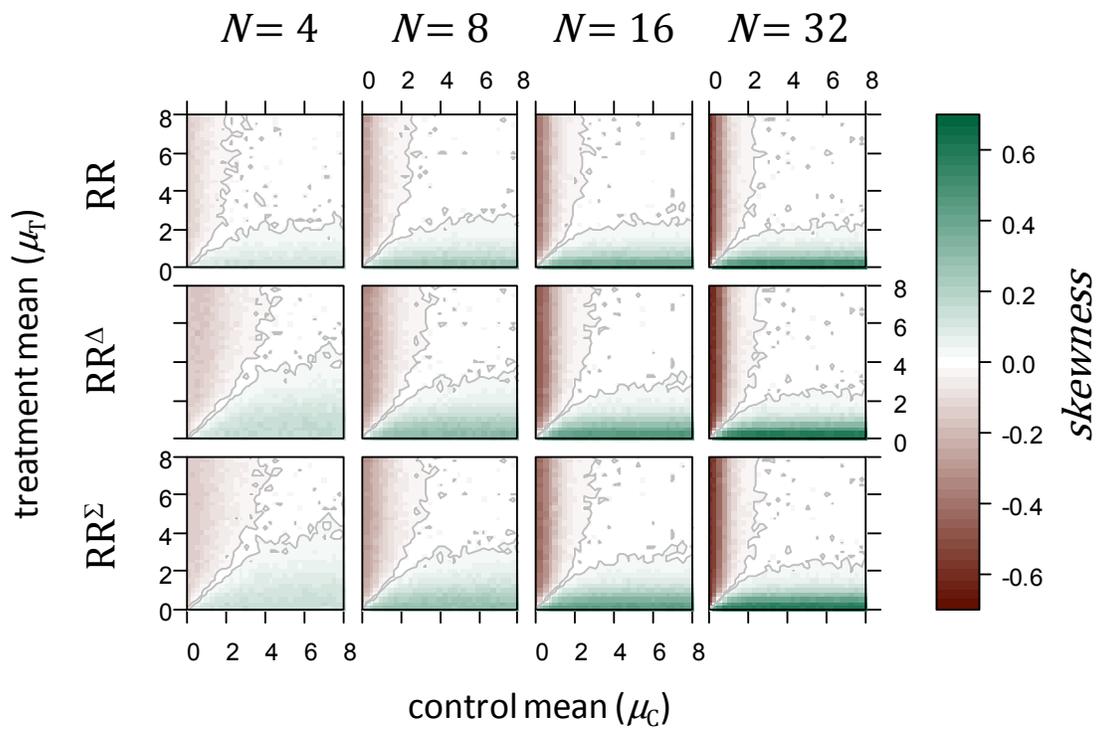


FIG. A3. Results from a Monte Carlo simulation exploring the ability of accuracy diagnostics (Eqs. 12 and 13 of the main text) to flag problematic effect sizes based on the log ratio of two means. Presented are the probabilities of these two diagnostics to identify accurate effect sizes using Geary's test of having both standardized means for the treatment and control groups being greater than three. Probabilities marked in red indicate the likelihood of detecting problematic effect sizes, and contour lines in black emphasize ranges when 95% of effect sizes are deemed accurate by the diagnostics (with accurate effect sizes emphasized in white). The methods of these simulations are the same as described in Fig. 1 of the main text.

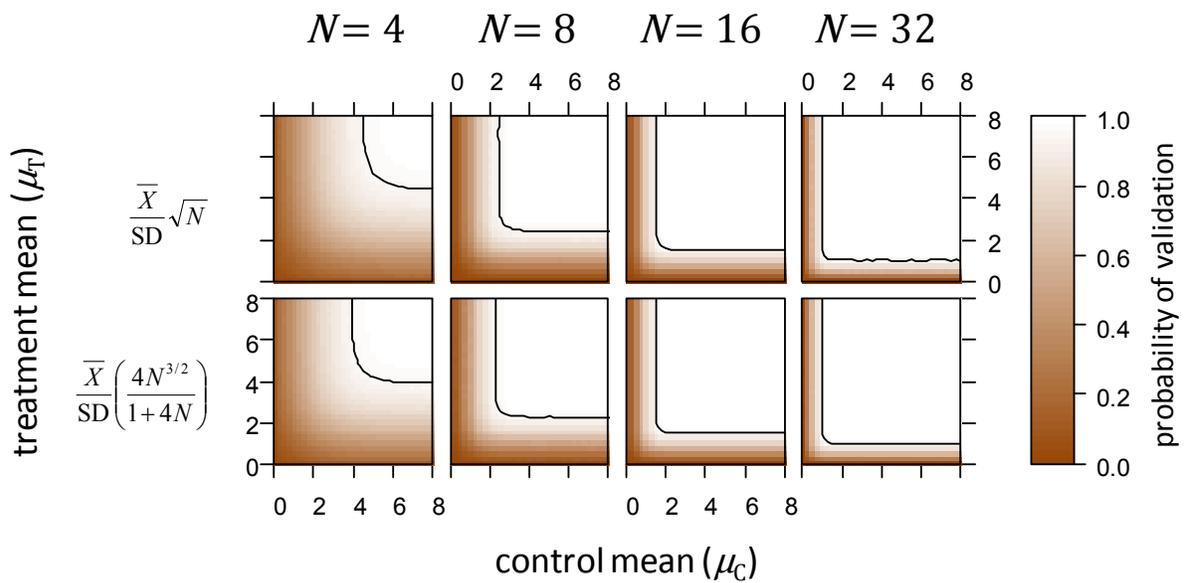
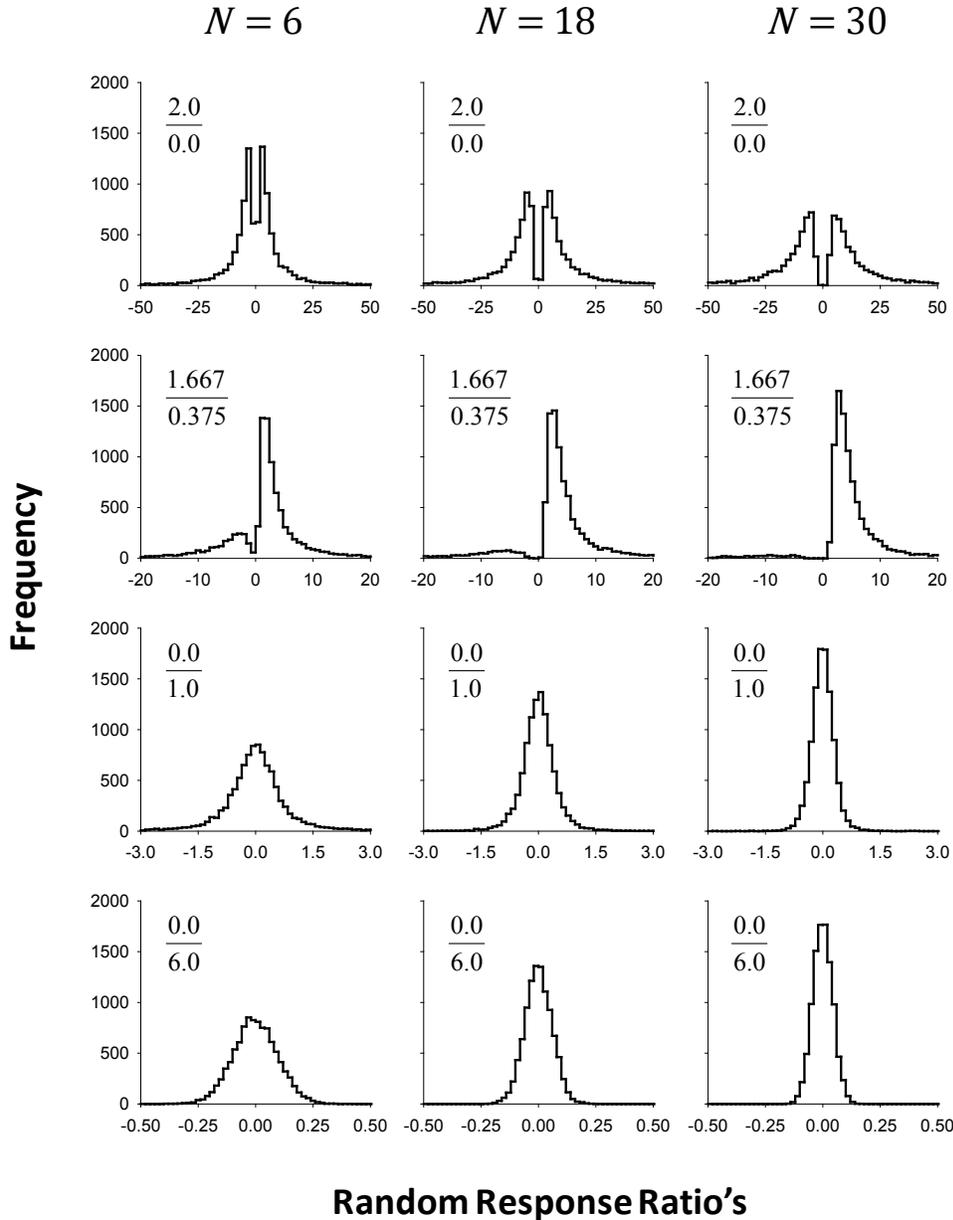


FIG. A4. The various shapes of distributions of unlogged response ratio's (a/b) when randomly simulated at different sample sizes (N) and with differing numerator (a) and denominator (b) values. Presented are the histograms of 10,000 ratio's of two random Normals with unit variances and means a and b , respectively. Random ratios are inlaid within each histogram. These shapes include from the top to bottom rows: bimodal with long tails ($a = 2, b = 0$), asymmetric with long tails ($a = 5/3, b = 3/8$), symmetric with long tails ($a = 0, b = 1$), and approximately Normal ($a = 0, b = 6$).



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