Title: The Most Difference in Means: A Statistic for Null and Near-Zero Results

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Abstract: Two-sample p-values test for statistical significance. Yet p-values cannot determine if a result has a negligible (near-zero) effect size, nor compare evidence for negligibility among independent studies. We propose the most difference in means (\(\delta_M\)) statistic to assess the practical insignificance of results by measuring the evidence for a negligible effect size. Both \(\delta_M\) and the relative form of \(\delta_M\) allow hypothesis testing for negligibility and outperform other candidate statistics in identifying results with stronger evidence of negligible effect. We compile results from broadly related experiments and use the relative \(\delta_M\) to compare practical insignificance across different measurement methods and experiment models. Reporting the relative \(\delta_M\) builds consensus for negligible effect size by making near-zero results more quantitative and publishable.

One-Sentence Summary: A two-sample statistic that compares the evidence for near-zero effect size among broadly related experiments.
Main Text:

Two-sample p-values from null hypothesis significance tests remain the gold standard for the analysis and reporting of scientific results despite calls to discontinue or de-emphasize their use (1). P-values can differentiate positive results (statistically significant) from null results (statistically insignificant). Yet p-values cannot give any indication of the practical insignificance of results: whether the observed effect size is close enough to zero to be considered negligible. Reporting the p-value gives no information about the practical insignificance of a result because p-values cannot differentiate null results with strong evidence of negligible effect size from those with inconclusive evidence with a broad range for potential effect size (Fig. 1A-D).

Consequently, designating results as practically insignificant with two-sample p-values is often considered a vague interpretation (2). Nevertheless, practically insignificant results play a key role in scientific research by falsifying scientific hypotheses and offering contrary evidence to previously reported positive results (3).

Characterizing practical insignificance requires assessing both the data and its context. An effective statistic should be useful for both tasks. A practically insignificant result has a negligible effect size, which requires some form of hypothesis test (either from a statistic (3–5) or interval (6)) to determine if the effect size is less than a maximum threshold for what is negligible. Determining the value of this threshold is context-specific and can greatly differ between scientists with dissimilar perspectives. Part of the process for determining this threshold must therefore depend on building a consensus for an appropriate value. Consensus can be built by comparing the degree of negligibility between previously published results from related experiments and citing the threshold for negligibility used in those investigations. Thresholds that greatly differ from those used in previous published works would require additional justification. An effective statistic would facilitate these comparisons and highlight noteworthy results that have exceptionally strong practical insignificance.

We present the most difference in means (δM) as a statistic that is capable of both tasks. We use a Bayesian approach to define δM using credibility intervals under the assumption of normality. The relative form of δM (rδM) can additionally compare the negligibility of results between broadly related experiments that have a combination of different experiment models, conditions, populations, species, timepoints, treatments, and measurement techniques. To test our statistics against previously developed candidates, we characterize the multidimensional problem of assessing the evidence of practical insignificance with various functions of population parameters. These functions serve as ground truth for simulation testing. We use an integrated risk assessment to test δM and rδM against several candidate statistics by evaluating their error rates in comparing the noteworthiness between simulated experiment results. Finally, we illustrate with real data how rδM can be used to assess the negligibility and noteworthiness of practically insignificant results.

Background

Bayesian Summary of Difference in Means

Let X1, ..., Xm be an i.i.d. sample from a control group with a distribution Normal(μX, σ2X), and Y1, ..., Yn be an i.i.d. sample from an experiment group with a distribution Normal(μY, σ2Y). Both samples are independent from one another, and we conservatively assume unequal variance, i.e., σ2X ≠ σ2Y (the Behrens-Fisher problem (7) for the means of normal distributions).
We analyze data in a Bayesian manner using minimal assumptions and therefore use a noninformative prior (8), specified as
\[ p(\mu_X, \mu_Y, \sigma^2_X, \sigma^2_Y) \propto (\sigma^2_X)^{-1} (\sigma^2_Y)^{-1}. \] (1)
The model has a closed-form posterior distribution. Specifically, the population means, conditional on the variance parameters and the data, follow normal distributions:
\[ \mu_X | \sigma^2, x_{1:m} \sim \text{Normal}\left(\bar{x}, \frac{\sigma^2_X}{m}\right) \text{ and } \mu_Y | \sigma^2, y_{1:n} \sim \text{Normal}\left(\bar{y}, \frac{\sigma^2_Y}{n}\right). \] (2)
Moreover, the population variances each independently follow an inverse gamma distribution (InvGamma):
\[ \sigma^2_X | x_{1:m} \sim \text{InvGamma}\left(\frac{m-1}{2}, \frac{(m-1)s^2_X}{2}\right) \text{ and } \sigma^2_Y | y_{1:n} \sim \text{InvGamma}\left(\frac{n-1}{2}, \frac{(n-1)s^2_Y}{2}\right). \] (3)

**Practical Insignificance Over a Raw Scale**
We define that there is stronger raw practical insignificance when the absolute difference in means between groups (|\(\mu_{DM}\)|) is smaller, where
\[ |\mu_{DM}| = |\mu_Y - \mu_X|. \] (6)
We summarize the posterior distribution of |\(\mu_{DM}\)| to convey the evidence of raw practical insignificance from sample data. For the sake of simplicity, we report a single number. We define raw disagreement as a conservative estimate of how large |\(\mu_{DM}\)| could be based on sample data and a given credible level. Results with lower values of disagreement convey stronger evidence of raw practical insignificance.

Our proposed statistic to quantify raw disagreement is the most difference in means (\(\delta_M\)), defined as an upper quantile of the posterior of |\(\mu_{DM}\)|. Specifically, if \(Q_{raw}(p)\) is the quantile function of this posterior, then \(\delta_M\) satisfies
\[ \delta_M = Q_{raw}(1 - \alpha_{DM}) \] (7)
for some “confidence” or credible level \(1 - \alpha_{DM}\).

However, this quantile function is difficult to compute, and there is no closed-form posterior distribution for the transformed quantity |\(\mu_Y - \mu_X\)|. We estimate its distribution using the Monte Carlo method (9), which simulates values from the posterior of the untransformed mean parameters.
We estimate the population absolute difference in means using an upper quantile of an empirical cumulative distribution function (ECDF). We do this by exploiting the fact that \(-c < \mu_Y - \mu_X < c\) if and only if |\(\mu_Y - \mu_X\)| < c, and we define \(F_{raw}(x)\) as the ECDF of the signed difference in sample means from \(K\) Monte Carlo simulations. With \(K\) samples from the posterior distribution of \(\mu_Y\) and \(\mu_X\), defined as the product of
\[ \mu_X | x_{1:m} \sim t_{m-1}(\bar{x}, s^2_X / m) \text{ and } \mu_Y | y_{1:n} \sim t_{n-1}(\bar{y}, s^2_Y / n), \] (8)
the cumulative distribution function is defined as
\[ F_{raw}(x) = K^{-1} \sum_{i=1}^{K} \mathbb{I}(\mu^i_Y - \mu^i_X \leq x). \] (9)
Then we numerically solve for the value of \( c \) such that
\[
F_{\text{raw}}(c) - F_{\text{raw}}(-c) = 1 - \alpha_{DM}. \tag{11}
\]
Because this interval is centered at 0 (i.e. (-c,c)), we can report only the upper tail.

As defined above, \( \delta_{M} \) is associated with a percentage (1 - \( \alpha_{DM} \)) to specify the credibility level in the same way that credibility intervals are annotated (i.e., 95% \( \delta_{M} \) has a credibility level of 0.95). Indeed, simulations of the posterior distribution confirms that credibility of the \( \delta_{M} \) is equal to (1 - \( \alpha_{DM} \)) (Fig. S1 A-D). Credible intervals can be used for hypothesis testing, meaning that \( \delta_{M} \) can be used to test if \( |\mu_{DM}| \) is less than a threshold value at a specified credibility level (6). Colloquially, the value of \( \delta_{M} \) represents the largest absolute difference between the population means of the experiment group and control group supported by the data. Lower values of \( \delta_{M} \) convey lower disagreement between two groups’ population means and suggest stronger practical insignificance.

**Practical Insignificance Over a Relative Scale**

To compare the practical insignificance of results across loosely related experiments, we extend the concept of raw practical insignificance to a relative scale. We define that there is stronger relative practical insignificance when the absolute relative difference between population means (\( |\mu_{DM}| \)) is smaller (assuming \( \mu_{X} > 0 \)), where
\[
|\text{r}_{\mu_{DM}}| = \left| \frac{|\mu_{Y} - \mu_{X}|}{\mu_{X}} \right|. \tag{12}
\]
We define relative disagreement as a conservative point estimate of how large \( |\mu_{DM}| \) could be based on sample data and a specified credibility level. Results with lower values of relative disagreement convey stronger evidence of relative practical insignificance. To calculate this conservative estimate, we again begin by estimating a credible interval that has a (1 - \( \alpha_{DM} \))% probability to contain \( |\mu_{DM}| \). Just as we did above, we force the left endpoint of this interval to be 0. By reporting the upper bound of this credibility interval, we conservatively assess the range of likely values for \( |\mu_{DM}| \) from sample data.

While there is no closed-form posterior distribution for \( |\mu_{DM}| \) either, we can estimate its upper quantile using Monte Carlo simulations of the same posterior distribution derived from the prior and likelihood introduced in definitions in Eq. (8) – (9). We exploit the fact that \( -c < \mu_{DM} < c \) if and only if \( |\mu_{DM}| < c \), and we define \( F_{\text{relative}}(x) \) as the ECDF of the signed relative difference in means approximated with Monte Carlo simulations from the posterior:
\[
F_{\text{relative}}(x) = K^{-1} \sum_{i=1}^{K} \mathbb{I} \left( \frac{\mu_{Y}^{i} - \mu_{X}^{i}}{\mu_{X}^{i}} \leq x \right). \tag{13}
\]
We define the relative most difference in means (\( \text{r}_{\delta_{M}} \)) as the one-tailed upper quantile of \( |\mu_{DM}| \). As before, we numerically solve for the value of \( c \) such that
\[
F_{\text{relative}}(c) - F_{\text{relative}}(-c) = 1 - \alpha_{DM}. \tag{14}
\]
Because this interval is centered at 0 (i.e. (-c,c)), we report only the upper tail. This upper bound is approximately equal to \( Q_{\text{relative}}(p) \) with \( p \) set to the confidence level \( \alpha_{DM} \):
\[
\text{r}_{\delta_{M}} = Q_{\text{relative}}(1 - \alpha_{DM}). \tag{15}
\]
The \( \text{r}_{\delta_{M}} \) is associated with a percentage (1 - \( \alpha_{DM} \)) to denote the credibility level as with \( \delta_{M} \). Indeed, simulations of the posterior distribution confirms that credibility of \( \text{r}_{\delta_{M}} \) is equal to (1 - \( \alpha_{DM} \)) (Fig. S1 E-H). Credible intervals can be used for hypothesis testing, meaning that \( \text{r}_{\delta_{M}} \) can be used to test if \( |\mu_{DM}| \) is less than a threshold value at a specified credibility level (6). Colloquially, the value of \( \text{r}_{\delta_{M}} \) represents the largest absolute percent difference between the population means of the experiment group and control group supported by the data. Results with lower values of \( \text{r}_{\delta_{M}} \) have lower relative disagreement and suggest stronger relative practical insignificance.
Measures of Raw and Relative Disagreement

While we have proposed two statistics to quantify the evidence of practical insignificance, we need to develop a structured characterization of disagreement to assess efficacy. This assessment relies on identifying the parameters that alter disagreement on a raw and relative scale. Disagreement is difficult to characterize in a controlled fashion because it depends on several parameters in addition to \( \mu_X \) and \( \mu_Y \). To characterize our statistics in a controlled fashion, we decompose disagreement into a set of previously defined functions of population parameters. These functions are used as measures of disagreement. We can vary each of these in isolation and study the effects they produce on our statistic.

For assessing raw disagreement between population means, we identify a set of four measures that can be altered independently (\(|\mu_{DM}|, \sigma_D, df_D, \text{ and } \alpha_{DM}\) defined in Table 1, Figure 2 B-F, see explanation in Supplementary Background: Explanation of Raw Disagreement Measures). For assessing the relative disagreement between population means, we divide the same disagreement measures by the control group mean when appropriate to form another set of variables that can be altered independently (\(|r\mu_{DM}|, r\sigma_D, df_D, \text{ and } \alpha_{DM}\) defined in Table 1, Figure 2 G-K, see explanation in Supplementary Background: Explanation of Relative Disagreement Measures). Note that some relative disagreement measures cannot be altered independently from raw disagreement measures (e.g., altering \(|\mu_{DM}|\) can also change \(|r\mu_{DM}|\) or \(r\sigma_D\)).

Results

A statistic that effectively estimates raw disagreement should covary with each measure of raw disagreement in a consistent direction. We generated a series of population parameter configurations where each measure of raw disagreement is individually altered towards lower raw disagreement (stronger evidence of raw practical insignificance). The mean of various candidate statistics was computed on repeated samples drawn from these configurations (candidate statistics listed in STable 1). The mean of a useful statistic should either increase for all disagreement measures or decrease. We found that only the mean values from \(\delta_M\) had a significant rank correlation in a consistent direction with disagreement for all measures (Fig. 2L, Fig S2-S3). Additionally, we generated sets of population parameter configurations where each measure of relative disagreement was altered towards lower relative disagreement. Only the mean values from \(r\delta_M\) had a significant rank correlation in a consistent direction for all measures (Fig. 2M, Fig S4-S5). However, this initial analysis had potential confounding effects since \(\mu_{DM}\) and \(r\mu_{DM}\) could not be altered independently from the other measures.

We next performed a risk assessment to examine how effective the candidate statistics were at determining which of two results had stronger practical insignificance and deemed more noteworthy (see Supplementary Methods: Integrated Risk Assessment of Noteworthiness). We represented this decision of noteworthiness with a 0-1 loss function that determined if the candidate statistics’ prediction of greater evidence of practical insignificance agreed with the ground truth established by each measure of disagreement. For a single population configuration, we calculated the expected value of the loss function to assess frequentist risk (10). This frequentist risk is the comparison error, defined as the probability of making an incorrect prediction when comparing noteworthiness. To explore general trends across the parameter space, we averaged comparison errors from many different parameter configurations with a similar approach to calculating various forms of integrated risk (10). Population configurations were stratified based on the expected t-ratio, approximated by Monte Carlo samples. The expected t-ratio is defined as the mean t-statistic of \(\mu_{DM}\) across samples scaled to the critical value (denoted as \(\bar{t}_{\text{statistic}} / |t_{\text{critical}}|\), see Materials and Methods: Parameter Space for Population
Configurations). Population configurations were separated between those associated with null results (absolute expected t-ratio \( \leq 1 \)) and critical results (absolute expected t-ratio \( > 1 \)). Investigations of comparison errors were conducted for each of the four independent measures for disagreement, both individually and simultaneously. \( \delta_M \) was the only candidate statistic that exhibited an error rate lower than random 50/50 guessing for all simulation studies for raw disagreement (Fig 3A, Fig. S6-S9). Similarly, \( r_{\delta M} \) was the only candidate statistic that exhibited an error rate lower than random for all simulation studies for relative disagreement (Fig 3B, Fig. S10-S13).

**Applied Examples**

We compiled results from studies of atherosclerosis to illustrate how the \( r_{\delta M} \) could be used to assess the negligibility and noteworthiness of practically insignificant results. Atherosclerosis is the underlying cause of approximately 50% of all deaths in developed nations (11) and is characterized by the build-up of fatty deposits, called plaques, on the inner wall of arteries. Researchers use dietary, behavioral, pharmacological, and genetic interventions to study atherosclerosis and measure various biological phenomenon to monitor disease severity, including plasma cholesterol and plaque size.

While lowering total plasma cholesterol is therapeutic in most cases (depending on the composition of the cholesterol (11)), many interventions treat atherosclerosis through other means. It is important to determine whether an intervention has a negligible effect size on total plasma cholesterol to help elucidate its underlying mechanisms. Plasma cholesterol levels vary from 60-3000 mg/dL across animal models used to research atherosclerosis and are reported in units of mmol/L as well (Fig. 4). This large variation in the measurement values makes it necessary to evaluate disagreement on a relative scale. The \( r_{\delta M} \) is the only statistic that can be used to build consensus and assess the noteworthiness of a practically insignificant result by scoring related results based on their degree of relative disagreement (Fig. 4A-B). A literature search for positive results associated with reducing total cholesterol reveals that the relative difference in means is larger than 30% for most cases (Fig. 4C). If this threshold is used to delineate a minimum negligible effect size, null results could be separated based on a hypothesis test (6) \((r_{\delta M} < 30\%)\) through a direct comparison of magnitudes. Moreover, results could be further separated between those with evidence of strong practical insignificance \((r_{\delta M} < 15\%)\), weak practical insignificance \((15\% < r_{\delta M} < 30\%)\), and inconclusive \((r_{\delta M} > 30\%)\). While all the cited publications in the table correctly stated that no difference was observed between the control and experiment group, most results were still used indirectly as evidence of negligible effect size (see NE column) either in the text or as a secondary negative control. With these thresholds, scientists could not use results with \( r_{\delta M} > 30\% \) as evidence of absence of effect. Instead, they could choose to present the data with an ambiguous interpretation or collect additional samples in an attempt to clarify the interpretation for \( r_{\delta M} \).

As a second example, a similar case study examines the practical insignificance of therapeutic interventions independent of reducing plaque size (Fig. 5A-B). Similar with measuring total cholesterol, plaque size is measured across units that span orders of magnitude. A review of positive results of plaque size reduction (Fig 5C) could yield a threshold of 40% for a negligible effect size. Using that threshold could separate results that are of strong practical insignificance \((r_{\delta M} < 20\%)\), weak practical insignificance \((20\% < r_{\delta M} < 40\%)\), and inconclusive \((r_{\delta M} > 40\%)\). Inconclusive results could not be interpreted as evidence of negligible effect size, as the authors intended in most cases.
Discussion

We have proposed two statistics, $\delta_M$ and $r\delta_M$, that assess the evidence of negligible effect size by quantifying the disagreement between population means. The $\delta_M$ and $r\delta_M$ statistics support hypothesis testing and were the only candidate statistics that exhibited lower than random error in determining greater noteworthiness across all disagreement measures. We demonstrated with applied examples how researchers can use $r\delta_M$ to build consensus and assess practical insignificance by evaluating both the negligibility and noteworthiness of experimental results. This statistic summarizes results as a simple percentage with an intuitive interpretation (largest percent change from control group mean supported by the data). We illustrate that researchers can apply a threshold and identify practically insignificant results. Critically, researchers can apply different thresholds based on their differing opinions or research applications without having to re-compute $r\delta_M$: the value of the statistic remains unchanged if different thresholds are used in Fig. 4 and 5. Results that are designated as strongly practically insignificant can be used to falsify scientific hypotheses or offer contrary evidence to related positive results.

Some fields may report the confidence or credible interval of the population DM to aid in interpreting the practical insignificance of results since intervals have a key characteristic for summarizing results: they combine both statistical and practical significance by yielding an interval for the effect size specified by the significance level. Yet comparing the evidence of practical insignificance with intervals must consider the width and location of the interval when there is no clear method to combine them. We solve this issue by developing a statistic that collapses an interval into a single value.

For experimental results, the presence or lack of negligible effect size should be interpreted in the context of related results. We recommend that $r\delta_M$ should be the default statistic used to evaluate the strength of practically insignificant results since it allows for comparisons between a broader range of related experiments than $\delta_M$. However, $\delta_M$ would be more appropriate for cases where the mean of the control group is close to zero and reporting the percent difference in means is spurious (e.g., see Fig 5A, last study, where $r\delta_M$ of 489% is almost three times the value of $\delta_M$ divided by the control mean: $\delta_M/\bar{x}=180\%$), or for comparisons between experiments where the control group mean is not expected to change. Reporting the $\delta_M$ or $r\delta_M$ encourages high quality results because it rewards the use of large sample sizes, high quality measurement techniques, and rigorous experiment design. Additionally, assessing null results with the $r\delta_M$ may reduce publication bias against null results (12), mitigate the File Drawer problem by encouraging their publication, and increase scientific rigor by allowing null results with low disagreement to serve as strong evidence of negligible effect size.

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Data and Material Availability: code used to generate all figures is written in R and available at: https://github.com/bac7wj/ACES.

Supplementary Materials

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Supplementary Text
Figs. S1 to S13
Tables S1
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Fig. 1: P-values give no indication of a result’s evidence of practical insignificance. (A-C) Data from pairs of simulated experiments (left, red, Exp 1; middle, blue, Exp 2) with a control group (X) and experiment group (Y). Plot comparing the 95% confidence interval of difference of means for each pair (right graph) illustrating that Exp 1 has stronger evidence of practical insignificance (range of values closer to zero). While the p-values between experiment pairs (A) remain constant, (B) increase, or (C) decrease, (D) the consistent increase of the most difference in means (δM) correctly suggests that Exp 1 has stronger evidence of practical insignificance in all cases (lower value of p-values and δM bolded between experiment pairs).
**Fig. 2: The δM statistic and measures of disagreement.** (A) Several illustrations of the most difference in means (orange line, δM). (B) Data from a simulated experiment (red, Exp 1) with a control group (X) and experiment group (Y) acting as a reference to illustrate the measures of disagreement. (C-G) Simulated experiment data (Exp 2, blue) with higher disagreement than Exp 1 through their difference in means (lower panel) via (C) increased difference in means, (D) increased standard deviation of the difference, (E) decreased degrees of freedom, and (G) decreased significance level (upper: error bars are standard deviation, lower: error lines are 95% confidence interval of the mean). (G) Simulated data from an experiment (red, Exp 1) acting as a reference to illustrate the measures of relative disagreement. (H-K) Simulated experiment data (Exp 2, blue) with higher relative disagreement than Exp 1 through their relative difference in
means (lower panel) via (H) increased relative difference in means, (I) increased relative standard deviation of the difference in means, (J) decreased degrees of freedom, and (K) decreased significance level. (L) Heatmap of Spearman ρ of candidate statistics’ mean across samples versus each raw disagreement measure altered towards lower disagreement (stronger evidence of practical significance). (M) Heatmap of Spearman ρ of candidate statistics’ mean across samples versus each relative disagreement measure altered towards lower disagreement (** denotes candidate statistic with all correlations significant and in same direction, underline denotes p < 0.05 for bootstrapped Spearman correlation, color displayed for significant correlations only). Abbreviations: $\bar{x}_{DM}, s_{DM}, r\bar{DM}, r_{SDM}$: mean, standard deviation, relative mean, and relative standard deviation of difference in sample means. CD: Cohen’s d; $P_N$: null hypothesis testing p-value; $P_E$: TOST equivalence p-value; BF: Bayes Factor; Rnd: random 50/50 guess.
**Fig. 3:** Comparison error rates of candidate statistics in identifying greater noteworthiness between results according to each measure of disagreement. (A) Heatmap of comparison error rates for each candidate statistic across investigations for identifying results with lower raw disagreement (color displayed for error rates that are different than random) (B) Heatmap of comparison error rates for each candidate statistic across investigations for identifying results with lower relative disagreement. Blue fill denotes comparison error less than random, red denotes greater than random. Numerical label in cells are comparison error rates from random.
behavior scaled to the lowest error rate for each column. Underlined numbers denote a comparison error rate that is statistically different than random. See Fig. 2 for abbreviations. Investigations alter one measure of disagreement individually or several simultaneously to serve as ground truth. Investigations are separated between population configurations associated with null results (expected t-ratio \(\leq 1\)) and positive results (expected t-ratio > 1).
Fig. 4: Interpreting null results from total plasma cholesterol in atherosclerosis research. (A) Table of null results measuring total plasma cholesterol with various candidate statistics computed (NE indicates whether result was used directly or indirectly as evidence of negligible effect size). (B) For visual reference, 95% confidence interval of the difference in means divided by the mean of the control group X for each study in (A) (confidence bounds calculated from Welch’s t-test, uncertainty added by division disregarded). (C) Table of positive results measuring total plasma cholesterol. (A, C) αDM is Bonferroni-corrected according to design of experiment for each study. Abbreviations: NE, negligible effect; \( \bar{x}, \bar{y} \), sample means of group \( X \) and \( Y \); \( s_X, s_Y \), sample standard deviations of group \( X \) and \( Y \); Sp, species; PMID, PubMed ID; Loc, location in manuscript; ms, mouse; rb, rabbit; pg, pig; mc, macaque; mk, monkey; hu, human (see respective publications for abbreviations used in group names).
Fig. 5: Interpreting null results from plaque size in atherosclerosis research. (A) Table of null results measuring plaque size, with various candidate statistics computed (NE indicates whether result was used directly or indirectly as evidence of negligible effect size). (B) For visual reference, 95% confidence interval of the difference in means divided by the mean of the control group X for each study in (A) (confidence bounds calculated from Welch’s t-test, uncertainty added by division disregarded). (C) Table of positive results measuring plaque size. (A, C) αDM is Bonferroni-corrected according to design of experiment for each study. See Fig. 4 for abbreviations.
Table 1: Measures of Disagreement

| Measure   | Scale                  | Equation                                      | Lower Disagreement |
|-----------|------------------------|-----------------------------------------------|--------------------|
| $|\mu_{DM}|$ | Raw | $|\mu_{DM}| = |\mu_Y - \mu_X|$, | — |
| $\sigma_D$ | Raw | $\sigma_D = \sqrt{\sigma_X^2 + \sigma_Y^2}$ | — |
| $df_D$   | Raw, Relative          | $df_D = m + n - 2$                           | + |
| $\alpha_{DM}$ | Raw, Relative  |                                           | + |
| $|r\mu_{DM}|$ | Relative | $|r\mu_{DM}| = \frac{|\mu_{DM}|}{\mu_X}$ | — |
| $r\sigma_D$ | Relative | $r\sigma_D = \frac{\sigma_D}{\mu_X}$ | — |

Note: Lower disagreement column indicates the direction of change for each measure to decrease disagreement when other measures held constant. Abbreviations: $D$, difference distribution of $X$ and $Y$. 
Supplementary Materials for

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Literature Search

The tables summarizing results in Fig. 4 and 5 were compiled based on a literature search using Pubmed, Google Scholar, and Google search. Included results were limited to papers that were indexed on Pubmed. Papers were identified based on searches with combinations of the following keywords:

- Total cholesterol example: atherosclerosis, total cholesterol, cholesterol, plasma cholesterol, reduce, protect, increase, independent, no change, mouse, rabbit, human, primate, rat.
- Plaque size example: plaque size, plaque area, lesion size, lesion area, reduce, protect, increase, independent, no change, mouse, rabbit, human, primate, rat.

The included results are not meant to be complete, but rather give the reader a simplified toy example with how the proposed metric could be used to ascertain the practical insignificance of results. The mean and standard deviation of each group were either copied directly from the source publication or estimated from the figure using Web Plot Digitizer (https://automeris.io/WebPlotDigitizer/).

Integrated Risk Assessment of Noteworthiness

Determining noteworthiness is a critical feature for assessing the practical insignificance of a result. Our risk assessment is designed to benchmark the efficacy of various candidate statistics in determining which of two experiments is most noteworthy (i.e. exhibiting lower disagreement). In many cases, determining noteworthiness is difficult since disagreement is a function of several parameters (see Table 1). To simulate instances where it is clear which experiment has lower disagreement, we hold all population parameters constant except those that alter a specified disagreement measure (referred to as the independent measure). Using this strategy, we can then benchmark performance of the candidate statistics in determining noteworthiness for each measure of disagreement in isolation. Since the disagreement measures represent known instances where disagreement changes, we set the criterion that a successful statistic must predict greater noteworthiness at a rate better than random for every measure of disagreement. We test for this criterion with simulations that use both frequentist and Bayesian approaches to assess risk (in this case, risk is defined as the probability of incorrectly predicting which of two results has stronger evidence for practical insignificance).

Simulation Design and Loss Function

Given the nomenclature defined in the background (Bayesian Summary of Difference in Means), let $\theta$ be a population parameter configuration for a hypothetical experiment 1. Specifically, $\theta$ is a vector of population parameters and the significant level specified for experiment 1 required to simulate sample data from a control group $X$ and experiment group $Y$.

$$\theta \in \left( \mu_X, \mu_Y, \sigma_X^2, \sigma_Y^2, \alpha_{DM} \right).$$  \hspace{1cm} \text{(S1)}$$

And let $\theta'$ be a population configuration from a second simulated experiment. For a pair of population configurations $\theta$ and $\theta'$, we determine which is more noteworthy based on the ground truth determined by the independent measure of disagreement. We then draw samples from these population configurations and use various candidate statistics to predict which experiment is most noteworthy and compare this prediction against the ground truth.

To establish ground truth, we defined a loss function for each disagreement measure that designates whether experiment 1 or experiment 2 had lower disagreement (Table S2). These loss functions assume that all other measures of disagreement are held constant between the two experiments. The loss functions compare the ground truth from the disagreement measure
A value of 1 from the ground truth and prediction designations denote experiment 1 having lower disagreement than experiment 2. A value of 0 from the loss function denotes that the candidate statistic agrees with the ground truth (inequalities for candidate designations are switched in loss functions).

Using these loss functions, we can approximate, using the Monte Carlo method, the frequentist risk \( (10) \) for a single population configuration by calculating the mean loss over \( M \) samples.

\[
\mathbb{P}_{\theta, \theta'}(|\delta(x, y, \alpha_{DM})| < |\delta(x', y', \alpha'_{DM})|) := \frac{1}{M} \sum_{i=1}^{M} \text{Loss}(x_i, y_i, x'_i, y'_i, \theta, \theta').
\]  

We define this evaluation of frequentist risk as comparison error, interpreted as the probability that a candidate statistic will incorrectly assign greater noteworthiness when comparing two experiments.

Since frequentist risk is a function of the population configuration, analyzing risk at one configuration will not be representative of general performance. To explore general trends across the parameter space, we averaged comparison errors from many different parameter configurations.

\[
\frac{1}{N} \sum_{i=1}^{N} \mathbb{P}_{\theta_i, \theta'_i}(|\delta(x, y, \alpha_{DM})| < |\delta(x', y', \alpha'_{DM})|) \approx \mathbb{E}_{\theta_i, \theta'_i}[[\mathbb{P}_{\theta_i, \theta'_i}(|\delta(x, y, \alpha_{DM})| < |\delta(x', y', \alpha'_{DM})|)]
\]  

This strategy of averaging frequentist risks follows the process for assessing integrated Bayesian risk \( (10) \). However, in an integrated Bayesian risk assessment, the population configurations must be generated randomly from a specific prior. We do not follow this strategy because our investigation requires a more structured characterization of trends within the parameter space.

A Bayesian risk assessment would simply generate a single value that globally summarizes risk, where a lower risk is considered better. However, our chosen criterion is that a successful statistic must successfully predict noteworthiness from changes to every disagreement measure in isolation. To accomplish this, the risk assessment must individually investigate each measure of disagreement so a direct relationship with the statistic’s performance can be ascertained. Generating population configurations from a specific prior could not achieve these objectives. Instead, we must carefully generate curated population configurations.

**Cases of Dependence Between Changes to Disagreement Measures**

We need to test comparison error of statistics across population configurations with changes in value to each disagreement measure. In principle, we would alter the independent measure across configurations and hold all other measures constant. Yet this approach is not possible because the raw and relative disagreement measures sometimes covary with each other. For instance, changing \( |\mu_{DM}| \) across configurations must also change one or more of \( \{|r\mu_{DM}|, r\sigma_{DM}, \sigma_{DM}\} \). This dependence between measures could introduce confounding relationships and prevent us from testing each measure in isolation. If confounding relationships are not dealt with, we cannot conclude if a candidate statistic can determine noteworthiness for each disagreement measure. For example, if a candidate statistic performs impressively in detecting changes to \( |\mu_{DM}| \), we cannot conclude that its performance is due to changes with \( |\mu_{DM}| \) since the statistic could be responding from indirect changes to \( |\mu_{DM}|, |r\mu_{DM}|, \) or \( |\sigma_{DM}| \).
We avoid this confounding issue by generating sets of population configurations where the ground truth designations between the independent measure and other measures do not have any correlation. While the value of covarying measures may correlate, the ground truth designations can remain uncorrelated from each other with carefully curated population parameter datasets. To accomplish this, we varied the independent measure so that both experiments have an equal and random chance to have lower disagreement (50/50 chance). To avoid correlation with ground truth designations from other measures, we generate configurations where the other disagreement measures must either:

1) Designate experiment 1 the winner in all cases.
2) Designate experiment 2 the winner in all cases.
3) Designate experiment 1 the winner half the time, but these designations are also random and not correlated with the designations from the independent measure.

All three cases will guarantee that there is no correlation between the ground truth designations between the independent measure and other measures. This lack of correlation is directly verified for each investigation with a binomial test ($H_0: \pi=0.5$) of the number of shared ground truth designations between the independent measure and each of the other measures. For an example, Fig 6A visualizes the lack of correlation of the ground truth designations for $|\mu_{DM}|$ compared to the other disagreement measures.

**Parameter Space for Population Configurations**

The population configurations were chosen to adequately sample the parameter space to ensure the error rates reflected general trends. A natural way to separate the parameter space is using the gold standard of quantifying the statistical significance of results with p-values or some other statistic. Since $\delta_M$ and $r\delta_M$ can be calculated and used regardless of statistical significance, it is not clear if their error rates would be consistent when analyzing null and positive results. We divided the population configurations associated with null and positive results into separate investigations (and differing error rates were indeed observed between these two cases in Fig 3).

One method to evaluate statistical significance is to check if the sample t-statistic for $\mu_{DM}$ is less than the critical t-value across the samples generated from the population configurations, where

$$t_{statistic} = \frac{\bar{y} - \bar{x}}{\sqrt{\frac{s_x^2}{m} + \frac{s_Y^2}{n}}},$$

$$t_{critical} := t_{\alpha_{DM, m+n-1}}.$$  \hspace{1cm} (54)

A result is deemed null if $t_{statistic} < |t_{critical}|$ and positive otherwise (absolute value is used because the distance from zero in either direction is relevant). To summarize the entire collection of samples drawn from a single population parameter, we can compute the mean value of the t-statistic and check if $\bar{t}_{statistic} < |t_{critical}|$. Population configurations where is expression is true is assigned as a null configuration. This calculation allows us to separate populations configurations associated with null results from positive results, but we also need to separate results based on their degree of statistical significance within each region. We therefore compute the ratio of $\bar{t}_{statistic} / |t_{critical}|$ (we define as the t-ratio) as a method to score results based on their statistical significance. Population configurations were chosen to provide adequate coverage for null results (absolute expected t-ratio $\leq 1$) and positive results (absolute expected t-ratio $> 1$).
This coverage was typically accomplished by altering the population parameters associated with the independent disagreement measure so that there was sufficient coverage. We generated population parameters associated with the independent measure from uniform distributions. For example, with the investigation where $|\mu_{DM}|$ is the independent measure for null results (SFig. 6), we generated values for $\mu_{DM}$ for experiment 1 and 2 from two different uniform distributions of $U(0.5, 3)$ or $U(2, 4.5)$ (for each population configuration, experiment 1 $\mu_{DM}$ used one of these distributions at random and experiment 2 $\mu_{DM}$ used the other). Two distributions were used so that a large enough difference between $\mu_{DM}$ for experiment 1 and 2 was found in each population configuration so that candidate statistics would be able to detect the signal in most cases. We wish to minimize cases where the change in disagreement between experiment results is so small that none of the candidate statistics can predict which experiment has lower disagreement. The standard deviations, sample sizes, and significance levels were set to fixed values between both experiments. While the control mean for the first experiment was $\mu_{X,1} = 20$, the control mean for the second experiment was $\mu_{X,2} = 200$. These values for $\mu_X$ were used so that the disagreement measure $|\mu_{DM}|$ would designate experiment 2 with lower disagreement for all population configurations and avoid any correlation between the ground truth designations for $|\mu_{DM}|$ and $|\mu_{DM}|$. Please see the associated R script files for more details, and SFig 6B for example histogram of $t$-ratios of population configurations within the null region.

**Simultaneous Risk Assessment**

Our approach of varying a single measure of disagreement at a time for the risk assessment of noteworthiness unfortunately does not simulate real world conditions. It would be reasonable to expect multiple measures of disagreement to vary simultaneously when comparing noteworthiness between experiments. To address this shortcoming, we designed population configurations that had multiple disagreement measures varied simultaneously as a more realistic scenario.

We designed a set of population configurations that allowed for all four raw disagreement measures to vary simultaneously (Fig 3A, columns under “Simultaneous” header). We examined whether candidate statistics could predict noteworthiness in a better than random fashion by comparing the prediction designations to the ground truth designations for each raw disagreement measure. Another set of population configurations were generated that allowed for all relative agreement measures to change simultaneously (Fig 3B, columns under “Simultaneous” header). We examined whether candidate statistics could predict noteworthiness in a better than random fashion by comparing the prediction designations to the ground truth designations for each relative disagreement measure.

**Supplementary Text**

**Explanation of Raw Disagreement Measures**

We defined raw disagreement as an estimate of how large $|\mu_{DM}|$ could be based on sample data. From a Bayesian perspective, this can be represented with an upper quantile of a posterior distribution summarizing $|\mu_{DM}|$. Therefore, we must consider not only the location, but also the dispersion of the distribution summarizing $|\mu_{DM}|$ because both will change its upper quantiles. From a frequentist perspective, we will now explain how a set of functions of population parameters change the distribution of raw disagreement when altered in isolation.

Based on our definition of raw disagreement, lower disagreement is found with lower
values of $|\mu_{DM}|$ with all other measures held constant, illustrated with lower disagreement from experiment 1 with its confidence interval for $\mu_{DM}$ centered closer to zero than experiment 2 (Fig 1B, C). Lower disagreement is also found with lower values of $\sigma_{DM}$ with all other measures held constant since it suggests a smaller upper bound for $|\mu_{DM}|$. Since $\sigma_{DM}$ is influenced by both the standard deviations and sample sizes of both groups, the contributions of each can be independently characterized with the standard deviation ($\sigma_D$) and degrees of freedom ($df_D$) of the difference between observations from group X and Y (i.e., $D = Y - X$).

$$\sigma_D = \sqrt{\sigma_X^2 + \sigma_Y^2} \quad (S5)$$

$$df_D = m + n - 2 \quad (S6)$$

There is lower disagreement with lower values of $\sigma_D$ (contributing to $\sigma_{DM}$ in the numerator) with all other measures held constant, illustrated with lower disagreement from experiment 1 with its narrower confidence interval (Fig 1D). There is also lower disagreement with higher values of $df_D$ (contributing to $\sigma_{DM}$ in the denominator) with all other measures held constant, illustrated with lower disagreement from experiment 1 with its narrower confidence interval (Fig 1E). In addition to $\sigma_{DM}$ indicating how large the range of $\mu_{DM}$ could be, the specified significance level ($\alpha_{DM}$) also effects the uncertainty associated with the comparison (often adjusted for experiments with multiple comparisons). There is lower disagreement with lower values of $\sigma_{DM}$ with all other measures held constant because there is an increase in the range of possible values for $\mu_{DM}$, illustrated with lower disagreement from experiment 1 with its narrower confidence interval (Fig 1F).

We have identified $|\mu_{DM}|$, $\sigma_D$, $df_D$, and $\alpha_{DM}$ as measures of disagreement (Table 1) by illustrating how changes to each of these measures in isolation leads to known changes to disagreement. Since the value of these measures can be altered independently, each of these measures can be altered as an independent measure to test the effectiveness of candidate statistics in quantifying disagreement. An effective statistic should be able to identify results with lower disagreement across all four of these measures.

**Explanation of Relative Disagreement Measures**

To quantify relative disagreement, we extend the measures of disagreement into units relative to the mean of the control sample. The relative difference in means ($r\mu_{DM}$) and relative standard deviation ($r\sigma_{DM}$) are normalized by the mean of the control group:

$$r\mu_{DM} = \frac{\mu_{DM}}{\mu_X} \quad (S7)$$

$$r\sigma_{DM} = \frac{\sigma_{DM}}{\mu_X} \quad (S8)$$

We quantify relative disagreement by estimating the upper bound of the magnitude of $r\mu_{DM}$, where smaller values exhibit lower disagreement.

Lower relative disagreement is found with lower values of the magnitude of $r\mu_{DM}$ (abbreviated as $|r\mu_{DM}|$) with all other measures held constant, illustrated with experiment 1 having a confidence interval for $r\mu_{DM}$ centered closer to zero (Fig 1G, H). Lower relative disagreement is also found with lower values $r\sigma_{DM}$ with all other measures held constant. Since $r\sigma_{DM}$ is influenced by both the relative standard deviations and sample sizes of both groups, the contributions of each can be independently characterized with the relative standard deviation ($r\sigma_D$) and degrees of freedom of the difference between observations:

$$r\sigma_D = \frac{\sigma_D}{\mu_A} \quad (S9)$$

There is lower relative disagreement with lower values of $r\sigma_D$ with all other measures.
held constant, illustrated with lower disagreement from experiment 1 with its narrower confidence interval (Fig. 1I). There is lower relative disagreement with higher values of $d_{f_D}$ (contributing to $\sigma_{DM}$ in the denominator) with all other measures held constant, illustrated with lower disagreement from experiment 1 with its narrower confidence interval (Fig. 1J). In addition to $r_{\sigma_{DM}}$ indicating how large the range of $r_{\mu_{DM}}$ could be, the specified significance level ($\alpha_{DM}$) also affects the uncertainty associated with the comparison (often adjusted for experiments with multiple comparisons). There is lower disagreement with lower values of $\alpha_{DM}$ with all other measures held constant because there is an increase in the range of possible values for $r_{\mu_{DM}}$, illustrated with lower disagreement from experiment 1 with its narrower confidence interval (Fig 1K).

We have identified $|r_{\mu_{DM}}|$, $r_{\sigma_D}$, $d_{f_D}$, and $\alpha_{DM}$ as measures of relative disagreement (Table 1) by illustrating changes to each of these measures in isolation leads to known changes to relative disagreement. Since the value of these measures can be altered independently, each of these measures can be varied as independent variables to test the effectiveness of candidate statistics in quantifying relative disagreement. An effective statistic should be able to identify results with lower relative disagreement across all four of these measures.
\[ \partial_M \text{ Cred. Rate} = N^{-1} \sum_{i=1}^{K} I(|\mu_i - \mu_X| \leq \partial_M) \]

\[ r\partial_M \text{ Cred. Rate} = N^{-1} \sum_{i=1}^{K} \left( \frac{|\mu_i - \mu_X|}{\mu_X} \leq r\partial_M \right) \]
Fig. S1: Credibility of $\delta_M$ and $r_{\delta M}$ is equal to one minus the significance level. (A) The $\delta_M$ credibility rate is defined as the fraction of Monte Carlo trials simulating the difference in population means from the posterior distribution that are less than or equal to $\delta_M$ (with a five-fold increase in trials compared to the calculation for $\delta_M$). (B) Mean credibility rate for a range of values for $\bar{x}_{DM}$ and $s_{DM}$ at different significance levels. (C) Representative heatmaps of credibility rates at various significance levels. (D) The $r_{\delta M}$ credibility rate is defined as the fraction of Monte Carlo trials simulating the relative difference in population means from the posterior distribution that are less than or equal to $r_{\delta M}$ (with five-fold increase in trials compared to the calculation for $r_{\delta M}$). (E) Mean credibility for a range of values for $\bar{x}_{DM}$ and $s_{DM}$ at several significance levels. (F) Representative heatmaps of credibility rates at various significance levels (equal variance for control and experiment group, N=6 measurements per sample).
A) Independent Variable: $\mu_{RM}$

B) Spearman's $\rho$

C) Mean Value

D) Independent Variable: $\sigma_{RM}$

E) Spearman's $\rho$

F) Mean Value
Fig. S2: correlation of candidate statistics with stronger practical insignificance via $\mu_{\text{DM}}$ and $\sigma_D$. (A) A series of population configurations with decreasing $\mu_{\text{DM}}$ towards lower disagreement (changes to $\mu_{\text{DM}}$ could not be completely isolated from all other disagreement measures, so $\sigma_D$ also changed with this series, but towards higher disagreement). (B) Spearman’s $\rho$ of each candidate statistic versus $\mu_{\text{DM}}$ and (C) mean value of candidate statistic across configurations. (D) A series of population configurations with decreasing $\sigma_D$ towards lower disagreement with all other disagreement measures held constant. (E) Spearman’s $\rho$ of each candidate statistic versus $\sigma_D$ and (F) mean value of candidate statistic across configurations. (B, E) Error bars are 95% confidence interval of Spearman’s $\rho$ with Bonferroni correction, with red plus denoting candidate statistics with a significant positive correlation and blue minus denoting a significance negative correlation (1E3 samples drawn for each point in the series).
Fig. S3: correlation of candidate statistics with stronger practical insignificance via $df_D$ and $\alpha_{DM}$. (A) A series of population configurations with decreasing $df_D$ toward lower disagreement with all other disagreement measures held constant. (B) Spearman’s $\rho$ of each candidate statistic versus $df_D$ and (C) mean value of candidate statistic across configurations. (D) A series of population configurations with decreasing $\alpha_{DM}$ toward lower disagreement with all other disagreement measures held constant. (E) Spearman’s $\rho$ of each candidate statistic versus $\alpha_{DM}$ and (F) mean value of candidate statistic across configurations. (B, E) Error bars are 95% confidence interval of Spearman’s $\rho$ with Bonferroni correction, with red plus denoting candidate statistics with a significant positive correlation and blue minus denoting a significance negative correlation.
**Fig. S4:** correlation of candidate statistics with stronger relative practical insignificance via $r_{\mu DM}$ and $r_{\sigma D}$. (A) A series of population configurations with decreasing $r_{\mu DM}$ towards lower relative disagreement (changes to $r_{\mu DM}$ could not be completely isolated from all variables, so $\sigma_D$ also changed with this series, but towards higher disagreement). (B) Spearman’s $\rho$ of each candidate statistic versus $r_{\mu DM}$ and (C) mean value of candidate statistic across configurations. (D) A series of population configurations with decreasing $r_{\sigma D}$ towards lower relative disagreement with all other disagreement measures held constant. (E) Spearman’s $\rho$ of each candidate statistic versus $r_{\sigma D}$ and (F) mean value of candidate statistic across configurations. (B, E) Error bars are 95% confidence interval of Spearman’s $\rho$ with Bonferroni correction, with red plus denoting candidate statistics with a significant positive correlation and blue minus denoting a significance negative correlation (1E3 samples drawn for each point in the series).
Fig. S5: correlation of candidate statistics with relative practical insignificance via dfD and αDM. (A) A series of population configurations with decreasing dfD toward lower relative disagreement with all other disagreement measures held constant. (B) Spearman’s ρ of each candidate statistic versus dfD and (C) mean value of candidate statistic across configurations. (D) A series of population configurations with αDM reduced toward lower relative disagreement with all other disagreement measures held constant. (E) Spearman’s ρ of each candidate statistic versus αDM and (F) mean value of candidate statistic across configurations. (B, E) Error bars are 95% confidence interval of Spearman’s ρ with Bonferroni correction, with red plus denoting candidate statistics with a significant positive correlation and blue minus denoting a significant negative correlation (1E3 samples drawn for each point in the series).
Fig. S6: The $\delta_M$ is the only statistic that has lower than random comparison error with null results for each measure of disagreement. (A) Fraction of population configurations where experiment 1 has lower disagreement than (LDT) experiment 2 according to each measure of disagreement, with $\mu_{DM}$ serving as ground truth. (B) Histogram of the ratio of $t_{\text{statistic}}$ to $t_{\text{critical}}$ for population configurations, indicating that results from experiment 1 (blue) and experiment 2 (pink) are both associated with null results ($|\bar{t}_{\text{statistic}} / t_{\text{critical}}| < 1$). (C) Mean comparison error rate of candidate statistics in identifying which experiment has lower disagreement via lower $\mu_{DM}$ across population configurations (50 observations per sample). (D) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with $\sigma_D$ serving as ground truth. (E) Histogram of the ratio of $t_{\text{statistic}}$ to $t_{\text{critical}}$ indicating population configurations are associated with null results. (F) Mean comparison error rate of candidate statistics in identifying which experiment has lower disagreement via lower $\sigma_D$ across population configurations (50 observations per sample). (G) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with $df_D$ serving as ground truth. (H) Histogram of the ratio of $t_{\text{statistic}}$ to $t_{\text{critical}}$ indicating population configurations are associated with null results. (I) Mean comparison error rate of candidate statistics in identifying which experiment has lower disagreement via higher $df_D$ across population configurations (6 - 40 observations per sample). (J) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with $\alpha_{DM}$ serving as ground truth. (K) Histogram of the ratio of $t_{\text{statistic}}$ to $t_{\text{critical}}$ indicating population configurations are associated with null results. (L) Mean comparison error rate of candidate statistics in identifying which experiment has lower disagreement via higher $\alpha_{DM}$ across population configurations (30 observations per sample). (A, D, G, J) ‘#’ denotes measures that have a nonrandom number of shared designations with independent measures (listed at top of y-axis) for which experiments are designated with lower disagreement ($p < 0.05$ from Bonferroni corrected two-tailed binomial test for coefficient equal to 0.5 between independent measure and each disagreement measure). (B, E, H, K) Discrete Kolmogorov-Smirnov test between histograms. (C, F, I, L) Pairwise t-test with Bonferroni correction for all combinations, where blue minus denotes a mean error rate lower than random, red plus denotes higher than random. N=1E3 population configurations generated for each study, n=1E2 samples drawn per configuration.
Fig. S7: The $\delta_M$ is the only statistic that has lower than random comparison error with null results across all measures of disagreement simultaneously. (A) Fraction of population configurations where experiment 1 has lower disagreement than (LDT) experiment 2 according to each measure of disagreement, with $\mu_{DM}$, $\sigma_{D}$, $df_{D}$, and $\alpha_{DM}$ serving as separate ground truths simultaneously. (B) Histogram of the ratio of $t_{\text{statistic}}$ to $t_{\text{critical}}$ for population configurations, indicating that results from experiment 1 (blue) and experiment 2 (pink) are both associated with null results ($|t_{\text{statistic}} / t_{\text{critical}}| < 1$). From a single data set, mean comparison error rate of candidate statistics in identifying which experiment has lower disagreement via (C) lower $\mu_{DM}$, (D) lower $\sigma_{D}$, (E) higher $df_{D}$, and (F) higher $\alpha_{DM}$ across population configurations. (A) ‘#’ denotes measures that have a nonrandom number of shared designations with each independent measure (listed at top of y-axis) for which experiments are designated with lower disagreement ($p < 0.05$ from Bonferroni corrected two-tailed binomial test for coefficient equal to 0.5 between each independent measure and every disagreement measure). (B) Discrete Kolmogorov–Smirnov test between histograms. (C, D, E, F) Pairwise t-test with Bonferroni correction for all combinations, where blue minus denotes a mean error rate lower than random, red plus denotes higher than random. N=1E3 population configurations generated for each study, n=1E2 samples drawn per configuration, 5 - 20 observations per sample.
Fig. S8: The $\delta M$ is the only statistic that has lower than random comparison error with positive results for each measure of disagreement. (A) Fraction of population configurations where experiment 1 has lower disagreement than (LDT) experiment 2 according to each measure of disagreement, with $\mu_{DM}$ serving as ground truth. (B) Histogram of the ratio of $\bar{t}_{\text{statistic}}$ to $t_{\text{critical}}$ for population configurations, indicating that results from experiment 1 (blue) and experiment 2 (pink) are both associated with positive results ($|\bar{t}_{\text{statistic}} / t_{\text{critical}}| > 1$). (C) Mean comparison error rate of candidate statistics in identifying which experiment has lower disagreement via lower $\mu_{DM}$ across population configurations (50 observations per sample). (D) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with $\sigma_D$ serving as ground truth. (E) Histogram of the ratio of $\bar{t}_{\text{statistic}}$ to $t_{\text{critical}}$ indicating that population configurations are associated with positive results. (F) Mean comparison error rate of candidate statistics in identifying which experiment has lower disagreement via lower $\sigma_D$ across population configurations (50 observations per sample). (G) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with $df_D$ serving as ground truth. (H) Histogram of the ratio of $\bar{t}_{\text{statistic}}$ to $t_{\text{critical}}$ indicating that population configurations are associated with positive results. (I) Mean comparison error rate of candidate statistics in identifying which experiment has lower disagreement via higher $df_D$ across population configurations (6 - 40 observations per sample). (J) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with $\alpha_{DM}$ serving as ground truth. (K) Histogram of the ratio of $\bar{t}_{\text{statistic}}$ to $t_{\text{critical}}$ indicating that population configurations are associated with positive results. (L) Mean comparison error rate of candidate statistics in identifying which experiment has lower disagreement via higher $\alpha_{DM}$ across population configurations (30 observations per sample). (A, D, G, J) “#” denotes measures that have a nonrandom number of shared designations with independent measure (listed at top of y-axis) for which experiments are designated with lower disagreement (p < 0.05 from Bonferroni corrected two-tailed binomial test for coefficient equal to 0.5 between independent measure and each disagreement measure). (B, E, H, K) Discrete Kolmogorov-Smirnov test between histograms. (C, F, I, L) Pairwise t-test with Bonferroni correction for all combinations, where blue minus denotes a mean error rate lower than random, red plus denotes higher than random. N=1E3 population configurations generated for each study, n=1E2 samples drawn per configuration.
Fig. S9: The $\delta_M$ is the only statistic that has lower than random comparison error with positive results across all measures of disagreement simultaneously. (A) Fraction of population configurations where experiment 1 has lower disagreement than (LDT) experiment 2 according to each measure of disagreement, with $\mu_M$, $\sigma_D$, $df_D$, and $\alpha_M$ serving as separate ground truths simultaneously. (B) Histogram of the ratio of $\bar{t}_{\text{statistic}}$ to $t_{\text{critical}}$ for population configurations, indicating that results from experiment 1 (blue) and experiment 2 (pink) are both associated with positive results ($|\bar{t}_{\text{statistic}}/t_{\text{critical}}| > 1$). From a single data set, mean comparison error rate of candidate statistics in identifying which experiment has lower disagreement via (C) lower $\mu_M$, (D) lower $\sigma_D$, (E) higher $df_D$, and (F) higher $\alpha_M$ across population configurations. (A) ‘#’ denotes measures that have a nonrandom number of shared designations with each independent measure (listed at top of y-axis) for which experiments are designated with lower disagreement ($p < 0.05$ from Bonferroni corrected two-tailed binomial test for coefficient equal to 0.5 between each independent measure and every disagreement measure). (B) Discrete Kolmogorov-Smirnov test between histograms. (C, D, E, F) Pairwise t-test with Bonferroni correction for all combinations, where blue minus denotes a mean error rate lower than random, red plus denotes higher than random. N=1E3 population configurations generated for each study, n=1E2 samples drawn per configuration, 6 - 30 observations per sample.
Fig. S10: The $\hat{r}_{\delta M}$ is the only statistic that has lower than random comparison error with null results for each measure of relative disagreement. (A) Fraction of population configurations where experiment 1 has lower disagreement than (LDT) experiment 2 according to each measure of disagreement, with $r_{\mu DM}$ serving as ground truth. (B) Histogram of the ratio of $I_{statistic}$ to $I_{critical}$ for population configurations, indicating that results from experiment 1 (blue) and experiment 2 (pink) are both associated with null results ($\mu_{DM}/\sigma_{DM} < 2.5$). (C) Mean comparison error rate of candidate statistics in identifying which experiment has lower relative disagreement via lower $r_{\mu DM}$ across population configurations (50 observations per sample). (D) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with $r_{\sigma D}$ serving as ground truth. (E) Histogram of the ratio of $I_{statistic}$ to $I_{critical}$ indicating population configurations are associated with null results. (F) Mean comparison error rate of candidate statistics in identifying which experiment has lower relative disagreement via lower $r_{\sigma D}$ across population configurations (50 observations per sample). (G) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with $df_{D}$ serving as ground truth. (H) Histogram of the ratio of $I_{statistic}$ to $I_{critical}$ indicating population configurations are associated with null results. (I) Mean comparison error rate of candidate statistics in identifying which experiment has lower relative disagreement via higher $df_{D}$ across population configurations (6 - 30 observations per sample). (J) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with $\alpha_{DM}$ serving as ground truth. (K) Histogram of the ratio of $I_{statistic}$ to $I_{critical}$ indicating population configurations are associated with null results. (L) Mean comparison error rate of candidate statistics in identifying which experiment has lower relative disagreement via higher $\alpha_{DM}$ across population configurations (30 observations per sample). (A, D, G, J) ‘#’ denotes measures that have a nonrandom number of shared designations with independent measure (listed at top of y-axis) for which experiments are designated with lower disagreement ($p < 0.05$ from Bonferroni corrected two-tailed binomial test for coefficient equal to 0.5 between independent measure and each disagreement measure). (B, E, H, K) Discrete Kolmogorov-Smirnov test between histograms. (C, F, I, L) Pairwise t-test with Bonferroni correction for all combinations, where blue minus denotes a mean error rate lower than random, red plus denotes higher than random. N=1E3 population configurations generated for each study, n=1E2 samples drawn per configuration.
Fig. S11: The $\rho_M$ is the only statistic that has lower than random comparison error with null results across all measures of relative disagreement simultaneously. (A) Fraction of population configurations where experiment 1 has lower disagreement than (LDT) experiment 2 according to each measure of disagreement, with $\rho_{DM}$, $\sigma_D$, $df_D$, and $\alpha_{DM}$ serving as separate ground truths simultaneously. (B) Histogram of the ratio of $t_{\text{statistic}}$ to $t_{\text{critical}}$ for population configurations, indicating that results from experiment 1 (blue) and experiment 2 (pink) are both associated with null results ($|t_{\text{statistic}} / t_{\text{critical}}| \leq 1$). From a single data set, mean comparison error rate of candidate statistics in identifying which experiment has lower relative disagreement via (C) lower $\rho_{DM}$, (D) lower $\sigma_D$, (E) higher $df_D$, and (F) higher $\alpha_{DM}$ across population configurations. (A) ‘#’ denotes measures that have a nonrandom number of shared designations with each independent measure (listed at top of y-axis) for which experiments are designated with lower disagreement ($p < 0.05$ from Bonferroni corrected two-tailed binomial test for coefficient equal to 0.5 between each independent measure and every disagreement measure). (B) Discrete Kolmogorov-Smirnov test between histograms. (C, D, E, F) Pairwise t-test with Bonferroni correction for all combinations, where blue minus denotes a mean error rate lower than random, red plus denotes higher than random. N=1E3 population configurations generated for each study, n=1E2 samples drawn per configuration, 5 - 30 observations per sample.
Fig. S12: The rᵦₘ is the only statistic that has lower than random comparison error with positive results for each measure of relative disagreement. (A) Fraction of population configurations where experiment 1 has lower disagreement than (LDT) experiment 2 according to each measure of disagreement, with rᵦᵩDM serving as ground truth. (B) Histogram of the ratio of \( \bar{I}_{\text{statistic}} / \bar{I}_{\text{critical}} \) for population configurations, indicating that results from experiment 1 (blue) and experiment 2 (pink) are both associated with positive results (\( |\bar{I}_{\text{statistic}} / \bar{I}_{\text{critical}}| > 1 \)). (C) Mean comparison error rate of candidate statistics in identifying which experiment has lower relative disagreement via lower rᵦᵩDM across population configurations (50 observations per sample). (D) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with rᵦᵩDM serving as ground truth. (E) Histogram of the ratio of \( \bar{I}_{\text{statistic}} / \bar{I}_{\text{critical}} \) indicating population configurations are associated with positive results. (F) Mean comparison error rate of candidate statistics in identifying which experiment has lower relative disagreement via lower rᵦᵩDM across population configurations (50 observations per sample). (G) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with rᵦᵩDM serving as ground truth. (H) Histogram of the ratio of \( \bar{I}_{\text{statistic}} / \bar{I}_{\text{critical}} \) indicating population configurations are associated with positive results. (I) Mean comparison error rate of candidate statistics in identifying which experiment has lower relative disagreement via higher rᵦᵩDM across population configurations (50 observations per sample). (J) Fraction of population configurations where experiment 1 has lower disagreement than experiment 2 according to each measure of disagreement, with rᵦᵩDM serving as ground truth. (K) Histogram of the ratio of \( \bar{I}_{\text{statistic}} / \bar{I}_{\text{critical}} \) indicating population configurations are associated with positive results. (L) Mean comparison error rate of candidate statistics in identifying which experiment has lower relative disagreement via higher rᵦᵩDM across population configurations (50 observations per sample). (A, D, G, J) ‘#’ denotes measures that have a nonrandom number of shared designations with independent measure (listed at top of y-axis) for which experiments are designated with lower disagreement (p < 0.05 from Bonferroni corrected two-tailed binomial test for coefficient equal to 0.5 between independent measure and each disagreement measure). (B, E, H, K) Discrete Kolmogorov-Smirnov test between histograms. (C, F, I, L) Pairwise t-test with Bonferroni correction for all combinations, where blue minus denotes a mean error rate lower than random, red plus denotes higher than random. N=1E3 population configurations generated for each study, n=1E2 samples drawn per configuration.
Fig. S13: The \( r_{\delta M} \) is the only statistic that has lower than random comparison error with positive results across all measures of relative disagreement simultaneously. (A) Fraction of population configurations where experiment 1 has lower disagreement than (LDT) experiment 2 according to each measure of disagreement, with \( r_{\mu DM} \), \( r_{\sigma D} \), df\(_D\), and \( \alpha_{DM} \) serving as separate ground truths simultaneously. (B) Histogram of the ratio of \( t_{\text{statistic}} / t_{\text{critical}} \) for population configurations, indicating that results from experiment 1 (blue) and experiment 2 (pink) are both associated with positive results (\( |t_{\text{statistic}} / t_{\text{critical}}| > 1 \)). From a single data set, mean comparison error rate of candidate statistics in identifying which experiment has lower relative disagreement via (C) lower \( r_{\mu DM} \), (D) lower \( r_{\sigma D} \), (E) higher df\(_D\), and (F) higher \( \alpha_{DM} \) across population configurations. (A) ‘#’ denotes measures that have a nonrandom number of shared designations with each independent measure (listed at top of y-axis) for which experiments are designated with lower disagreement (p < 0.05 from Bonferroni corrected two-tailed binomial test for coefficient equal to 0.5 between each independent measure and every disagreement measure). (B) Discrete Kolmogorov-Smirnov test between histograms. (C, D, E, F) Pairwise t-test with Bonferroni correction for all combinations, where blue minus denotes a mean error rate lower than random, red plus denotes higher than random. N=1E3 population configurations generated for each study, n=1E2 samples drawn per configuration, 6 - 50 observations per sample.
| Statistic | Equation | Decision Rule |
|-----------|----------|--------------|
| $\bar{x}_{DM}$ | $\bar{y} - \bar{x}$ | $|\bar{x}_{DM,1}| < |\bar{x}_{DM,2}|$ |
| $\bar{r}_{x_{DM}}$ | $\bar{x}_{DM}$ | $|\bar{x}_{DM,1}| < |\bar{x}_{DM,2}|$ |
| $s_{DM}$ | $\sqrt{\frac{s^2_x + s^2_y}{m + n}}$ | $|s_{DM,1}| < |s_{DM,2}|$ |
| $r_{s_{DM}}$ | $\frac{s_{DM}}{\bar{x}}$ | $|r_{s_{DM},1}| < |r_{s_{DM},2}|$ |
| BF (4) | $\frac{Pr(D|M_1)}{Pr(D|M_2)}$ | BF$_1 <$ BF$_2$ |
| $p_{N}(13)$ | $p\left(Z \geq \frac{\bar{y} - \bar{x}}{\sqrt{\frac{s^2_x}{m} + \frac{s^2_y}{n}}}\right)$ | $p_{NHST,1} > p_{NHST,2}$ |
| $p_{E}(3)$ | Max $\left\{ \left(\bar{y} - \bar{x} - \bar{r}_{\Delta} \right) \left(\frac{\bar{y} - \bar{x} + \bar{r}_{\Delta}}{\sqrt{\frac{s^2_x}{m} + \frac{s^2_y}{n}}}\right) \right\}$ | $p_{TOST,1} > p_{TOST,2}$ |
| CD (14) | $\frac{\bar{y} - \bar{x}}{\sqrt{\frac{(m - 1)s^2_x + (n - 1)s^2_y}{m + n - 2}}}$ | $|CD_1| < |CD_2|$ |
| $\delta_{DM}$ | $N^{-1} \sum_{i=1}^{K} \mathbb{I}(\mu^y_i - \mu^x_i \leq c) - N^{-1} \sum_{i=1}^{K} \mathbb{I}(\mu^y_i - \mu^x_i \leq -c) = 1 - \alpha_{DM}$ | $\delta_{DM,1} < \delta_{DM,2}$ |
| $r_{\delta_{DM}}$ | $N^{-1} \sum_{i=1}^{K} \mathbb{I}(\frac{\mu^y_i - \mu^x_i}{\mu^x_i} \leq c) - N^{-1} \sum_{i=1}^{K} \mathbb{I}(\frac{\mu^y_i - \mu^x_i}{\mu^x_i} \leq -c) = 1 - \alpha_{DM}$ | $r_{\delta_{DM},1} < r_{\delta_{DM},2}$ |
| Rnd | $\text{Rnd}_1 < \text{Rnd}_2$ |

Note: decision rule is logical expression that predicts experiment 1 has lower disagreement than experiment 2.

Abbreviations: $\bar{x}$, sample mean of control group; $\bar{y}$, sample mean of experiment group; $s_x$, sample standard deviation of control group; $s_y$, sample standard deviation of experiment group; $\bar{x}_{DM}$, difference in sample means; $r_{x_{DM}}$, relative difference in sample means; $s_{DM}$, standard deviation of the difference in sample means; $r_{s_{DM}}$, relative standard deviation of the difference in sample means; BF, Bayes Factor; $p_{NHST}$, $p$-values from null hypothesis significance test; $p_{TOST}$, $p$-value from two one sided t-tests; CD, cohen’s d; $\delta_{DM}$, most difference in means; $r_{\delta_{DM}}$, relative most mean difference in sample means; Rnd, random.
Table S2: Loss functions for Each Measure of Disagreement

| Measure       | Loss Functions: $\text{Loss}(x, y, x', y', \theta, \theta') := \cdots$   | Eq. |
|---------------|---------------------------------------------------------------------|-----|
| $|\mu_{DM}|$     | $1 - \mathbb{1}(|\mu_{DM}| < |\mu'_{DM}| \text{ and } |\delta(x, y, \alpha_{DM})| > |\delta(x', y', \alpha'_{DM})|)$ | (S8) |
| $\sigma_D$    | $1 - \mathbb{1}(\sigma_{D} < \sigma'_{D} \text{ and } |\delta(x, y, \alpha_{DM})| > |\delta(x', y', \alpha'_{DM})|)$ | (S9) |
| $\text{df}_D$ | $1 - \mathbb{1}(\text{df}_{D} > \text{df}'_{D} \text{ and } |\delta(x, y, \alpha_{DM})| > |\delta(x', y', \alpha'_{DM})|)$ | (S10) |
| $\alpha_{DM}$ | $1 - \mathbb{1}(\alpha_{DM} > \alpha'_{DM} \text{ and } |\delta(x, y, \alpha_{DM})| > |\delta(x', y', \alpha'_{DM})|)$ | (S11) |
| $|r\mu_{DM}|$  | $1 - \mathbb{1}(|r\mu_{DM}| < |r\mu'_{DM}| \text{ and } |\delta(x, y, \alpha_{DM})| > |\delta(x', y', \alpha'_{DM})|)$ | (S12) |
| $r\sigma_D$   | $1 - \mathbb{1}(r\sigma_{DM} < r\sigma'_{DM} \text{ and } |\delta(x, y, \alpha_{DM})| > |\delta(x', y', \alpha'_{DM})|)$ | (S13) |

Note: decision rule for candidate prediction ($\delta$) may by a “greater than” or “less than” operation depending on candidate statistic. The loss functions specify when the prediction disagrees with the ground truth designation. In this case, the ground truth designations are for lower disagreement for experiment 1, and the candidate predictions test for higher disagreement for experiment 1.