IQ: Intrinsic measure for quantifying the heterogeneity in meta-analysis

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Abstract

Quantifying the heterogeneity is an important issue in meta-analysis, and among the existing measures, the $I^2$ statistic is the most commonly used measure in the literature. In this paper, we show that the $I^2$ statistic was, in fact, defined as problematic or even completely wrong from the very beginning. To confirm this statement, we first present a motivating example to show that the $I^2$ statistic is heavily dependent on the study sample sizes, and consequently it may yield contradictory results for the amount of heterogeneity. Moreover, by drawing a connection between ANOVA and meta-analysis, the $I^2$ statistic is shown to have, mistakenly, applied the sampling errors of the estimators rather than the variances of the study populations. Inspired by this, we introduce an Intrinsic measure for Quantifying the heterogeneity in meta-analysis, and meanwhile study its statistical properties to clarify why it is superior to the existing measures. We further propose an optimal estimator, referred to as the IQ statistic, for the new measure of heterogeneity that can be readily applied in meta-analysis. Simulations and real data analysis demonstrate that the IQ statistic provides a nearly unbiased estimate of the true heterogeneity and it is also independent of the study sample sizes.

\textit{Key words:} Heterogeneity, intraclass correlation coefficient (ICC), meta-analysis, random-effects model, the $I^2$ statistic, the IQ statistic

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1 Introduction

Meta-analysis is a statistical tool for evidence-based practice, which aims to synthesize multiple studies and produce a summary conclusion for the whole body of research [Egger and Smith, 1997]. In the literature, there are two most commonly used statistical models for meta-analysis, namely, the fixed-effect model and the random-effects model. Among them, the fixed-effect model assumes that the effect sizes of different studies are all the same, which is somewhat restrictive and may not be realistic in practice. The effect sizes often differ between the studies due to variability in study design, outcome measurement tools, risk of bias, and the participants, interventions and outcomes studied [Higgins et al., 2019]. Such diversity in the effect sizes is known as the heterogeneity. When the heterogeneity exists, the random-effects model ought to be applied for meta-analysis. In such scenarios, it is of great importance to properly quantify the heterogeneity so as to explore the generalizability of the findings from a meta-analysis.

Among the several statistics for quantifying the heterogeneity, the $I^2$ statistic proposed by Higgins and Thompson (2002) and Higgins et al. (2003) is the most widely used statistic. In Google Scholar, as of 07 September 2021, Higgins and Thompson (2002) has been cited 22,481 times, and Higgins et al. (2003) has been cited 39,832 times. To describe the $I^2$ statistic in detail, we first introduce the random-effects model in meta-analysis.

Let $k$ be the total number of studies, and $y_i$ be the observed effect sizes for each study that are normally distributed with $\mu_i = E(y_i)$ and $\sigma_{y_i}^2 = \text{var}(y_i|\mu_i)$ for $i = 1, \ldots, k$. In addition, we assume that the individual means, $\mu_i = \mu + \delta_i$, follow a normal distribution with mean $\mu$ and variance $\tau^2 > 0$. With the above notations, the random-effects model in meta-analysis can be expressed as

$$y_i = \mu + \delta_i + \epsilon_i, \quad \delta_i \overset{\text{i.i.d.}}{\sim} N(0, \tau^2), \quad \epsilon_i \overset{\text{ind}}{\sim} N(0, \sigma_{y_i}^2),$$

(1)

where “i.i.d.” represents independent and identically distributed, “ind” represents independently distributed, $\tau^2$ is the between-study variance, and $\sigma_{y_i}^2$ are the within-study variances. In addition, $\delta_i$ and $\epsilon_i$ are assumed to be independent of each other.
To quantify the heterogeneity for model (1), Higgins and Thompson (2002) and Higgins et al. (2003) proposed the $I^2$ statistic by a two-step procedure as follows.

S1) Assuming that the within-study variances $\sigma_y^2$ are all equal as $\sigma_y^2$, they defined the measure of heterogeneity between the studies as

$$ICC_{HT} = \frac{\tau^2}{\tau^2 + \sigma_y^2}. \quad (2)$$

S2) They then proposed the statistic

$$I^2 = \max\left\{ \frac{Q - (k - 1)}{Q}, 0 \right\}. \quad (3)$$

as a sample estimate of $ICC_{HT}$, where $Q = \sum_{i=1}^{k} w_i (y_i - \sum_{i=1}^{k} w_i y_i / \sum_{i=1}^{k} w_i)^2$ is Cochran’s $Q$ statistic, and $w_i = 1/\sigma_{y_i}^2$ are the inverse-variance weights.

Rücker et al. (2008) reviewed several common measures for quantifying the heterogeneity in random-effects meta-analysis, which include Cochran’s $Q$ statistic (Cochran, 1954), the between-study variance $\tau^2$ (DerSimonian and Laird, 1986), and the $I^2$ statistic (Higgins and Thompson, 2002). Cochran’s $Q$ statistic was originally used for testing the existence of heterogeneity for meta-analysis. When used as a measure for quantifying the heterogeneity, it is often criticized in that the value of $Q$ will increase with the number of studies. While for the between-study variance $\tau^2$, it is specific to a particular effect metric, making it difficult to compare the heterogeneity between different meta-analyses. In contrast, the $I^2$ statistic was proposed to estimate the proportion of variability due to the heterogeneity between the studies so that its value varies from 0 to 1. It is appealing in that it does not depend on the number of studies and is irrespective of the effect metric. Because of these nice properties, the $I^2$ statistic is nowadays routinely reported in the forest plots for meta-analyses, and meanwhile it is also used as a criterion for model selection between the fixed-effect model and the random-effects model.

The main purpose of this paper is to examine whether or not the $I^2$ statistic can serve as a proper measure for quantifying the heterogeneity between the studies. To answer
this question, we first demonstrate by a motivating example that the \( I^2 \) statistic was, in fact, defined as problematic or even completely wrong from the very beginning. More specifically, we note that ICC\(_{HT}\) in [2] fails to provide a meaningful measure for the heterogeneity between the studies. Moreover, by drawing a connection between the one-way analysis of variance (ANOVA) and the random-effects meta-analysis, we introduce an intrinsic measure for quantifying the heterogeneity in the random-effects model. For details, see ICC\(_{MA}\) defined by formula (7) in Section 3.2. Finally, it is noteworthy that a similar measure has also been proposed by Sangnawakij et al. (2019), yet little work has been done on the statistical properties of the new measure. In particular, noting that ICC\(_{MA}\) is unknown in practice and needs to be estimated, their proposed algorithm may not converge and thus fails to provide a valid sample estimate for practical use. In comparison with their paper, our work has two main contributions. First, we derived the statistical properties for the new measure of heterogeneity and clarified why it is superior to the existing measures. Second, we provided an optimal estimator, referred to as the IQ statistic, which performs much better than the existing estimator and is also easy to implement.

The remainder of the paper is organized as follows. In Section 2, we give a motivating example to illustrate why ICC\(_{HT}\) fails to provide a valid measure of heterogeneity in meta-analysis. In Section 3, by drawing a close connection between ANOVA and the random-effects meta-analysis, we introduce an intrinsic measure for quantifying the heterogeneity between the studies. In Section 4, we derive the IQ statistic as an optimal estimator for the new measure. Simulation studies are conducted in Section 5 to evaluate the performance of the IQ statistic and also compare it with the existing methods. Section 6 applies the IQ statistic to analyze a real data example. We then conclude the paper in Section 7 and provide the technical details in the Appendix.
2 A motivating example

The main purpose of this section is to show that $\text{ICC}_\text{HT}$ in (2) fails to provide a valid measure of heterogeneity between the studies, and consequently, the $I^2$ statistic which is to estimate $\text{ICC}_\text{HT}$ can also be problematic. To confirm this statement, we first consider a motivating example of three studies with data generated from three normal populations $N(-3, 100)$, $N(0, 100)$ and $N(3, 100)$, respectively. From the top-left panel in Figure 1, it is evident that there does not have a large amount of heterogeneity between the three populations. More specifically, by [Veroniki et al. (2016)](#), the between-study variance of the three populations is given as

$$\tau^2 = \frac{(-3 - 0)^2 + (0 - 0)^2 + (3 - 0)^2}{3} = 6.$$ 

Now to explain why $\text{ICC}_\text{HT}$ may not serve as a valid measure of heterogeneity, we consider a meta-analysis for the three studies under several scenarios. For simplicity, we treat the population means as the effect sizes to be synthesized. In the first scenario, we assume that there are $n = 4$ patients in each study. Then by taking the sample means, the sampling distributions of the effect sizes are $N(-3, 25)$, $N(0, 25)$ and $N(3, 25)$, respectively. That is, $\sigma_y^2 = 25$ for all three studies. Finally, by the definition in (2), we have

$$\text{ICC}_\text{HT} = \frac{6}{6 + 25} = 19.4\%.$$ 

In the second scenario, we consider $n = 40$ for each study. It then yields the sampling distributions of the effect sizes as $N(-3, 2.5)$, $N(0, 2.5)$ and $N(3, 2.5)$, respectively. Further by $\sigma_y^2 = 2.5$, the measure of heterogeneity is

$$\text{ICC}_\text{HT} = \frac{6}{6 + 2.5} = 70.6\%.$$ 

In the third scenario, we consider $n = 400$ for each study. This leads to the sampling distributions of the effect sizes as $N(-3, 0.25)$, $N(0, 0.25)$ and $N(3, 0.25)$, respectively. Now since $\sigma_y^2 = 0.25$, the measure of heterogeneity is computed as large as

$$\text{ICC}_\text{HT} = \frac{6}{6 + 0.25} = 96\%.$$
Figure 1: Population distributions of the three studies and the sampling distributions of the effect sizes. Top-left panel: Population distributions are $N(-3, 100)$, $N(0, 100)$ and $N(3, 100)$, respectively. Top-right panel: Sampling distributions are $N(-3, 25)$, $N(0, 25)$ and $N(3, 25)$, respectively. Bottom-left panel: Sampling distributions are $N(-3, 2.5)$, $N(0, 2.5)$ and $N(3, 2.5)$, respectively. Bottom-right panel: Sampling distributions are $N(-3, 0.25)$, $N(0, 0.25)$ and $N(3, 0.25)$, respectively.
Finally, for ease of comparison, we also plot the sampling distributions of the effect sizes in Figure 1 for the three hypothetical scenarios with different study sample sizes.

The above example clearly shows that $ICC_{HT}$ in (2) is unable to provide a consistent measure of heterogeneity between the study populations, mainly because of its heavy dependence on the study sample sizes. Moreover, as a sample estimate of the wrong measure $ICC_{HT}$ in their S2 step, the $I^2$ statistic will also be problematic for practical use. To further clarify, by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019), a value of $I^2$ from 0% – 40% represents that the heterogeneity may not be important, a value from 30% – 60% represents a moderate heterogeneity, a value from 50% – 90% represents a substantial heterogeneity, and a value from 75% – 100% represents a considerable heterogeneity. Consequently, if we follow the above criterion for meta-analysis, it will then be concluded that the three populations in the first scenario have a negligible heterogeneity, the three populations in the second scenario have a substantial heterogeneity, and the three populations in the third scenario have a considerable heterogeneity. To summarize, if the $I^2$ statistic is applied and assuming that it can provide a good estimate of $ICC_{HT}$, then it will very likely yield contradictory results for model selection in meta-analysis.

Last but not least, there are also evidences in the literature reporting the limitations of the $I^2$ statistic. In particular, Rücker et al. (2008) found that the $I^2$ statistic will always increase rapidly to 1 when the sample sizes are large, regardless of whether or not the true heterogeneity between the studies is clinically important. For other criticisms on the $I^2$ statistic as a measure of heterogeneity, one may refer to, for example, Riley et al. (2016); IntHout et al. (2016); Borenstein et al. (2017); Sangnawakij et al. (2019); Holling et al. (2020), and the references therein.
3 A new measure of heterogeneity

We first review the one-way analysis of variance (ANOVA), and then by drawing a connection between ANOVA and meta-analysis, we introduce a new measure of heterogeneity for meta-analysis. We will further study the statistical properties of the new measure, and explain why it can serve as an intrinsic measure for quantifying the heterogeneity.

3.1 Connection between ANOVA and meta-analysis

Suppose that there are \( k \) populations in the experiment. Let \( y_{ij} \) be the \( j \)th observation in the \( i \)th population, where \( i = 1, \ldots, k \) and \( j = 1, \ldots, n_i \). For the random effects ANOVA, the observations \( y_{ij} \) can be modeled by

\[
y_{ij} = \mu + \delta_i + \xi_{ij}, \quad \delta_i \overset{i.i.d.}{\sim} N(0, \tau^2), \quad \xi_{ij} \overset{i.i.d.}{\sim} N(0, \sigma^2), \tag{4}
\]

where \( \mu \) is the grand mean, \( \delta_i \) are the treatment effects, and \( \xi_{ij} \) are the random errors. We further assume that \( \delta_i \) are i.i.d. normal random variables with zero mean and variance \( \tau^2 \geq 0 \), \( \xi_{ij} \) are i.i.d. normal random errors with zero mean and variance \( \sigma^2 > 0 \), and that \( \delta_i \) and \( \xi_{ij} \) are independent of each other. In addition, we refer to \( \mu_i = \mu + \delta_i \) as the individual means, \( \tau^2 \) as the between-study variance, \( \sigma^2 \) as the common error variance for all \( k \) populations, and \( \tau^2 + \sigma^2 \) as the total variance of each observation.

To draw a connection between ANOVA and meta-analysis, we consider a hypothetical scenario in which the experimenter first computed the sample mean and its variance for each population, namely \( y_i = \sum_{j=1}^{n_i} y_{ij}/n_i \) and \( \hat{\sigma}_{y_i}^2 = \sum_{j=1}^{n_i} (y_{ij} - y_i)^2/n_i(n_i - 1) \) for \( i = 1, \ldots, k \), and then reported these summary data rather than the raw data to the public. In practice, there are a few reasons that we need to do so, including, for example, the privacy protection that the individual patient data cannot be released. Given this, if, at a later time, researchers want to re-analyze the experiment using the publicly available data, it will then yield a summary model as

\[
y_i = \mu + \delta_i + \epsilon_i, \quad \delta_i \overset{i.i.d.}{\sim} N(0, \tau^2), \quad \epsilon_i \overset{ind}{\sim} N(0, \sigma^2/n_i), \tag{5}
\]
Table 1: Connection between the ANOVA model in (4) and the meta-analysis model in (5), where \( y_i = \sum_{j=1}^{n_i} y_{ij}/n_i \) and \( \epsilon_i = \sum_{j=1}^{n_i} \xi_{ij}/n_i \) for \( i = 1, \ldots, k \) and \( j = 1, \ldots, n_i \).

|                      | ANOVA                  | Meta-analysis          |
|----------------------|------------------------|------------------------|
| Model                | \( y_{ij} = \mu + \delta_i + \xi_{ij} \) | \( y_i = \mu + \delta_i + \epsilon_i \) |
| Between-study variance | \( \tau^2 \)   | \( \tau^2 \)                     |
| Error (or within-study) variance | \( \sigma^2 \) | \( \sigma^2/n_i \)              |
| Total variance       | \( \text{var}(y_{ij}) = \tau^2 + \sigma^2 \) | \( \text{var}(y_i) = \tau^2 + \sigma^2/n_i \) |

where \( y_i \) are the sample means, \( \mu \) and \( \delta_i \) are the same as defined in model (4), and \( \epsilon_i = \sum_{j=1}^{n_i} \xi_{ij}/n_i \) are independent (ind) random errors with zero mean and variance \( \sigma^2/n_i \), where \( i = 1, \ldots, k \). Now from the point of view of meta-analysis, if we treat \( y_i \) as the reported mean and \( \hat{\sigma}_y^2 \) as the true within-study variances, then model (5) is, in fact, the same as the random-effects model in (1). To conclude, when the ANOVA model only reports the summary data, it will result in a meta-analysis of summary data.

For ease of comparison, we also summarize in Table 1 some key components for the ANOVA model in (4) and for the meta-analysis model in (5). For the meta-analysis model, under the assumption that the within-study variances, i.e. \( \sigma^2/n_i \), are all equal, Higgins and Thompson (2002) interpreted the measure of heterogeneity as the proportion of total variance that is “between studies”. More specifically, by the last column of Table 1, they introduced the measure of heterogeneity for meta-analysis as in (2), where \( \sigma_y^2 = \sigma^2/n_i \) is the common within-study variance for the observed effect sizes. By (2), it is apparent that ICC_{HT} will be heavily dependent on the study sample sizes. When the sample sizes go to infinity, the within-study variances will converge to zero so that ICC_{HT} will increase to one, as having been observed in Rücker et al. (2008). This also coincides with the motivating example that, when the sample size varies from 4 to 400, their measure of heterogeneity will increase from 19.4% to 96% and so it yields contradictory results.

For the ANOVA model, it is well known that the intraclass correlation coefficient...
(ICC) is the most commonly used measure of heterogeneity [Fisher 1925, Smith 1957, Donner 1979, McGraw and Wong, 1996], which interprets the proportion of total variance that is “between populations”. More specifically, by the notation in Table 1, ICC can be expressed as

\[
ICC = \frac{\tau^2}{\text{var}(y_{ij})} = \frac{\tau^2}{\tau^2 + \sigma^2}.
\]  

(6)

As shown in the hypothetical scenario, the ANOVA model in (4) and the meta-analysis model in (5) are, in fact, associated with the same populations, even though one uses the raw data and the other uses the summary data. Because of this, we expect that the measures of heterogeneity for the two models should again be identical no matter whether the whole data or the summary data are being used. Moreover, by Table 1, we note that the within-study variances in meta-analysis are indeed the sampling variances of the effect sizes, or more accurately should be referred to as the square of the standard error (SE). Nevertheless, since the SE is inversely proportional to the study sample size, it may not be reasonable to assume a common SE for all the studies included in meta-analysis, especially when some studies are relatively big or small.

3.2 An intrinsic measure of heterogeneity

To have a reasonable assumption for meta-analysis, we follow the same assumption as in ANOVA that the population variances \( n_i \sigma^2_{y_i} \) are all equal, rather than an equality of the within-study variances. And for ease of presentation, we denote the common error variance as \( (n \sigma^2_y) \), which is a whole notation but should not be interpreted as the product of \( n \) and \( \sigma^2_y \). Then by the connection between ANOVA and meta-analysis, an intrinsic measure of heterogeneity for meta-analysis is given as

\[
\text{ICC}_{\text{MA}} = \frac{\tau^2}{\text{var}(y_{ij})} = \frac{\tau^2}{\tau^2 + n \sigma^2_y}.
\]  

(7)

Since \( n \sigma^2_y > 0 \) and \( \tau^2 \geq 0 \), the range of \( \text{ICC}_{\text{MA}} \) is \([0, 1]\). By (6) and (7), it is also evident that \( \text{ICC}_{\text{MA}} \) for meta-analysis is essentially the same as ICC for ANOVA. In addition,
we note that ICC\textsubscript{MA} is also consistent with the measure proposed by Sangnawakij et al. (2019). To further study the properties of ICC\textsubscript{MA}, we will compare it with ICC\textsubscript{HT} and explain why ICC\textsubscript{MA} can serve as an intrinsic measure of heterogeneity for meta-analysis.

Following Higgins and Thompson (2002), their measure of heterogeneity ICC\textsubscript{HT} has three statistical properties as follows.

(i) \textit{Monotonicity}. ICC\textsubscript{HT} is a monotonically increasing function of the ratio \( \tau^2 / \sigma_y^2 \). In particular, when the common within-study variance \( \sigma_y^2 \) is fixed, ICC\textsubscript{HT} will increase with the between-study variance \( \tau^2 \). This property was referred to as the “dependence on the extent of heterogeneity” in Higgins and Thompson (2002).

(ii) \textit{Location and scale invariance}. ICC\textsubscript{HT} is not affected by the different location and scale of the effect sizes. This property was referred to as the “scale invariance” in Higgins and Thompson (2002).

(iii) \textit{Study size invariance}. ICC\textsubscript{HT} is not affected by the total number of studies. This property was referred to as the “size invariance” in Higgins and Thompson (2002), which, in fact, only indicates the study size invariance.

Despite the above-mentioned properties, one has to admit that ICC\textsubscript{HT} does suffer from a heavy dependence on the study sample sizes, as pointed out in the motivating example and also by the historical evidence reported in the literature.

While for our new measure in (7), it can be shown that ICC\textsubscript{MA} also possesses the same three properties as ICC\textsubscript{HT} with the modified monotonicity property as

(i)' \textit{Monotonicity}. ICC\textsubscript{MA} is a monotonically increasing function of the ratio \( \tau^2 / (n \sigma_y^2) \). In particular, when the common error variance \( n \sigma_y^2 \) is fixed, ICC\textsubscript{MA} will increase with the between-study variance \( \tau^2 \).

And more importantly, we note that ICC\textsubscript{MA} also enjoys the following invariance property on the study sample sizes:
(iv) **Sample size invariance.** ICC\textsubscript{MA} is not affected by the sample size of each study.

The proofs of the above properties are given in Appendix A. Property (iv) indicates that ICC\textsubscript{MA} is able to provide a consistent measure of heterogeneity between the study populations in meta-analysis, regardless of whether the study sample sizes go to infinity. To further clarify, we also revisit the motivating example. Specifically, if we apply ICC\textsubscript{MA}, then the new measure of heterogeneity will constantly be $6/(6 + 100) = 5.7\%$ when the sample size varies from 4 to 400. To conclude, it is because of this sample size invariance property that distinguishes between our new ICC\textsubscript{MA} and the existing ICC\textsubscript{HT}, and it also explains why our new measure can serve as an intrinsic measure for quantifying the heterogeneity in meta-analysis.

### 4 Estimation of ICC\textsubscript{MA}

Recall that ICC\textsubscript{MA} for meta-analysis and ICC for ANOVA are essentially the same. In this section, we first review the existing literature on the estimation of ICC, and then apply the same spirit to find the optimal estimator of ICC\textsubscript{MA} for practical use.

#### 4.1 Methods for estimating ICC

For the ANOVA model, the estimation of ICC defined in (6) has been extensively studied in the literature. Among the existing estimators, the most widely used is the one derived from the ANOVA table, in which the total variation of the observations $y_{ij}$ can be partitioned into two components as

$$
\sum_{i=1}^{k} \sum_{j=1}^{n_i} (y_{ij} - \bar{y})^2 = \sum_{i=1}^{k} n_i (y_i - \bar{y})^2 + \sum_{i=1}^{k} \sum_{j=1}^{n_i} (y_{ij} - y_i)^2,
$$

where $y_i = \sum_{j=1}^{n_i} y_{ij}/n_i$ are the individual sample means, and $\bar{y} = \sum_{i=1}^{k} \sum_{j=1}^{n_i} y_{ij}/\sum_{i=1}^{k} n_i$ is the grand sample mean. More specifically, the term on the left-hand side of (8) is the total sum of squares (SST), and the two terms on the right-hand side are the sum of squares between the populations (SSB) and the error sum of squares within the populations.
(SSW), respectively. Cochran (1939) derived the expectations of SSB and SSW, and then by equating these two terms to their respective expectations, the method of moments estimators of $\tau^2$ and $\sigma^2$ was derived. Further by plugging these two estimators in formula (6), it led to the ANOVA estimator for the unknown ICC. By Smith (1957), the ANOVA estimator is a biased but consistent estimator. Moreover, as it may take a negative value when $SSB/k < SSW/(\sum_{i=1}^{k} n_i - k)$, one often truncates the negative value to zero when it occurs. For the balanced case when the sample sizes are all equal, Searle (1971) derived an exact confidence interval for ICC based on the ANOVA table. Nevertheless, the exact confidence interval from the ANOVA table is not available for the unbalanced case. As a remedy, Thomas and Hultquist (1978) and Donner (1979) suggested an adjusted confidence interval in which the common sample size in the balanced case is replaced by the average sample size. They further showed by simulation studies that the adjusted confidence interval performs very well in terms of the coverage probability.

Besides the above ANOVA estimator, it is also noteworthy that there are other methods for estimating ICC in the literature. To name a few, Thomas and Hultquist (1978) constructed a confidence interval for ICC based on the unweighted average of the individual sample means $\bar{y} = \sum_{i=1}^{k} y_i / k$. Noting also that $ICC = (\tau^2/\sigma^2) / (\tau^2/\sigma^2 + 1)$, Wald (1940) proposed another estimator for ICC by first estimating $\tau^2/\sigma^2$, yet it does not exist a closed form for both the point estimator and its confidence interval. As another alternative, by the facts that $cov(y_{ij}, y_{il}) = \tau^2$ for $j \neq l$ and $\text{var}(y_{ij}) = \tau^2 + \sigma^2$, Karlin et al. (1981) proposed to estimate ICC by the Pearson product-moment correlation computed over all the possible pairs of $(y_{ij}, y_{il})$ for $j \neq l$ with some weighting schemes. In addition, Donner and Koval (1980a,b) proposed an iterative algorithm to compute the maximum likelihood estimator (MLE) for ICC directly, and presented its performance by simulations when the number of studies is large. For more estimators of ICC, one may also refer to Donner (1986); Sahai and Ojeda (2004), and the references therein.

Despite the rich literature on the estimation of ICC, none of the existing estimators is known to be uniformly better than the others in the unbalanced case.
In practice, thanks to its simple and elegant form, the ANOVA estimator is routinely regarded as the optimal estimator and so is also the most commonly used estimator for estimating ICC. Finally, we note that the ANOVA estimator and the confidence interval suggested by Thomas and Hultquist (1978) and Donner (1979) can be readily implemented by the function ICCest in the R package ‘ICC’.

4.2 The IQ statistic

For the meta-analysis model, let $y_i$ be the observed effect size and $\hat{\sigma}^2_{y_i}$ be the within-study variance of the $i$th study, where $i = 1, \ldots, k$. We further define the between-population mean square as $MSB_{MA} = \{\sum_{i=1}^{k} n_i (y_i - \bar{y})^2\}/(k - 1)$ and the within-population mean square as $MSW_{MA} = \{\sum_{i=1}^{k} n_i (\hat{\sigma}^2_{y_i})\}/(\sum_{i=1}^{k} n_i - k)$, where $\bar{y} = (\sum_{i=1}^{k} n_i y_i)/\sum_{i=1}^{k} n_i$.

To estimate ICC$_{MA}$ for the balanced case, we first consider the scenario where the sample sizes are all equal. Then with $n_i = n$ for all $i = 1, \ldots, k$, the two mean squares can be further simplified as $MSB_{MA} = \{n \sum_{i=1}^{k} (y_i - \bar{y})^2\}/(k - 1)$ with $\bar{y} = \sum_{i=1}^{k} y_i/k$, and $MSW_{MA} = \{n \sum_{i=1}^{k} \hat{\sigma}^2_{y_i}\}/k$. By Lemma 1 in Appendix B, we have

$$E(MSB_{MA}) = n\tau^2 + n\sigma_y^2,$$
$$E(MSW_{MA}) = n\sigma_y^2.$$

Finally by (7), if we replace $\tau^2$ and $n\sigma_y^2$ with their moment estimators $(MSB_{MA} - MSW_{MA})/n$ and $MSW_{MA}$, it yields a new estimator for ICC$_{MA}$ as

$$IQ = \max \left\{ \frac{MSB_{MA} - MSW_{MA}}{MSB_{MA} + (n - 1)MSW_{MA}}, 0 \right\}.$$

We refer to the proposed estimator as the IQ statistic since it is used to estimate the Intrinsic measure for Quantifying the heterogeneity, and the truncation in formula (9) is to make the estimated measure ranging from 0 to 1.

Also in Appendix B we show that $MSB_{MA}$ is distributed with $n(\tau^2 + \sigma_y^2)\chi^2_{k-1}/(k - 1)$, and $MSW_{MA}$ is distributed with $n\sigma_y^2\chi^2_{kn-k}/(kn - k)$, where $\chi^2_{\nu}$ is a chi-square distribution with $\nu$ degrees of freedom. In addition, $MSB_{MA}$ and $MSW_{MA}$ are independent of each
other. Based on these results, an exact $100(1 - \alpha)\%$ confidence interval for $\text{ICC}_{\text{MA}}$ can be constructed as
\[
\left[ \max \left\{ \frac{\bar{F}_{\text{MA}}/F_{1-\alpha/2} - 1}{\bar{n} + \bar{F}_{\text{MA}}/F_{1-\alpha/2} - 1}, 0 \right\}, \max \left\{ \frac{\bar{F}_{\text{MA}}/F_{\alpha/2} - 1}{\bar{n} + \bar{F}_{\text{MA}}/F_{\alpha/2} - 1}, 0 \right\} \right],
\]  
where $\bar{F}_{\text{MA}} = \text{MSB}_{\text{MA}}/\text{MSW}_{\text{MA}}$, and $F_{\alpha}$ is the $(100\alpha)$th percentile of the $F$ distribution with $k - 1$ and $kn - k$ degrees of freedom.

In meta-analysis, however, the sample sizes often differ from study to study. To estimate $\text{ICC}_{\text{MA}}$ under the unbalanced case, we define the adjusted sample size as $\bar{n} = (\sum_{i=1}^{k} n_{i} - \sum_{i=1}^{k} n_{i}^{2}/\sum_{i=1}^{k} n_{i})/(k - 1)$. Then by Lemma 3 in Appendix C we have
\[
E(\text{MSB}_{\text{MA}}) = \bar{n}\tau^2 + n\sigma_y^2, \\
E(\text{MSW}_{\text{MA}}) = n\sigma_y^2.
\]
We reiterate here that, for the unbalanced case, $(n\sigma_y^2)$ is a whole notation representing the common error variance, but not a product of two quantities as neither $n$ or $\sigma_y^2$ is well defined. Then accordingly, by replacing $\tau^2$ and $n\sigma_y^2$ in (7) with their estimators $(\text{MSB}_{\text{MA}} - \text{MSW}_{\text{MA}})/\bar{n}$ and $\text{MSW}_{\text{MA}}$, the IQ statistic for the unbalanced case is
\[
\text{IQ} = \max \left\{ \frac{\text{MSB}_{\text{MA}} - \text{MSW}_{\text{MA}}}{\text{MSB}_{\text{MA}} + (\bar{n} - 1)\text{MSW}_{\text{MA}}}, 0 \right\}.
\]  
(11)

For the interval estimation, given that $\text{MSB}_{\text{MA}}$ does not follow a chi-square distribution when the sample sizes are not all equal, an exact confidence interval for $\text{ICC}_{\text{MA}}$ can no longer be derived. In view of this, we follow the same spirit as in Thomas and Hultquist (1978) and Donner (1979) and apply $\bar{n}$ to replace $n$ in the confidence interval for the balanced case. This leads to an approximate $100(1 - \alpha)\%$ confidence interval for $\text{ICC}_{\text{MA}}$ as
\[
\left[ \max \left\{ \frac{\bar{F}_{\text{MA}}/F_{1-\alpha/2} - 1}{\bar{n} + \bar{F}_{\text{MA}}/F_{1-\alpha/2} - 1}, 0 \right\}, \max \left\{ \frac{\bar{F}_{\text{MA}}/F_{\alpha/2} - 1}{\bar{n} + \bar{F}_{\text{MA}}/F_{\alpha/2} - 1}, 0 \right\} \right].
\]  
(12)
Finally, it is noteworthy that when $n_{i} = n$ for all $i = 1, \ldots, k$, the point estimator in (11) and the confidence interval in (12) will reduce to (9) and (10), respectively. In this regard, we can also treat (11) and (12) as the unified estimators for both balanced and unbalanced cases, and so will not distinguish them in the remainder of the paper.
5 Numerical results

In this section, we first introduce the $J^2$ statistic proposed by Sangnawakij et al. (2019) in Section 5.1, and then conduct simulation studies to evaluate the performance of the IQ statistic, the $I^2$ statistic, and the $J^2$ statistic in Section 5.2.

5.1 The $J^2$ statistic

As pointed out by Rücker et al. (2008) and Borenstein et al. (2017), the $I^2$ statistic is not an absolute measure of heterogeneity and so is often misused. In particular, a meta-analysis with larger study sample sizes will often yield a value of $I^2$ close to 1, regardless of whether the true heterogeneity between the study populations is large or not. To remove the sample size effect, although in a different context (in which the sample standard deviations are assumed to be unavailable), Sangnawakij et al. (2019) also applied ICC as the heterogeneity measure for meta-analysis. For more details, see their formula (13) and the related text. They further proposed to estimate $\tau^2$ and $\sigma^2$ separately by the maximum likelihood estimation, and then applied the direct plug-in method to estimate ICC. We refer to their proposed estimator as the $\hat{J}^2$ statistic. Noting also that the MLEs have no closed-form solutions, they proposed a fixed point iterative algorithm to estimate $\tau^2$ and $\sigma^2$. By following the notations in model (5), their iterative procedure is to take the estimates of $\mu$, $\tau^2$ and $\sigma^2$ from the fixed-effect model as the initial values. Specifically, they are

$$\hat{\mu}_0 = \frac{\sum_{i=1}^k n_i y_i}{\sum_{i=1}^k n_i}, \quad \hat{\tau}^2_0 = 0 \quad \text{and} \quad \hat{\sigma}^2_0 = k^{-1} \sum_{i=1}^k n_i (y_i - \hat{\mu}_0)^2.$$  

Next, with the values of $\hat{\mu}_s$, $\hat{\tau}^2_s$ and $\hat{\sigma}^2_s$ from step $s$, the updated estimates of the parameters are

$$\hat{\mu}_{s+1} = \frac{\sum_{i=1}^k y_i / (\hat{\tau}^2_s + \hat{\sigma}^2_s / n_i)}{\sum_{i=1}^k 1 / (\hat{\tau}^2_s + \hat{\sigma}^2_s / n_i)},$$

$$\hat{\tau}^2_{s+1} = \frac{\sum_{i=1}^k \left((\hat{\tau}^2_s + \hat{\sigma}^2_s / n_i)^{-2} \left((y_i - \hat{\mu}_s)^2 - \hat{\sigma}^2_s / n_i\right)\right)}{\sum_{i=1}^k (\hat{\tau}^2_s + \hat{\sigma}^2_s / n_i)^{-2}},$$

$$\hat{\sigma}^2_{s+1} = \frac{\sum_{i=1}^k \left((\hat{\tau}^2_s + \hat{\sigma}^2_s / n_i)^{-2} \left((y_i - \hat{\mu}_s)^2 / n_i - \hat{\tau}^2_s / n_i\right)\right)}{\sum_{i=1}^k (\hat{\tau}^2_s / n_i + \hat{\sigma}^2_s)^{-2}}.$$
Finally, if the algorithm converges, we let $\hat{\tau}^2$ and $\hat{\sigma}^2$ denote the final estimates of the between- and within-study variances so that the $\hat{J}^2$ statistic is given as

$$\hat{J}^2 = \frac{\hat{\tau}^2}{\hat{\tau}^2 + \hat{\sigma}^2}.$$ 

We note, however, that there are three main limitations in the $\hat{J}^2$ statistic. First, as pointed out by the authors, there is no guarantee that their fixed point algorithm will converge in theory. Second, based on the the identifiability condition by Sangnawakij et al. (2019), the MLEs of $\tau^2$ and $\sigma^2$ may not be unique if the sample sizes are all equal. Third, their algorithm does not guarantee the between- and within-study variance estimates to be positive. To avoid a negative estimate for the heterogeneity measure, we truncate the negative estimate to zero and define the $J^2$ statistic as $J^2 = \max\{\hat{J}^2, 0\}$. Our simulations (not given to save space) show that the $J^2$ statistic always performs better than the original $\hat{J}^2$ statistic.

5.2 Comparison of the three statistics

We now conduct simulation studies to compare the performance of the IQ statistic, the $I^2$ statistic and the $J^2$ statistic as different measures of the heterogeneity. Without loss of generality, we consider the random-effects model (5) with $\mu = 0$ and $\sigma^2 = 100$. While for the between-study variance, we consider $\tau^2 = 6$ or 60 that corresponds to ICC$_{MA}$ as $6/(6 + 100) = 0.057$ or $60/(60 + 100) = 0.375$, respectively. We also let $k = 3$ or 10 to represent the small or large number of studies included in the meta-analysis. Finally, for the sample size of each study, both the balanced and unbalanced cases will be considered as in Section 4.

For the balanced case, we let the common sample size $n$ range from 10 to 100. Following the above settings, we then generate the raw data from model (5) and report the summary data $y_i$ and $\hat{\sigma}_{y_i}^2$ for each of the $k$ studies. Note also that, due to the identifiability problem, the $J^2$ statistic is excluded for comparison under the balanced case. Finally, with $M = 10,000$ simulations, we compute the mean values of the IQ and $I^2$ statistics and plot the
Figure 2: Simulated mean values of the two statistics under the balanced case with 10,000 simulations. The red lines with circles represent the IQ statistic, the green lines with triangles represent the $I^2$ statistic, and the dashed lines stand for the true heterogeneity ICC$_{MA}$. 
numerical results in Figure 2. With each dashed line representing the true heterogeneity $\text{ICC}_{\text{MA}}$, it is evident that our newly proposed IQ statistic performs much better than the $I^2$ statistic in all simulation settings. In particular, the performance of the IQ statistic is not impacted by the sample size; and in fact, it performs even better when the sample size is large, which coincides with the asymptotic results on the consistent estimates of the unknown quantities. In contrast, the $I^2$ statistic is always monotonically increasing with the sample size. This is consistent with the one observed by Rücker et al. (2008) that the $I^2$ statistic always increases rapidly to 1 when the sample sizes are large, regardless of whether the true heterogeneity is large or not. To conclude, the $I^2$ statistic provides a wrong measure of heterogeneity and should be prohibited for practical use.

For the unbalanced case, we let the sample size of the $i$th study be $i \times n$, where $i = 1, \ldots, k$ and the common $n$ ranges from 10 to 100. All other settings are the same as those for the balanced case, and we once again generate the raw data from model (5) and report the summary data $y_i$ and $\hat{\sigma}^2_{y_i}$ for each of the $k$ studies. With $M = 10,000$ repetitions, we compute and plot the mean values of the IQ, $I^2$ and $J^2$ statistics in Figure 3. Based on the simulation results, the performance of the IQ statistic and the $I^2$ statistic and their relative comparison remain the similar as those for the balanced case. In particular, the $I^2$ statistic also shows the same increasing pattern as in Figure 2. While for the $J^2$ statistic, we note that it is always close to zero and thus results in a large negative bias for the measure of heterogeneity. Possible reasons of the poor performance can be, for example, the $J^2$ statistic does not use the information in $\hat{\sigma}^2_{y_i}$ and/or the algorithm may stop not because of convergence but due to the zero estimates in the denominator. To summarize, the IQ statistic provides a much more reliable and more accurate estimate for the heterogeneity compared with the two existing statistics. Lastly, we have also enclosed the R code for computing the IQ statistic, the $I^2$ statistic, and the $J^2$ statistic in Appendix D.
Figure 3: Simulated mean values of the two statistics under the unbalanced case with 10,000 simulations. The red lines with circles represent the IQ statistic, the green lines with triangles represent the $I^2$ statistic, the blue lines with crosses represent the $J^2$ statistic, and the dashed lines stand for the true heterogeneity ICC_{MA}. 

$k = 3, \text{ICC}_{MA} = 0.057$

$k = 3, \text{ICC}_{MA} = 0.375$

$k = 10, \text{ICC}_{MA} = 0.057$

$k = 10, \text{ICC}_{MA} = 0.375$
To compare the three statistics for quantifying the heterogeneity, we now revisit the meta-analysis from Jeong et al. (2014). Stem cell-based therapy is a potential new approach in the treatment of stroke. Jeong et al. (2014) conducted a meta-analysis to evaluate the efficacy and safety of stem cell-based therapy in the treatment of stroke. Among the several measures of the efficacy and safety, we consider the one with the point difference in National Institutes of Health Stroke Scale (NIHSS) as the outcome. For ease of reference, we also present the summary data of the 10 studies in Table 2.

Table 2: Summary data of the 10 studies for the meta-analysis from Jeong et al. (2014).

| Study            | $y_i$ | $n_i$ | $\hat{\sigma}_{y_i}^2$ |
|------------------|-------|-------|------------------------|
| Wang (2013)      | -3.10 | 8     | 1.81                   |
| Prasad (2012)    | -6.30 | 11    | 3.16                   |
| Moniche (2012)   | -9.40 | 10    | 0.53                   |
| Friedrich (2012) | -14.20| 20    | 3.04                   |
| Honmou (2011)    | -7.00 | 12    | 1.40                   |
| Savitz (2011)    | -9.00 | 10    | 1.60                   |
| Battistella (2011)| -3.40 | 6   | 2.41                   |
| Suarez (2009)    | -2.20 | 5     | 1.15                   |
| Savitz (2005)    | -1.40 | 5     | 0.97                   |
| Bang (2005)      | -2.00 | 5     | 1.06                   |

To compute the $I^2$ statistic, by treating $\hat{\sigma}_{y_i}^2$ in Table 2 as the true values of $\sigma_{y_i}^2$, we have $\sum_{i=1}^{10} w_i = 7.68$ and $\sum_{i=1}^{10} w_i y_i = -43.39$. This leads to Cochran’s $Q$ statistic as

$$Q = \frac{(-3.10 + 43.39/7.68)^2}{1.81} + \cdots + \frac{(-2.00 + 43.39/7.68)^2}{1.06} = 106.26.$$  

Further by formula (3), the $I^2$ statistic is given as

$$I^2 = \max \left\{ \frac{106.26 - (10 - 1)}{106.26}, 0 \right\} = 0.92.$$  

For the IQ statistic, also by Table 2 we have $\sum_{i=1}^{10} n_i = 92$ and $\bar{y} = \sum_{i=1}^{10} n_i y_i / \sum_{i=1}^{10} n_i =$
Moreover,\[
\text{MSB}_{\text{MA}} = \frac{8 \times (-3.10 + 7.55)^2 + \cdots + 5 \times (-2.00 + 7.55)^2}{9} = 189.83
\]
and\[
\text{MSW}_{\text{MA}} = \frac{8 \times 7 \times 1.81 + 11 \times 10 \times 3.16 + \cdots + 5 \times 4 \times 1.06}{92 - 10} = 25.81.
\]
Finally, by formula (11) together with the adjusted sample size
\[
\bar{n} = \frac{\sum_{i=1}^{10} n_i - \sum_{i=1}^{10} n_i^2 / \sum_{i=1}^{10} n_i}{9} = 8.97,
\]
the IQ statistic is given as\[
\text{IQ} = \max \left\{ \frac{189.83 - 25.81}{189.83 + (8.97 - 1) \times 25.81}, 0 \right\} = 0.41.
\]

While for the $J^2$ statistic, by the R code in Appendix D it yields the value of $\hat{J}^2$ as -0.25. Then by truncation, we have\[
J^2 = \max \{ \hat{J}^2, 0 \} = 0.
\]

Moreover, to assess the observed $I^2$, IQ and $J^2$ values, we assume that all the 10 studies are normally distributed. Then for visualization, using the reported means and variances, we plot their respective population distributions in Figure 4 of Appendix E. From the figure, it is evident that the 10 studies do not look very homogeneous, which shows that a measure of 0 for $J^2$ may not provide a reliable estimate for the heterogeneity among the studies. On the other side, the $I^2$ statistic is as high as 0.92, indicating that the 10 study populations are extremely divergent. Nevertheless, this may not be the truth since most of the study populations are largely overlapped in the range from -15 to 5. Finally, as a reasonable compromise, our newly proposed IQ statistic has the capacity to provide a moderate extent of the heterogeneity.
Based on the above comparison and also following the spirit of ICC, it is not difficult for us to conclude that the IQ statistic provides the most accurate measure for quantifying the extent of heterogeneity in meta-analysis. Specifically for this real data example, the IQ statistic at 0.41 can be regarded as the most reliable estimate for the heterogeneity of the 10 studies for meta-analysis.

7 Conclusion

Quantifying the heterogeneity is an important issue for meta-analysis. By the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019), the presence of heterogeneity affects the extent to which generalizable conclusions can be formed. Among the several heterogeneity measures, the $I^2$ statistic is undoubtedly the most commonly used measure in the literature. Despite of its popularity, the $I^2$ statistic has however a fatal drawback that it depends heavily on the sample size of each study. In particular, it will always yield a large heterogeneity when the sample sizes are large, as already pointed out by Rücker et al. (2008) and other researchers.

In this paper, we first explore the key reasons why and how the $I^2$ statistic depends significantly on the study sample sizes. Specifically, as presented in the motivating example, the measure ICC$_{HT}$ proposed by Higgins and Thompson (2002) is shown to be a function of the study sample sizes; and then consequently, as an estimator of ICC$_{HT}$, the $I^2$ statistic will also be largely affected by the study sample sizes. To overcome the drawback in the $I^2$ statistic, we further draw a connection between ANOVA and meta-analysis, and introduce a new measure ICC$_{MA}$ as the intrinsic measure of heterogeneity in meta-analysis. Meanwhile, its statistical properties including the monotonicity, the location and scale invariance, the study size invariance, and the sample size invariance are also investigated. Finally, by following the same spirit in the estimation of ICC, we propose an optimal estimator, referred to as the IQ statistic, and also construct a confidence interval for ICC$_{MA}$ that can be readily applied in meta-analysis. Simulations and real
data analysis also demonstrate that the IQ statistic provides a nearly unbiased estimate of the true heterogeneity and it is independent of the study sample sizes.

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Wald, A. (1940). A note on the analysis of variance with unequal class frequencies. *The Annals of Mathematical Statistics*, 11(1):96–100.
Appendix A  Proof of the properties of ICC\textsubscript{MA}

Proof of Monotonicity. By the definition in (7), we can rewrite ICC\textsubscript{MA} as

\[
\text{ICC}_{\text{MA}} = \frac{1}{1 + (n\sigma_y^2)/\tau^2}.
\]

This shows that ICC\textsubscript{MA} is a monotonically increasing function of \(\tau^2/(n\sigma_y^2)\) and so property (i)' holds.

Proof of Location and scale invariance. To prove the location and scale invariance, for any constants \(a\) and \(b > 0\), we assume that the newly observed effect sizes are \(y_{ij}' = a + by_{ij}\) for \(i = 1, \ldots, k\) and \(j = 1, \ldots, n_i\). Let also \(\mu_i' = a + b\mu_i\) be the true effect sizes of the new study populations. Then consequently, the between-study variance and the common error variance are given as

\[
(\tau^2)' = \text{var}(\mu_i') = \text{var}(a + b\mu_i) = b^2\tau^2,
\]
\[
(n\sigma_y^2)' = \text{var}(a + by_{ij}|a + b\mu_i) = b^2n\sigma_y^2.
\]

Further by (7), the measure of heterogeneity between the new studies is

\[
\text{ICC}'_{\text{MA}} = \frac{(\tau^2)'}{(\tau^2)' + (n\sigma_y^2)'} = \frac{b^2\tau^2}{b^2\tau^2 + b^2n\sigma_y^2} = \frac{\tau^2}{\tau^2 + n\sigma_y^2} = \text{ICC}_{\text{MA}}.
\]

This verifies the property of location and scale invariance.

Proof of Study size invariance. To prove the study size invariance, we assume there are a total of \(k'\) studies. Then by the random-effects model in (1), since the individual means \(\mu_i\) are i.i.d. from \(N(\mu, \tau^2)\), the between-study variance will remain unchanged as \(\tau^2\) regardless of the number of studies. Further by the common error variance assumption, we have \(\text{var}(y_{ij}|\mu_i) = n\sigma_y^2\) for all \(i = 1, \ldots, k'\) and \(j = 1, \ldots, n_i\). This proves the property of study size invariance.

Proof of Sample size invariance. To prove the sample size invariance, we assume that the new sample sizes are \(n_i'\) for each study, and consequently \(y_i' = \sum_{j=1}^{n_i'} y_{ij}/n_i'\) are the new effect sizes. Then under the common error variance assumption that \(\text{var}(y_{ij}|\mu_i) = n\sigma_y^2\)
for all $i$ and $j$, we have $\sigma^2_{y_i} = \text{var}(y'_i|\mu_i) = (n\sigma^2_y)/n'_i$, or equivalently, $n'_i\sigma^2_{y_i} = n\sigma^2_y$. That is, no matter how the sample sizes vary, the common error variance will always remain unchanged. Finally, noting that $\tau^2$ also remains since the study populations are unaltered, we thus have the property of sample size invariance.

### Appendix B  The derivation of the point estimate (9) and the confidence interval (10) for ICC$_{MA}$ in the balanced case

To prove the properties of the point estimate and the confidence interval for ICC$_{MA}$ in (9) and (10), we first introduce the following two lemmas.

**Lemma 1.** In the balanced case, with model (4) and the summary data $y_i$, $\sigma^2_y$ for $i = 1, \ldots, k$ in meta-analysis, denote by $\text{MSB}_{MA} = \{n \sum_{i=1}^{k} (y_i - \bar{y})^2\} / (k - 1)$ with $\bar{y} = \sum_{i=1}^{k} y_i / k$, and $\text{MSW}_{MA} = (n \sum_{i=1}^{k} \hat{\sigma}^2_{y_i}) / k$. Then $E(\text{MSB}_{MA}) = n(\tau^2 + \sigma^2_y)$, and $E(\text{MSW}_{MA}) = n\sigma^2_y$.

**Proof of Lemma 1.** Denote by $\sigma^2_y = \sigma^2/n$. With the summary data, $y_i$ are independent normal random variables with mean $\mu$ and variances $\tau^2 + \sigma^2_y$. Then the variance of $n \sum_{i=1}^{k} y_i$ is

$$\text{Var} \left( n \sum_{i=1}^{k} y_i \right) = n^2 \sum_{i=1}^{k} \text{Var} (y_i) = kn^2 \tau^2 + kn^2 \sigma^2_y.$$ 

Thus,

$$E \left( n \sum_{i=1}^{k} y_i \right)^2 = \text{Var} \left( n \sum_{i=1}^{k} y_i \right) + \left\{ E \left( n \sum_{i=1}^{k} y_i \right) \right\}^2$$

$$= kn^2 \tau^2 + kn^2 \sigma^2_y + k^2 n^2 \mu^2.$$
Further, it can be derived that

\[
E\left\{ n \sum_{i=1}^{k} (y_i - \bar{y})^2 \right\} = n \sum_{i=1}^{k} E\left( y_i^2 \right) - \frac{1}{kn} E\left( n \sum_{i=1}^{k} y_i \right)^2
\]

\[
= n \sum_{i=1}^{k} \left[ \text{Var}(y_i) + \{E(y_i)\}^2 \right] - \frac{1}{kn} E\left( n \sum_{i=1}^{k} y_i \right)^2
\]

\[
= kn \left( \tau^2 + \sigma_y^2 + \mu^2 \right) - \frac{1}{kn} \left( kn^2 \tau^2 + kn^2 \sigma_y^2 + k^2 n^2 \mu^2 \right)
\]

\[
= \tau^2 \left( kn - kn^2 \frac{1}{kn} \right) + kn \sigma_y^2 - \frac{kn^2 \sigma_y^2}{kn}
\]

\[
= n(k - 1) (\tau^2 + \sigma_y^2).
\]

Thus, \( E(\text{MSB}_{MA}) = n(\tau^2 + \sigma_y^2) \).

As for \( E(\text{MSW}_{MA}) = n\sigma_y^2 \), it is derived directly by the fact that \( E(n\hat{\sigma}_y^2) = n\sigma_y^2 \).

**Lemma 2.** With model (4) and the notations in Lemma 1, \( \text{MSB}_{MA} \) is distributed with \( \left( n\tau^2 + n\sigma_y^2 \right) \chi^2_{k-1} / (k-1) \), \( \text{MSW}_{MA} \) is distributed with \( n\sigma_y^2 \chi^2_{kn-k} / (kn - k) \), and they are independent of each other.

**Proof of Lemma 2.** With model (4) and the notations in Lemma 1, \( y_i \) is independent of \( n\hat{\sigma}_y^2 \) for \( i = 1, \ldots, k \). Given that \( \text{MSB}_{MA} \) is a function of \( y_i \), and \( \text{MSW}_{MA} \) is a function of \( n\hat{\sigma}_y^2 \), they are independent of each other.

Let \( Y = (y_1, \ldots, y_k)^T \), \( \Sigma = \text{Var}(Y) = (\tau^2 + \sigma_y^2)I_k \) with \( I_k \) being the \( k \times k \) identity matrix, and \( 1_k \) be the column vector of length \( k \) with all the elements being 1. Let \( Z \sim N(0, I_k) \). Then \( Y \) can be expressed as \( Y = \Sigma^{1/2}Z + \mu 1_k = (\tau^2 + \sigma_y^2)^{1/2}Z + \mu 1_k \). By the above notations, \( \sum_{i=1}^{k} n (y_i - \bar{y})^2 \) can be written as

\[
\sum_{i=1}^{k} n (y_i - \bar{y})^2 = nY^T \left( I_k - \frac{1}{k} 1_k 1_k^T \right) Y
\]

\[
= n \left( \Sigma^{1/2}Z + \mu 1_k \right)^T \left( I_k - \frac{1}{k} 1_k 1_k^T \right) \left( \Sigma^{1/2}Z + \mu 1_k \right)
\]

\[
= (n\tau^2 + n\sigma_y^2)Z^T \left( I_k - \frac{1}{k} 1_k 1_k^T \right) Z.
\]

Note that \( \left( I_k - \frac{1}{k} 1_k 1_k^T \right) \) is an idemponent matrix with rank \( k-1 \). So it can be decomposed as \( \left( I_k - \frac{1}{k} 1_k 1_k^T \right) = V\Lambda V^T \), where \( \Lambda = \text{diag}(1, \ldots, 1, 0) \) and \( V = (v_1, \ldots, v_k) \) is an orthogonal
matrix. With $\mathbf{v}_i^T \mathbf{Z} \overset{\text{i.i.d.}}{\sim} N(0, 1)$, the distribution of $\sum_{i=1}^k (y_i - \bar{y})^2$ can be derived as

$$
\sum_{i=1}^k n (y_i - \bar{y})^2 = (n\tau^2 + n\sigma^2_y) (\mathbf{V}^T \mathbf{Z})^T \Lambda (\mathbf{V}^T \mathbf{Z})
$$

$$
= (n\tau^2 + n\sigma^2_y) \sum_{i=1}^{k-1} (\mathbf{v}_i^T \mathbf{Z})^2
$$

$$
= (n\tau^2 + n\sigma^2_y) \chi^2_{k-1}.
$$

Thus, $\text{MSB}_{MA} = \{\sum_{i=1}^k n(y_i - \bar{y})^2\}/(k - 1)$ is distributed with $(n\tau^2 + n\sigma^2_y)\chi^2_{k-1}/(k - 1)$.

Since $n_i(n_i - 1)\hat{\sigma}_{yi}^2$ follow distributions $n\sigma^2_y\chi^2_{n_i-1}$ and are independent of each other for $i = 1, \ldots, k$, $\text{MSW}_{MA} \sim n\sigma^2_y\chi^2_{\sum_{i=1}^k n_i-k}/(\sum_{i=1}^k n_i-k)$.

**Proof of the point estimate for ICC$_{MA}$ in (9).** With Lemma 1, $E(\text{MSB}_{MA} - \text{MSW}_{MA}) = n\tau^2$, and $E\{\text{MSB}_{MA} + (n-1)\text{MSW}_{MA}\} = n(\tau^2 + n\sigma^2_y)$. Thus, ICC$_{MA} = \tau^2/(\tau^2 + n\sigma^2_y)$ can be estimated by $(\text{MSB}_{MA} - \text{MSW}_{MA})/(\text{MSB}_{MA} + (n-1)\text{MSW}_{MA})$.

Truncating the negative value to zero, the IQ statistic in (9) can be derived.

**Proof of the confidence interval for ICC$_{MA}$ in (10).** Denote $F_{k-1, kn-k}$ by the $F$ distribution with $k - 1$ and $kn - k$ degrees of freedom. Let $F_\alpha$ be the $(100\alpha)$th percentile of $F_{k-1, kn-k}$ and $\bar{F}_{MA} = \text{MSB}_{MA}/\text{MSW}_{MA}$. Then with Lemma 2 $n\sigma^2_y/(n\tau^2 + n\sigma^2_y) \cdot \bar{F}_{MA}$ is distributed with $F_{k-1, kn-k}$. We have

$$
1 - \alpha = \Pr \left( F_{\alpha/2} \leq \frac{n\sigma^2_y}{n\tau^2 + n\sigma^2_y} \bar{F}_{MA} \leq F_{1-\alpha/2} \right)
$$

$$
= \Pr \left( \frac{\bar{F}_{MA}}{F_{1-\alpha/2}} \leq \frac{n\tau^2 + n\sigma^2_y}{n\sigma^2_y} \leq \frac{\bar{F}_{MA}}{F_{\alpha/2}} \right)
$$

$$
= \Pr \left\{ \frac{1}{n} \left( \bar{F}_{MA}/F_{1-\alpha/2} - 1 \right) \leq \frac{\tau^2}{n\sigma^2_y} \leq \frac{1}{n} \left( \bar{F}_{MA}/F_{\alpha/2} - 1 \right) \right\}.
$$

For the left inequality,

$$
\Pr \left\{ \frac{1}{n} \left( \bar{F}_{MA}/F_{1-\alpha/2} - 1 \right) \leq \frac{\tau^2}{n\sigma^2_y} \right\} = \Pr \left\{ \frac{1}{n} \left( \bar{F}_{MA}/F_{1-\alpha/2} - 1 \right) \leq 0 \right\} + \Pr \left( \frac{\tau^2 + n\sigma^2_y}{\tau^2} \leq \frac{n + \bar{F}_{MA}/F_{1-\alpha/2} - 1}{\bar{F}_{MA}/F_{1-\alpha/2} - 1} \right)
$$

$$
= \Pr \left( \frac{\bar{F}_{MA}/F_{1-\alpha/2} - 1}{n + \bar{F}_{MA}/F_{1-\alpha/2} - 1} \leq \frac{\tau^2}{\tau^2 + n\sigma^2_y} \right).
$$
For the right inequality,
\[
\Pr\left\{ \frac{\tau^2}{n\sigma_y^2} \leq \frac{1}{n} \left( \bar{F}_{MA}/F_{\alpha/2} - 1 \right) \right\} = \Pr\left\{ \frac{1}{n} \left( \bar{F}_{MA}/F_{\alpha/2} - 1 \right) > 0, \frac{n + \bar{F}_{MA}/F_{\alpha/2} - 1}{\bar{F}_{MA}/F_{\alpha/2} - 1} \leq \frac{\tau^2 + n\sigma_y^2}{\tau^2} \right\}
\]
= \Pr\left( \frac{\tau^2}{\tau^2 + n\sigma_y^2} \leq \frac{\bar{F}_{MA}/F_{\alpha/2} - 1}{n + \bar{F}_{MA}/F_{\alpha/2} - 1} \right).

Thus, the $100(1 - \alpha)$% confidence interval for ICC_{MA} is
\[
\left[ \frac{\bar{F}_{MA}/F_{1-\alpha/2} - 1}{n + \bar{F}_{MA}/F_{1-\alpha/2} - 1}, \frac{\bar{F}_{MA}/F_{\alpha/2} - 1}{n + \bar{F}_{MA}/F_{\alpha/2} - 1} \right].
\]

The confidence interval in (10) is derived by truncating the negative values of the above limits to zero.

**Appendix C  The derivation of the point estimate (11) for ICC_{MA} in the unbalanced case**

To prove the properties of the point estimate for ICC_{MA} in (11), we first introduce the following lemma.

**Lemma 3.** With model (4) and the summary data $y_i, \hat{\sigma}^2_y$ for $i = 1, \ldots, k$ in meta-analysis, denote by $\bar{n} = (\sum_{i=1}^k n_i - \sum_{i=1}^k n_i^2 / \sum_{i=1}^k n_i) / (k-1)$, MSB_{MA} = $\{\sum_{i=1}^k n_i(y_i - \bar{y})^2\} / (k-1)$ with $\bar{y} = (\sum_{i=1}^k n_i y_i) / \sum_{i=1}^k n_i$, and MSW_{MA} = $\{\sum_{i=1}^k n_i(n_i - 1)\hat{\sigma}^2_y\} / \sum_{i=1}^k n_i - k$. Then $E(MSB_{MA}) = \bar{n}\tau^2 + n\sigma_y^2$, and $E(MSW_{MA}) = n\sigma_y^2$.

**Proof of Lemma 3**. Denote by $\sigma^2_{y_i} = \sigma^2 / n_i$. With the summary data, $y_i$ are independent normal random variables with mean $\mu$ and variances $\tau^2 + \sigma^2_{y_i}$. Then the variance of $\sum_{i=1}^k n_i y_i$ is
\[
\text{Var} \left( \sum_{i=1}^k n_i y_i \right) = \sum_{i=1}^k \text{Var} \left( n_i y_i \right) = \tau^2 \sum_{i=1}^k n_i^2 + \sum_{i=1}^k n_i^2 \sigma^2_{y_i}.
\]

Thus,
\[
E \left( \sum_{i=1}^k n_i y_i \right)^2 = \text{Var} \left( \sum_{i=1}^k n_i y_i \right) + \left\{ E \left( \sum_{i=1}^k n_i y_i \right) \right\}^2
\]
= $\tau^2 \sum_{i=1}^k n_i^2 + \sum_{i=1}^k n_i^2 \sigma^2_{y_i} + \mu^2 \left( \sum_{i=1}^k n_i \right)^2$.
Further, it can be derived that

\[
E \left\{ \sum_{i=1}^{k} n_i (y_i - \bar{y})^2 \right\} = \sum_{i=1}^{k} n_i E \left( y_i^2 \right) - \frac{1}{\sum_{i=1}^{k} n_i} E \left( \sum_{i=1}^{k} n_i y_i \right)^2
\]

\[
= \sum_{i=1}^{k} n_i \left[ \text{Var}(y_i) + \{E(y_i)\}^2 \right] - \frac{1}{\sum_{i=1}^{k} n_i} E \left( \sum_{i=1}^{k} n_i y_i \right)^2
\]

\[
= \sum_{i=1}^{k} n_i \left( \tau^2 + \sigma_y^2 + \mu^2 \right) - \frac{1}{\sum_{i=1}^{k} n_i} \left\{ \tau^2 \sum_{i=1}^{k} n_i^2 + \sum_{i=1}^{k} n_i^2 \sigma_y^2 + \mu^2 \left( \sum_{i=1}^{k} n_i \right)^2 \right\}
\]

\[
= \tau^2 \left( \sum_{i=1}^{k} n_i - \frac{\sum_{i=1}^{k} n_i^2}{\sum_{i=1}^{k} n_i} \right) + \sum_{i=1}^{k} n_i \sigma_y^2 - \frac{\sum_{i=1}^{k} n_i^2 \sigma_y^2}{\sum_{i=1}^{k} n_i}.
\]

Since \( \sigma_y^2 = n \sigma_y^2 / n_i \), and \( \bar{n} = \left( \sum_{i=1}^{k} n_i - \sum_{i=1}^{k} n_i^2 / \sum_{i=1}^{k} n_i \right) / (k - 1) \)

\[
E \left\{ \sum_{i=1}^{k} n_i (y_i - \bar{y})^2 \right\} = (k - 1) \bar{n} \tau^2 + (k - 1) n \sigma_y^2.
\]

Thus, \( E(\text{MSB}_{\text{MA}}) = \bar{n} \tau^2 + n \sigma_y^2 \).

As for \( E(\text{MSW}_{\text{MA}}) = n \sigma_y^2 \), it is derived directly by the fact that \( E(n_i \sigma_y^2) = n \sigma_y^2 \).

**Proof of the point estimate for ICC_{\text{MA}} in (11).** With Lemma 3 \( E(\text{MSB}_{\text{MA}} - \text{MSW}_{\text{MA}}) = \bar{n} \tau^2 \), and \( E\{\text{MSB}_{\text{MA}} + (\bar{n} - 1)\text{MSW}_{\text{MA}}\} = \bar{n} (\tau^2 + n \sigma_y^2) \). Thus, \( ICC_{\text{MA}} = \tau^2 / (\tau^2 + n \sigma_y^2) \) can be estimated by \( (\text{MSB}_{\text{MA}} - \text{MSW}_{\text{MA}}) / \{\text{MSB}_{\text{MA}} + (\bar{n} - 1)\text{MSW}_{\text{MA}}\} \).

Truncating the negative value to zero, the IQ statistic in (11) can be derived.

**Appendix D**  **R code of functions to compute IQ, \( I^2 \), and \( J^2 \).**

```R
iq<-function(n,y,sigy2){
  alpha =0.05
  k=length(n)
  N=sum(n)
  n0=(N-sum(n^2)/N)/(k-1)
  ybar=sum(n*y)/N
  MSA=sum(n*(y-ybar)^2)/(k-1)
  MSE=sum(n*(n-1)*sigy2)/(N-k)
  Ft=MSA/MSE
}
```
ra = \max(0, (\text{MSA} - \text{MSE}) / (\text{MSA} + (n_0 - 1) \times \text{MSE}))
lower = (F_t / qf(1 - \alpha / 2, k - 1, N - k - 1)) / (n_0 + F_t / qf(1 - \alpha / 2, k - 1, N - k - 1))
upper = (F_t / qf(\alpha / 2, k - 1, N - k - 1)) / (n_0 + F_t / qf(\alpha / 2, k - 1, N - k - 1))
\text{lis} = \text{list}(\text{iq} = \text{ra}, \text{lowlim} = \text{lower}, \text{upplim} = \text{upper})
\text{return(\text{lis})}

i2 = \text{function}(n, y, sigy2)\
\text{\{}
\text{k = length(y)}
w = 1 / sigy2
yb = \text{sum(w} \times y) / \text{sum(w)}
q = \text{sum(w} \times (y - yb)^2)
i2 = (q - (k - 1)) / q
i2 = \max(0, i2)
\text{return(i2)}
\text{\}}

j2 = \text{function}(wi, di)\
\text{\{}
diff1 = 1
diff2 = 1
diff3 = 1
it = 0
mu.hat = \text{sum(di}/wi)/\text{sum(1}/wi)
sigma2.hat = \text{mean((di-mu.hat)^2}/wi)
tao2.hat = 0
\text{while((diff1 > 0.00001) || (diff2 > 0.00001) || (diff3 > 0.00001))}\n\text{\{}
mu.old = mu.hat
sigma2.old = sigma2.hat
tao2.old = tao2.hat
mu.hat = \text{(sum(di}/(tao2.hat+sigma2.hat*wi))}/(\text{sum(1}/(tao2.hat+sigma2.hat*wi)))
sigma2.hat = \text{(sum((di-mu.hat)^2*wi}/wi*tao2.hat)/(tao2.hat+sigma2.hat*wi)^2})/(\text{sum((w}^2)/(tao2.hat+sigma2.hat*wi)^2))
tao2.hat = \text{(sum(((di-mu.hat)^2-sigma2.hat*wi})/(tao2.hat+sigma2.hat*wi)^2))/(\text{sum(1}/(tao2.hat+sigma2.hat*wi)^2))
\text{\}}
Appendix E  Population distributions of the ten studies.
Figure 4: Population distributions of the ten studies. For each study, the population distribution is assumed to be normal with mean $y_i$ and variance $n_i\sigma_{y_i}^2$. 