Beyond sex differences in mean: meta-analysis of differences in skewness, kurtosis, and correlation

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Abstract

Biological differences between males and females are pervasive. Researchers often focus on sex differences in mean or, occasionally, in variation, albeit other measures can be useful for biomedical and biological research. For instance, differences in skewness (asymmetry of a distribution), kurtosis (heaviness of a distribution's tails), and correlation (relationship between two variables) might be crucial to improve medical diagnosis and to understand natural processes. Yet, there are currently no meta-analytic ways to measure differences in these metrics between two groups while accounting for sampling error. We propose three effect size statistics to fill this gap: Δ*sk*, Δ*ku*, and Δ*Zr*, which measure differences in skewness, kurtosis, and correlation, respectively. Besides presenting the rationale for the calculation of these effect size statistics, we illustrate their potential using a large dataset of mice traits. For example, we found that females show, on average, greater skewness and kurtosis than males in both fat mass and heart weight. Although calculating Δ*sk*, Δ*ku*, and Δ*Zr* may require large sample sizes of individual data, technological advancements in data collection create increasing opportunities to use these effect size statistics. Importantly, Δ*sk*, Δ*ku*, and Δ*Zr* can be used to compare any two groups, allowing a new generation of meta-analyses that explore such differences and potentially leading to new insights in multiple fields of study.

Key-words: covariance, individual participant meta-analysis, meta-regression, nonnormality, normal distribution, sex characteristics

Background

Sex is a biological attribute that can strongly impact organisms' traits, with differences between males and females being central to questions in the biological sciences (e.g., [1,2]). In contrast, biomedical research has primarily focused on male subjects [3], posing a danger to female health [4,5]. Aware of these issues, the US National Institutes of Health and other health agencies have demanded the use of multiple sexes in animal studies when possible [6]. As a consequence, the number of biological and biomedical studies using both female and male animals as research subjects has increased in the last decade [7], leading to the accumulation of data that can be used to synthesise and quantify sex differences across biological domains.

Realising the accumulation of sex-specific data, many perspective pieces have encouraged researchers to investigate sex differences more carefully (e.g., [8–10]). Yet, some of these pieces, and most of the biological literature, focus exclusively on mean differences between males and females. A fixation on mean differences has been present for a long time in science because of an obsession with dimorphism in trait averages (e.g., [11]), a lack of sufficiently powerful data, or limited (or difficult to use) statistical tools available to researchers. Yet, measures such as variance, correlation, skewness, and kurtosis can be critical to understanding sex differences. For example, certain traits in mice may exhibit no disparity in average values between sexes, but substantial differences emerge in terms of variability [12,13]. These differences could be more easily assessed because of an effect size statistic that measures differences in variability between two groups (proposed by [14]), illustrating how novel statistical tools can expand possible research questions and provide new scientific insights, such as identifying sex differences in trait selection or canalisation.

Beyond variability, the relative shape of trait distributions to the normal distribution (measured by skewness and kurtosis, i.e. asymmetry of a distribution and heaviness of a distribution's tails, respectively; Fig. 1A-B) can also be crucial to understanding ecological and evolutionary processes and patterns (e.g., [15–19]), as well as improving medical diagnostics (e.g., [20,21]). For instance, skewness can bias heritability estimates because evolutionary biologists assume that phenotypic components (genetic and environmental) are normally distributed [18]. Furthermore, kurtosis can be used to understand community assembly processes (e.g., [16]). Besides the shape of trait distributions, evolutionary biologists and quantitative geneticists can quantify correlation matrices to understand trait plasticity and evolvability (e.g., [22–24]), which could then be used for group comparisons (as in [25]; Fig.1C). Despite this, there are no effect size statistics that can easily measure between-group differences (e.g., males and females) in skewness, kurtosis, or within-group correlations.

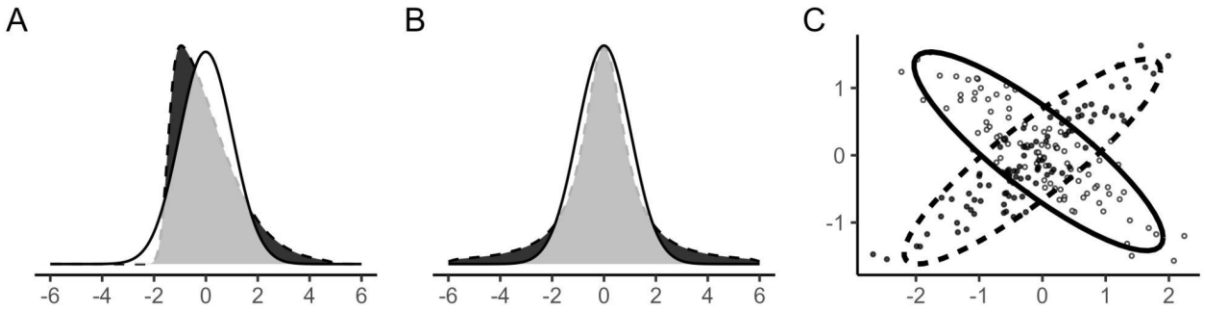

Figure 1. Simulated trait distributions for two groups with different shapes (A: distinct skewness, B: distinct kurtosis), and different correlations between two traits for two groups (C).

Here, we propose three new effect size statistics to evaluate between-group differences in skewness (Δsk), kurtosis (Δku), and correlation (ΔZr), key moments of a distribution that are usually unexplored. These effect size statistics will be valuable to explore sex differences but can

also be applied in other fields of study and used to compare differences between any two groups of interest. Meta-analyses using these new effect sizes will create multiple avenues for novel biological enquiries. The time is particularly ripe for analyses using these new effect sizes because the individual-level data (e.g., individual participant data [26,27]) required for their calculation are increasingly available from new technological advances that allow faster data collection and sharing (e.g., automated phenotyping).

Difference in skewness and kurtosis

The mean and variance represent the first and second moments of a distribution, respectively. However, the third and fourth moments of a distribution (i.e. skewness and kurtosis, respectively) can also be valuable as they characterise the distribution's shape. More specifically, skewness reflects the distribution's asymmetry around its mean. While positive skewness indicates an elongated right tail with an excess of high values, negative skewness suggests an elongated left tail with an excess of low values. This asymmetry can influence the interpretation of means and variation, as the mean tends to be larger than the median in positively skewed distributions, while the mean tends to be smaller than the median in negatively skewed distributions. Note that a perfectly normal distribution is symmetric (i.e. skewness = 0), where the mean is equal to the median. Skewness (*sk*) can be expressed as:

$$\mathrm{sk} = \frac{\frac{1}{\mathrm{n}}\sum_{\mathrm{i}=1}^{\mathrm{n}}(\mathrm{x_i}-\bar{\mathrm{x}})^3}{\left[\frac{1}{\mathrm{n}}\sum_{\mathrm{i}=1}^{\mathrm{n}}(\mathrm{x}-\bar{\mathrm{x}})^2\right]^{\frac{3}{2}}}\frac{\sqrt{n(n-1)}}{n-2} \quad \text{(eq. 1)}$$

where x_i is a raw data value, $\bar{x}$ is the sample mean, and n is the sample size. Skewness sampling variance (s^2_{sk}) can then be expressed as:

$$s^2_{sk} = \frac{6n(n-1)}{(n-2)(n+1)(n+3)} \quad \text{(eq. 2)}$$

On the other hand, kurtosis measures tail heaviness: high kurtosis distributions have heavier tails (i.e., proportionally more extreme values than central values), whereas low kurtosis distributions have lighter tails. For comparison, a normal distribution is expected to have kurtosis = 3. Kurtosis (*ku*) can be expressed as:

$$ku = \frac{n(n+1)(n-1)}{(n-2)(n-3)} \frac{\sum_{i=1}^{n}(x_i-\bar{x})^4}{\left[\sum_{i=1}^{n}(x_i-\bar{x})^2\right]^2} - \frac{3(n-1)^2}{(n-2)(n-3)} \text{ (eq. 3)}$$

and its with sampling variance (s^2_{ku}) as:

$$s^2_{ku} = \frac{24n(n-1)^2}{(n-3)(n-2)(n+3)(n+5)} \text{ (eq. 4)}$$

Evaluating skewness and kurtosis provides valuable insights into a variable distribution, which is crucial for interpreting means, assessing variability, and making informed decisions in statistical analyses. Although meta-analyses can use skewness (eq. 1) and kurtosis (eq. 3) to investigate single variables, effect size statistics that compare these metrics between two groups are lacking. Thus, we propose the difference between two groups in skewness (Δ*sk*), expressed as:

$$\Delta sk = sk_1 - sk_2 \text{ (eq. 5)}$$

and its sampling variance ($s^2_{\Delta sk}$) as:

$$s^2_{\Delta sk} = s^2_{sk_1} + s^2_{sk_2} - 2\rho_{sk} s_{sk_1} s_{sk_2} \text{ (eq. 6)}$$

Where ρ_{sk} represents the sampling correlation in skewness between the two groups (zero if assumed to be independent). Similarly, we propose the difference between two groups in kurtosis (Δ*ku*), expressed as:

$$\Delta ku = ku_1 - ku_2 \text{ (eq. 7)}$$

and its sampling variance ($s^2_{\Delta ku}$) as:

$$s^2_{\Delta ku} = s^2_{ku_1} + s^2_{ku_2} - 2\rho_{ku} s_{ku_1} s_{ku_2} \text{ (eq. 8)}$$

where ρ_{ku} represents the sampling correlation in kurtosis between the two groups (zero if assumed to be independent).

Difference in correlation

Numerous meta-analyses measure correlation between two variables (e.g., [28,29]). To do so, researchers use the effect size statistic *Zr*, which can be expressed as:

$$Zr = \frac{ln\left(\frac{1+r}{1-r}\right)}{2} \text{ (eq. 9)}$$

and its sampling variance (s^2_{Zr}) as:

$$s^2_{Zr} = \frac{1}{n-3} \text{ (eq. 10)}$$

where *r* is Pearson's correlation coefficient between two variables and *n* is the sample size.

Although *Zr* alone remains extremely useful to test correlational hypotheses, researchers from all fields would benefit from being able to compare *Zr* values between two groups. Although Cohen [30] proposed the difference between two groups in *Zr* as *q*, he did not provide an equation to calculate its sampling variance. Consequently, this effect size statistic has not been used despite its potential. We therefore propose the difference between two groups in *Zr* with a new name (ΔZr), as:

$$\Delta Zr = Zr_1 - Zr_2 \text{ (eq. 11)}$$

and its sampling variance ($s^2_{\Delta Zr}$) as:

$$s^2_{\Delta Zr} = s^2_{Zr_1} + s^2_{Zr_2} - 2\rho_{Zr} s_{Zr_1} s_{Zr_2} \text{ (eq. 12)}$$

where ρ_{Zr} represents the sampling correlation in Fisher's *Zr* between the two groups (zero if assumed to be independent).

Worked examples: sex differences in mice

To illustrate the application of our proposed effect size statistics, we used data compiled by the International Mouse Phenotyping Consortium (IMPC, version 18.0; [31]; http://www.mousephenotype.org/). We examined differences between male and female mice regarding two pairs of traits from distinct functional domains: morphology (fat mass and heart weight) and physiology (glucose and total cholesterol). We selected these traits because they are widely understood traits, even by non-specialists, and had a large sample size. More specifically, we assessed differences between the sexes in mean (using the natural logarithm of the response ratio [32], hereby *lnRR*), variability (using the natural logarithm of the variance ratio [14], hereby *lnVR*), skewness (using Δsk), and kurtosis (using Δku) for each trait, as well as in the difference in correlation for each trait pair (using ΔZr). The IMPC dataset contains data from multiple phenotyping centres and mice strains, so we selected the ones with the most data points for our analyses here, computing the aforementioned effect size statistics separately for each one of them.

We performed a meta-analysis for each effect size statistic to obtain a mean effect size for each trait (or pair of traits, in the case of ΔZr), using 'phenotyping centre' and 'mice strain' as random factors in meta-analytical models. In these analyses, positive effect sizes denoted a greater estimate (mean, variability, skewness, kurtosis, or correlation) for males than females. We conducted all statistical analyses in the software R 4.4.0 [33]. We fitted meta-analytical models using the *rma.mv* function from the package *metafor* [34]. All methodological details and additional information can be found in our tutorial, at https://pietropollo.github.io/new_effect_size_statistics/.

We found that males, on average, had greater fat mass and heart weight than females regardless of phenotyping centre and mice strain (Fig. 2A, B, F, G). The variability among

individuals regarding these traits was also greater for males than for females, except for fat mass from one specific phenotyping centre and mice strain (Fig 2C). By contrast, females tended to have greater skewness in fat mass and heart weight than males (i.e., negative Δsk values, but note they overlap zero; Fig. 2D, I). Most importantly, Δsk values for fat mass and heart weight varied across phenotyping centres and mice strains, with negative and positive values present (Fig. 2D, I). Sex differences in kurtosis for fat mass and heart weight followed a very similar pattern to the one described for skewness: negative mean Δku values (i.e., greater kurtosis for females than for males, but overlapping zero) with some variation across individual effect sizes (Fig. 2E, J). Moreover, the correlation between fat mass and heart weight was, on average, greater for females than males (Fig. 3A, B). However, this difference in correlation was absent for some phenotyping centres and mice strains (Fig. 3A, B).

We also found that male and female mice were, on average, similar in terms of blood glucose levels (Fig. 4A, B), although males had higher total cholesterol than females (Fig. 4F, G). We observed the same pattern regarding the variability of these traits: on average, the sexes were similarly variable in glucose (Fig 4C), but the variability of total cholesterol was greater in males than in females (Fig. 4H). Contrasting with morphological traits, sex differences in skewness and kurtosis were mostly absent (Fig. 4D, E, I, J). Lastly, males and females showed a similar relationship between glucose and total cholesterol, albeit this relationship was stronger for males than for females in some instances (Fig. 3C, D).

Our findings that females have, on average, lower (Fig. 2B, G), less variable (Fig. 2C, H), more concentrated at low values (higher skewness; Fig. 2D, I), and more extreme values (higher kurtosis; Fig. 2E, I) of fat mass and heart weight compared with males may contribute to sex-related differences in the development of diseases associated with these traits and their biomarkers

(e.g., QTc interval length [35]). Moreover, a stronger relationship between fat mass and heart weight in females than in males (Fig. 3B) may represent a greater risk of cardiohypertrophy arising from obesity in the former compared with the latter [36]. Meanwhile, absent or less pronounced sex differences in glucose and total cholesterol (Fig. 4) may suggest other sources of variation may contribute to sex differences in the symptomology of diseases associated with these measurements (e.g., [37–39]). Characterising sex differences in biological traits, as we have done here, can provide new perspectives on evolutionary, ecological, and medical patterns, possibly improving healthcare and environmental interventions.

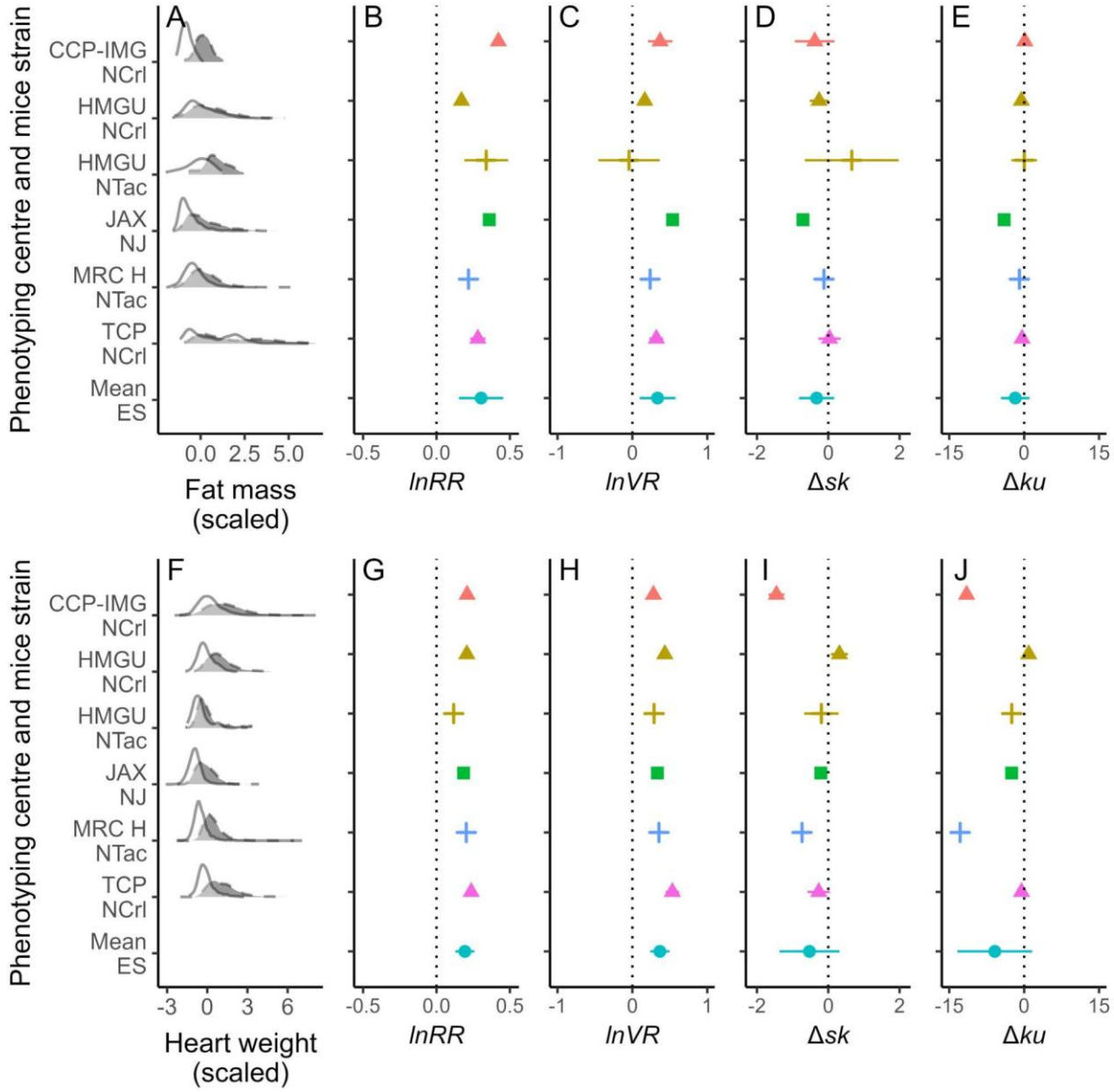

Figure 2. Examples of morphological sex differences in mice (fat mass, A-E; heart weight, F-J) for various phenotype centres (each with a different colour in panels B-E and G-J) and mice strains (each with a different shape in panels B-E and G-J), with the bottom estimate in panels B-E and G-J (turquoise) representing the mean effect size. While A and F show distributions of these traits for males (black with dashed borders) and females (white with solid borders), panels B-E and G-J

show effect sizes (*lnRR*: natural logarithm of the response ratio; *VR*: variance ratio; Δ*sk*: difference in skewness; Δ*ku*: difference in kurtosis).

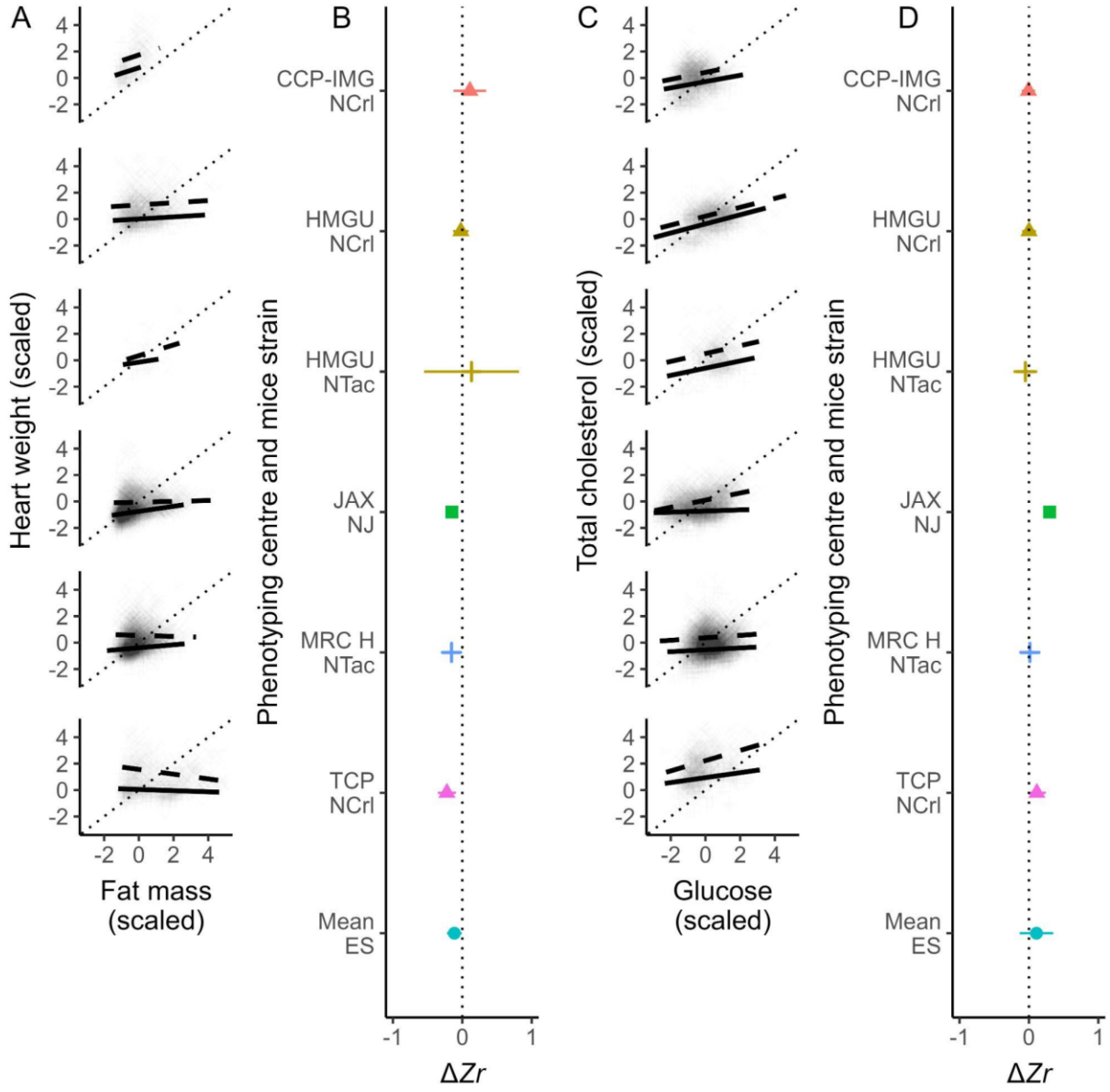

Figure 3. Relationship between fat mass and heart weight (A, B) and glucose and total cholesterol (C, D) in mice. Panels A and C show these relationships separately for males (dashed line) and females (solid line), each panel representing a different phenotyping centre and/or mice strain.

Panels B and D then show differences in correlation (ΔZr) between males and females, where each colour represents a distinct phenotype centre and each shape represents a distinct mice strain, with the bottom estimate in each panel (pink) representing the mean effect size. Note that panels A and C contain individual data points, which may appear as background shading in cases with large sample sizes.

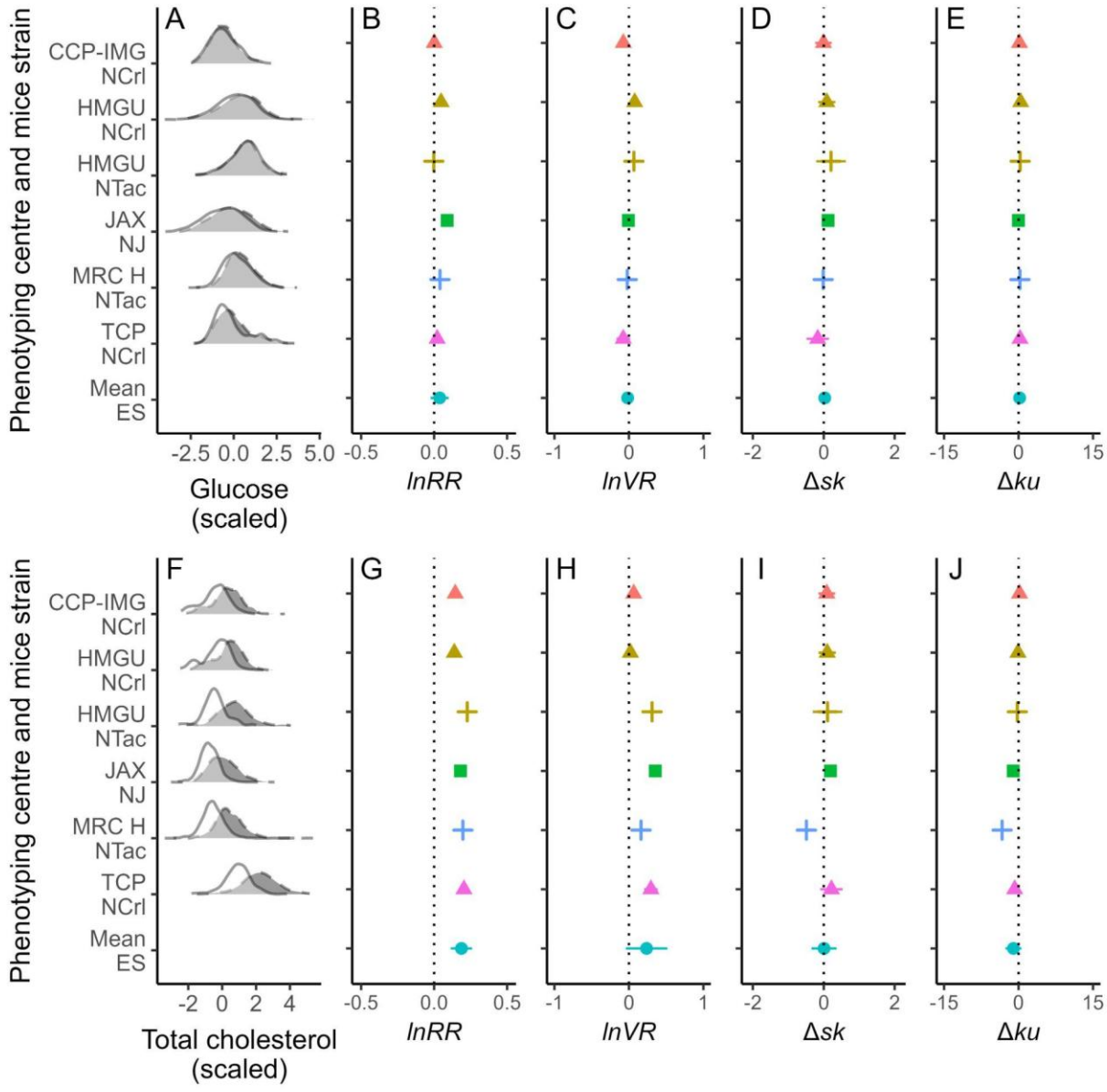

Figure 4. Examples of physiological sex differences in mice (glucose, A-E; total cholesterol, F-J) for various phenotype centres (each with a different colour in panels B-E and G-J) and mice strains (each with a different shape in panels B-E and G-J), with the bottom estimate in panels B-E and G-J (turquoise) representing the mean effect size. While A and F show distributions of these traits for males (black with dashed borders) and females (white with solid borders), panels B-E and G-J show effect sizes (*lnRR*: natural logarithm of the response ratio; *VR*: variance ratio; Δ*sk*: difference in skewness; Δ*ku*: difference in kurtosis).

Limitations

Despite the enormous potential of the effect size statistics we proposed here, they are not free of limitations. For instance, skewness and kurtosis (and therefore the difference in these estimates between two groups; i.e., Δ*sk* and Δ*ku*, respectively) are more likely to become extreme with small sample sizes and with variables with few unique values, either because the variable is discrete or because it is naturally constant (e.g., number of vertebrae in mice). We thus recommend researchers only to compute Δ*sk* and Δ*ku* for continuous variables with a minimum sample size of 50 for each group. Lastly, although Δ*sk*, Δ*ku*, and Δ*Zr* can be calculated, respectively, from reported skewness, kurtosis, or within-group correlations for different samples, empirical studies rarely report these estimates. Thus, the calculation of these effect sizes will probably require raw data, which are only now fortunately becoming more easily available.

Future opportunities

The effect size statistics proposed in the present study can be useful across the life sciences, social sciences, and medicine. This is because skewness and kurtosis, and consequently differences

between any two or more groups in these estimates (i.e., Δ*sk* and Δ*ku*), may help researchers to understand epidemiological trends [40], genetic patterns relevant to medical diagnosis [20,21], disruptive selection on quantitative traits [41], body size patterns across individuals [42] and species [43], reproductive patterns [44], regime shifts in ecosystems [45], heritability [18], community assembly processes [16], and possibly many other topics. Meanwhile, comparisons regarding correlations have been used to explore memory processing during sleep [46], physiological patterns in patients with certain medical conditions [47], and selection patterns [22–24], to name a few. Because Δ*Zr* can be used in virtually any comparison between two groups of correlational data, the opportunities for its use are endless. Most importantly, Δ*sk*, Δ*ku*, and Δ*Zr* are unitless measures, so they can be meta-analysed to uncover patterns between two groups (e.g. males and females). Moreover, the growing availability of raw data and big data approaches, facilitated by technological advances, make these effect size statistics particularly valuable for modern research.

Data and code availability

All data and code used in this study are available at: https://github.com/pietropollo/new_effect_size_statistics.

Declaration of AI use

The authors declare that they occasionally used GPT-4-turbo (OpenAI) to improve the clarity and readability of this work. After using these tools, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Author contributions

Conceptualisation: PP, SN; data curation: PP; formal analysis: PP; funding acquisition: SN; investigation: PP; methodology: PP, SN; project administration: PP, SN; software: PP; supervision: SN; visualisation: PP; writing – original draft: PP, SN; writing – review & editing: all authors.

Competing interests

We declare no competing interests.

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