

Article

Consistency of the Estimator for the Common Mean in Fixed-Effect Meta-Analyses

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Abstract: Fixed-effect meta-analyses aim to estimate the common mean parameter by the best linear unbiased estimator. Besides unbiasedness, consistency is one of the most fundamental requirements for the common mean estimator to be valid. However, conditions for the consistency of the common mean estimator have not been discussed in the literature. This article fills this gap by clarifying conditions for making the common mean estimator consistent in fixed-effect meta-analyses. In this article, five theorems are devised, which state regularity conditions for the common mean estimator to be consistent. These theorems are novel applications of the classical large sample theory to meta-analyses. Numerical illustrations are also given to help understand the needs of the regularity conditions. Three real datasets illustrate the practical consequences of the devised theorems. This article concludes that the inconsistency of the common mean estimator occurs under some conditions in real meta-analyses.

Keywords: best linear unbiased estimator; common mean; fixed-effect model; large sample theory; law of large number; meta-analysis

MSC: 62D05; 62E20; 62F12; 62P10



Citation: Taketomi, N.; Emura, T. Consistency of the Estimator for the Common Mean in Fixed-Effect Meta-Analyses. *Axioms* **2023**, *12*, 503. <https://doi.org/10.3390/axioms12050503>

Academic Editors: Hari Mohan Srivastava, Hans J. Haubold and Piergiulio Tempista

Received: 1 March 2023

Revised: 30 April 2023

Accepted: 17 May 2023

Published: 21 May 2023



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1. Introduction

Meta-analysis is a statistical method for summarizing results from published studies [1]. Meta-analysis has been applied to all areas of science, including educational studies [2,3] and medical studies [4,5]. Additionally, meta-analysis has played an especially important role in studies on the impact of COVID-19 [6–8].

The most basic model in meta-analyses is the fixed-effect model, where all of the studies share the common mean parameter [5,9]. The goal of fixed-effect meta-analyses is to estimate the common mean parameter using the observations from all the studies. The estimator of the common mean optimally combines all the studies to yield minimum variance and unbiased estimation for the common mean; see Section 2 for details.

The consistency of an estimator is one of the most fundamental requirements for good estimators, as mentioned in almost all textbooks of mathematical statistics [10–12]. Most of the commonly used estimators are shown to be consistent, such as the Bayes estimators, nonparametric estimators, least squared estimators, moment estimators, jackknife estimators, and others [12]. Many statisticians would find it distasteful to apply an inconsistent estimator [11] to statistical analysis. Note that such examples of inconsistent estimators exist even if they are unbiased and have minimum variance [10]. This is exactly the case for fixed-effect meta-analyses; the estimator of the common mean may be inconsistent if individual studies exhibit pathological patterns.

However, the regularity conditions for the consistency of the common mean estimator have been largely neglected in the context of fixed-effect meta-analyses. For instance, the well-known review articles “the statistical basis of meta-analysis” [5] and “a re-evaluation

of fixed effect (s) meta-analysis" [9] do not talk about the consistency of the common mean estimator since their main interest is how to apply the estimator to a finite number of studies. Even the well-known books of meta-analyses, including [1], do not discuss the consistency of the common mean estimator at all. Furthermore, users of meta-analyses typically do not pay attention to the consistency of the common mean estimator (as they pay attention to the results and interpretation of the analysis). Recently, Shih et al. [13,14] suggested applying the strong law of large numbers for the independent but not identically distributed sequence [12] to regularize the common mean estimator. However, they only imposed regularity conditions (as the assumptions) without deep explorations and concrete examples of inconsistency.

This article fills this gap by clarifying the assumptions/conditions for making the common mean estimator to be consistent in fixed-effect meta-analyses. We give five theorems stating the regularity conditions for the common mean estimator to be consistent; this also provides concrete examples of inconsistent estimators for the common mean. These theorems are novel applications of the classical large sample theory [10] to fixed-effects meta-analyses. To deepen the understanding of our theory, we also performed simulation studies, demonstrating both consistent and inconsistent cases. Finally, we analyzed three real datasets to illustrate the practical consequences of the proposed theory.

This article is organized as follows. Section 2 reviews fixed-effect meta-analyses. Section 3 proposes our theory for the consistency of the common mean estimator and describes its demonstration via simulations. Section 4 analyzes three datasets to explain how our theory is applied to real examples. Section 5 extends our theory to the case of unknown variances. Section 6 concludes the article.

2. Fixed-Effect Meta-Analysis

We review fixed-effect meta-analyses along with some mathematical notations and basic assumptions. Let n be the number of studies in a meta-analysis. For $i = 1, 2, \dots, n$, the i -th study produces a random variable Y_i having the unknown common mean $\mu = E(Y_i)$ and known variance $\sigma_i^2 = V(Y_i) > 0$. The known variance is reasonable since each study provides σ_i as the standard error (SE) of the estimate Y_i .

In some meta-analyses, Y_i is a mean difference (MD) that takes the form $Y_i = \sum_{j=1}^{n_{i1}} Y_{ij1} / n_{i1} - \sum_{j=1}^{n_{i2}} Y_{ij2} / n_{i2}$, where Y_{ijk} is the j -th individual observation and n_{ik} is the sample size from the k -th group in the i -th study. In this case, $\sigma_i^2 = V(Y_i) = V(Y_{ij1}) / n_{i1} + V(Y_{ij2}) / n_{i2}$ is the pooled variance estimate (Appendix A). For this reason, there could be a different setting where the variance is unknown and estimated [15–17]. However, we mostly follow usual meta-analyses where the variances are treated as known by studies (even if they are estimated). In a meta-analysis, available information is $\{(Y_i, \sigma_i); i = 1, 2, \dots, n\}$. The case of unknown σ_i being estimated will be considered shortly in Section 5.

Meta-analyses aim to estimate μ by optimally combining Y_i s [1,5,9]. The three principles of the estimators, best linear unbiased estimation (BLUE), least squared estimation (LSE), and maximum likelihood estimation (MLE), lead to the same estimator for the common mean μ by

$$\hat{\mu}_n = \frac{\sum_{i=1}^n (\sigma_i^2)^{-1} Y_i}{\sum_{i=1}^n (\sigma_i^2)^{-1}}.$$

See [5,10,12] for details. The estimator is unbiased, i.e., $E_\mu(\hat{\mu}_n) = \mu$, irrespective of the values of μ and $\sigma_1, \dots, \sigma_n$. However, it will be shown that the estimator is *not always* consistent.

We say that the estimator $\hat{\mu}_n$ is *consistent* for μ if

$$\lim_{n \rightarrow \infty} P_\mu(|\hat{\mu}_n - \mu| > \varepsilon) = 0 \quad \forall \varepsilon > 0. \quad (1)$$

We emphasize the fact that the consistency is not trivial unless the constant variance $\sigma_i^2 = c$ is assumed. The following section describes the regularity conditions for the consistency to hold.

3. Consistency

In order to find regularity conditions for the consistency of Equation (1), it is necessary to find a suitable large sample theory for independent but not identically distributed (i.n.i.d.) samples [18,19]. To this end, we adopt the mathematical arguments in the book of Lehmann [10]. This is a novel application of the classical large sample theory to meta-analyses.

To show the consistency of Equation (1), we apply Chebychev’s inequality so that

$$P_\mu(|\hat{\mu}_n - \mu| > \varepsilon) \leq \frac{1}{\varepsilon^2} V_\mu(\hat{\mu}_n) = \frac{1}{\varepsilon^2} \frac{1}{\sum_{i=1}^n (\sigma_i^2)^{-1}}.$$

Therefore, $P_\mu(|\hat{\mu}_n - \mu| > \varepsilon) \rightarrow 0$ if the right-hand side goes to zero. The following theorem arises:

Theorem 1: *The common mean estimator $\hat{\mu}_n$ is consistent if $\lim_{n \rightarrow \infty} \sum_{i=1}^n (\sigma_i^2)^{-1} = \infty$.*

Theorem 1 provides a regularity condition for the sequence $\{\sigma_i\}_{i=1}^\infty$ to meet the consistency of Equation (1). An obvious example is the constant sequence of $\sigma_i = \sigma$ by which $\sum_{i=1}^n (\sigma_i^2)^{-1} = n\sigma^{-1}$. In this case, Y_1, \dots, Y_n are i.i.d., so that Theorem 1 reduces to the well-known consistency of the sample mean for i.i.d. samples. However, the i.i.d. samples do not arise in usual meta-analyses.

An example of non-constant sequences is a bounded sequence satisfying $\sup_i (\sigma_i^2) < \infty$. In this case, there exists a number $M > 0$ such that $\sigma_i^2 \leq M \forall i$, or simply, $M = \sup_i (\sigma_i^2)$. Then, $(\sigma_i^2)^{-1} \geq M^{-1} \forall i$. Thus, $\sum_{i=1}^n (\sigma_i^2)^{-1} \geq nM^{-1} \rightarrow \infty$ as $n \rightarrow \infty$. This argument yields the following:

Theorem 2: *The common mean estimator $\hat{\mu}_n$ is consistent if $\sup_i (\sigma_i^2) < \infty$.*

The condition $\sup_i (\sigma_i^2) < \infty$ in Theorem 2 is easy to interpret. It means that an individual study should not have a large value for σ_i^2 .

Another case is where σ_i^2 is generated from a distribution that has finite support. For instance, if $\sigma_i^2 \sim U(0, c)$, then $\sup_i (\sigma_i^2) = c < \infty$. Theorem 2 may explain the reason why [13,14,20–22] made σ_i^2 to be a random variable following a chi-squared distribution bounded on a finite range in their simulation studies of fixed-effect meta-analysis models.

However, the condition $\sup_i (\sigma_i^2) < \infty$ in Theorem 2 is much stronger than necessary. To see why, we consider the case of $\sigma_i^2 = i$. In this case, the variance increases linearly toward infinity, yet the consistency holds by the divergence of the *harmonic series*

$$\lim_{n \rightarrow \infty} \sum_{i=1}^n \frac{1}{i} = \infty,$$

and Theorem 1. Another case is σ_i^2 generated from a distribution having non-finite support. For instance, if σ_i^2 follows a chi-squared distribution, then $\sup_i (\sigma_i^2) = \infty$. In this case, it is unclear if the consistency holds. In summary, Theorem 2 provides an easy-to-check and easy-to-interpret, but a quite stronger condition than Theorem 1.

The above discussions show that the consistency holds for the linear increasing case $\sigma_i^2 = i$. How about a faster-increasing case, such as $\sigma_i^2 = i^2$? To see how fast the variances can increase while keeping the consistency, we adopt the model of Lehmann [10], defined

as $\sigma_i^2 = ci^\alpha$ for $c > 0$ and $-\infty < \alpha < \infty$. The case of $\alpha = 0$ leads to the i.i.d. case, while the case of $\alpha = 1$ is the case of linear increasing. By the property of the Riemann zeta function,

$$\lim_{n \rightarrow \infty} \sum_{i=1}^n (ci^\alpha)^{-1} = c^{-1} \lim_{n \rightarrow \infty} \sum_{i=1}^n i^{-\alpha} = \begin{cases} = \infty & \text{if } \alpha \leq 1, \\ < \infty & \text{if } \alpha > 1. \end{cases}$$

Thus, the case $\alpha = 2$ makes σ_i^2 increases too fast. In this case, it is unclear if the consistency holds since neither $\lim_{n \rightarrow \infty} \sum_{i=1}^n (\sigma_i^2)^{-1} = \infty$ nor $\sup_i (\sigma_i^2) < \infty$ holds.

Nonetheless, a reasonable question to ask is the following: Is the estimator inconsistent if the variance increases too fast? What about the case of $\sigma_i^2 = ci^\alpha$ with $\alpha > 1$? A fine answer can be obtained by imposing additional assumptions on the distributional form.

Theorem 3: Suppose $Y_i \sim N(\mu, \sigma_i^2)$ for $i = 1, 2, \dots, n$. Then, the necessary and sufficient condition for $\hat{\mu}_n$ to be consistent is $\lim_{n \rightarrow \infty} \sum_{i=1}^n (\sigma_i^2)^{-1} = \infty$.

The proof is given in Appendix B.

The following theorem is a consequence of Theorem 3.

Theorem 4: Suppose $Y_i \sim N(\mu, \sigma_i^2)$, $\sigma_i^2 = ci^\alpha$, $c > 0$, $-\infty < \alpha < \infty$, for $i = 1, 2, \dots, n$. Then, the necessary and sufficient condition for $\hat{\mu}_n$ to be consistent is $\alpha \leq 1$.

The proof of Theorem 4 is given in Appendix C.

Theorem 4 makes it clear that $\hat{\mu}_n$ is inconsistent for the quadratically increasing variance $\sigma_i^2 = ci^2$, but consistent for the linearly increasing variance $\sigma_i^2 = ci$.

Numerical illustrations help understand the consistency/inconsistency of $\hat{\mu}_n$. Let $Y_i \sim N(\mu, \sigma_i^2)$ with $\mu = 1$ and $\sigma_i^2 = ci^\alpha$, where $c > 0$ and $-\infty < \alpha < \infty$. We considered six cases:

- $\alpha = -1$ giving a consistent estimator by $\lim_{n \rightarrow \infty} \sum_{i=1}^n i^1 = \infty$
- $\alpha = 0$ giving a consistent estimator by $\lim_{n \rightarrow \infty} \sum_{i=1}^n i^0 = \infty$
- $\alpha = 1$ giving a consistent estimator by $\lim_{n \rightarrow \infty} \sum_{i=1}^n i^{-1} = \infty$
- $\alpha = 1.5$ giving an inconsistent estimator by $\lim_{n \rightarrow \infty} \sum_{i=1}^n i^{-1.5} = 2.612 \dots < \infty$
- $\alpha = 2$ giving an inconsistent estimator by $\lim_{n \rightarrow \infty} \sum_{i=1}^n i^{-2} = \pi^2/6 = 1.644 \dots < \infty$
- $\alpha = 3$ giving an inconsistent estimator by $\lim_{n \rightarrow \infty} \sum_{i=1}^n i^{-3} = 1.202 \dots < \infty$

Figure 1 depicts the trajectory of $\hat{\mu}_n$ for $n = 1, 2, \dots, 10000$. For the cases of $\alpha = -1$, $\alpha = 0$ and $\alpha = 1$, the estimates $\hat{\mu}_n$ converged to the true value of $\mu = 1$. For the case of $\alpha = 1$, the convergence is slower than in the cases of $\alpha = -1$ and $\alpha = 0$. However, for the cases of $\alpha = 1.5, \alpha = 2$, and $\alpha = 3$, the estimates $\hat{\mu}_n$ did not converge to the true value since the estimates keep away from $\mu = 1$. These observations exactly agree with the statements of Theorem 4.

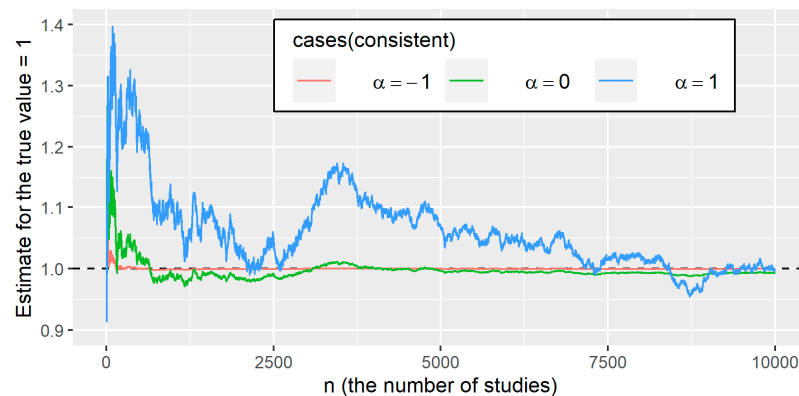


Figure 1. Cont.

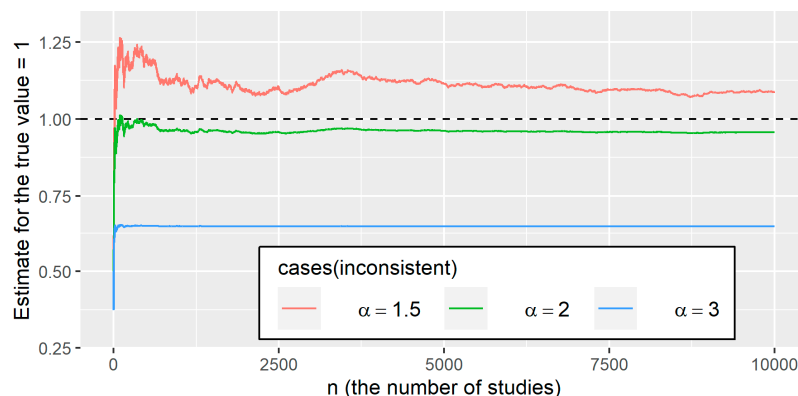


Figure 1. The estimates $\hat{\mu}_n$ for $n = 1, 2, \dots, 10000$, based on $Y_i \sim N(\mu, \sigma_i^2)$ with $\mu = 1$ and $\sigma_i^2 = ci^\alpha$ under $\alpha = -1, \alpha = 0, \alpha = 1, \alpha = 1.5, \alpha = 2$, and $\alpha = 3$.

4. Data Analysis

This section analyzes three real datasets to illustrate the developed theory in Section 3.

4.1. Allergic Reaction Data

We analyzed a dataset on the allergic reaction of medical students who were exposed to formaldehyde during an anatomy course [23]. The symptoms were measured by a score defined as the sum of answers (1: low, 2: medium, 3: high) to a series of questions in a questionnaire. A higher score corresponds to a more severe symptom. Besides the scores, the questionnaire provides explanatory variables, such as gender.

Table 1 summarizes the dataset that was collected in the years 2015, 2016, 2018, 2019, and 2022 in which the questionnaire was delivered. In this analysis, we focused on the mean difference (MD) of the scores between the male and female students for eye symptoms. Let $Y_i (i = 1, \dots, 5)$ be the MD of the score between the male and female students (male–female). We assume that Y_i is normally distributed. Let $\sigma_i^2 = V(Y_i)$ that was computed by the pooled variance (Appendix A) based on the standard deviations of male and female groups (Table 1). Since the students are all different across years, the scores are independent.

Table 1. The dataset on the allergic reaction of medical students who were exposed to formaldehyde during an anatomy course [23].

<i>i</i> (Year)	Sample Size (Male)	Mean (Male)	SD (Male)	Sample Size (Female)	Mean (Female)	SD (Female)	$Y_i = MD$	SE	$\sigma_i^2 = SE^2$
1 (2015)	74	5.09	1.59	42	5.26	1.65	−0.17	0.3114	0.0970
2 (2016)	79	4.84	1.62	37	5.42	1.69	−0.58	0.3272	0.1071
3 (2018)	79	4.81	1.54	34	5.26	1.69	−0.45	0.3253	0.1058
4 (2019)	74	4.86	1.62	33	5.61	1.58	−0.75	0.3366	0.1133
5 (2022)	73	4.79	1.68	37	5.35	1.83	−0.56	0.3494	0.1221

NOTE: Sample sizes are the number of medical students. Means are the mean scores. SDs are the standard deviations of the scores. MD is the mean difference between male and female (male–female) scores. SE is computed as the square root of the pooled variance using the SDs of male and female groups.

We applied Theorem 4 to the dataset of Table 1 to check the consistency of $\hat{\mu}_n$. First, note that the sequence $\{\sigma_i^2\}_{i=1}^5$ is increasing (Table 1; Figure 2) so that the model $\sigma_i^2 = ci^\alpha$ is applicable for $\alpha > 0$. Figure 2 shows that the parameters c and α were estimated by the LSE regressing $\{\log(\sigma_i^2)\}_{i=1}^5$ on $\{\log(i)\}_{i=1}^5$. Thus, the LSE resulted in $(\hat{c}, \hat{\alpha}) = (0.0964, 0.13)$ and the coefficient of determination (R-squared) was 0.87. Therefore, 87% of $\{\sigma_i^2\}_{i=1}^5$ was explained by the fitted value $\hat{c}i^{\hat{\alpha}}$. By applying Theorem 4, as $\hat{\alpha} = 0.13 \leq 1$, we conclude that $\hat{\mu}_n$ is consistent.

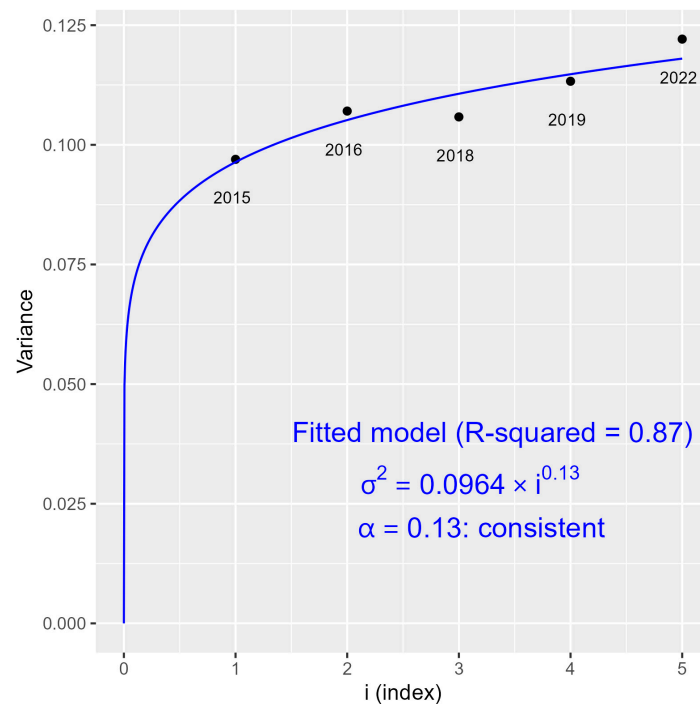


Figure 2. Observed value σ_i^2 vs. fitted value $\hat{c}i^{\hat{\alpha}}$ based on the allergic reaction data. The LSE $(\hat{c}, \hat{\alpha}) = (0.0964, 0.13)$ was obtained for the sequence $\{\log(\sigma_i^2)\}_{i=1}^5$ against $\{\log(i)\}_{i=1}^5$.

4.2. Diabetes Data

We analyzed a dataset from pregnant women with diabetes, which is available from Dingena et al. [24]. Dingena et al. [24] conducted a meta-analysis to examine the influence of lifestyle interventions on dysglycemia. Table 2 shows the available information from eight studies that examined the effect of the intake of nutritional supplements on fasting plasma glucose (mmol/L). Each study reports the mean difference (MD) between the intervention group and the control group.

Table 2. The summary of 8 studies that examined the mean difference (MD) between the intervention group and the control group for pregnant women with diabetes [24].

Study	Sample Size	$Y_i = \text{MD (mmol/L)}$	SE	$\sigma_i^2 = \text{SE}^2$
Aslfalah 2020	60	−0.70	0.0256	0.0007
Fei 2014	97	−0.47	0.1224	0.0150
Hajimoosayi 2020	70	−0.20	0.0816	0.0067
Jamilian 2018	40	−0.40	0.1786	0.0319
Jamilian 2019	60	−0.10	0.0765	0.0059
Jamilian 2020	51	−0.33	0.0918	0.0084
Lindsay 2015	100	0.01	0.0867	0.0075
Ostadmohammadi 2019	54	−0.20	0.1633	0.0267

NOTE: Sample sizes are the number of pregnant women with diabetes. MD is the mean difference between the intervention group and the control group. SE is the standard error of the ML.

Let Y_i ($i = 1, \dots, 8$) be the MD of fasting plasma glucose (mmol/L) between the intervention group and the control group as previously obtained from the original reference. Let $\sigma_i^2 = V(Y_i)$ be the square of the SE of Y_i , which we calculated from the 95% confidence interval ($\text{SE} = |\text{CI}| / 2 / 1.96$).

We applied Theorem 4 to check the consistency of $\hat{\mu}_n$ to the dataset of Table 2. To this end, we fitted the model $\sigma_i^2 = ci^\alpha$, where $c > 0$ and $-\infty < \alpha < \infty$ using the increasing sequence $\{\log(\sigma_i^2)\}_{i=1}^8$ against $\{\log(i)\}_{i=1}^8$. The LSE becomes $(\hat{c}, \hat{\alpha}) = (0.0009, 1.63)$ as shown in Figure 3. The coefficient of determination (R-squared) was 0.91, showing that

91% of $\{\sigma_i^2\}_{i=1}^8$ are explained by the fitted value $\hat{c}i^{\hat{\alpha}}$. Therefore, by applying Theorem 4 with $\hat{\alpha} = 1.63 > 1$, we conclude that $\hat{\mu}_n$ is not consistent.

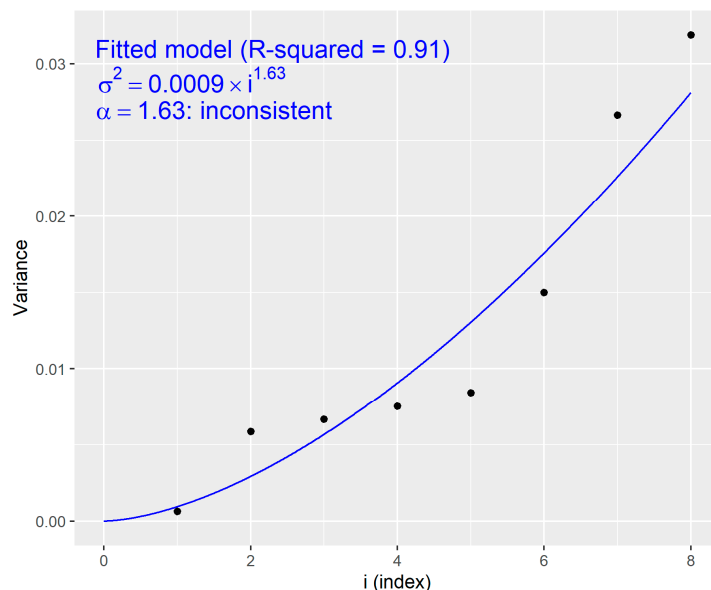


Figure 3. Observed value σ_i^2 vs. fitted value $\hat{c}i^{\hat{\alpha}}$ based on the diabetes data. The LSE $(\hat{c}, \hat{\alpha}) = (0.0009, 1.63)$ was obtained for the increasing sequence $\{\log(\sigma_i^2)\}_{i=1}^8$ against $\{\log(i)\}_{i=1}^8$.

4.3. COVID-19 Data

We analyze a dataset from COVID-19 pneumonia patients, which is available from Pranata et al. [7]. Their studies examined the effect of hypertension on mortality for patients with COVID-19 pneumonia. One of their conclusions was that hypertension increases mortality. We summarize the data consisting of 11 published studies (Table 3).

Table 3. Summary of the 11 studies (shown by the author and publication year) on COVID-19 patients for examining the effects of hypertension on mortality.

Study	Sample Size	$Y_i = \log(\text{RR})$	SE	$\sigma_i^2 = \text{SE}^2$
Akbari 2020	440	0.6881	0.6732	0.4532
Bai 2000	127	0.5933	0.2754	0.0758
Cao 2020	102	1.1756	0.2821	0.0796
Chen 2020	123	0.5365	0.2493	0.0621
Chen T 2020	274	0.6780	0.1713	0.0294
Fu 2020	200	0.5878	0.3302	0.1090
Grasselli 2020	1591	0.4637	0.0956	0.0091
Li 2020	102	0.5247	0.3272	0.1071
Luo 2020	403	1.2326	0.1489	0.0222
Yuan 2020	27	2.8904	1.4263	2.0344
Zhou 2020	191	1.1378	0.2097	0.0440

NOTE: Sample sizes are the number of patients with COVID-19. $\log(\text{RR})$ is the log of the risk ratio for examining the association (mortality vs. hypertension). SE is the standard error of the $\log(\text{RR})$. SE is the standard error of the $\log(\text{RR})$.

Let $Y_i, i = 1, \dots, 11$, be the log of the risk ratio (RR) for examining the association (mortality vs. hypertension) as previously obtained from the original reference. Let $\sigma_i^2 = V(Y_i)$ be the square of the SE for $i = 1, \dots, 11$, also quoted from the original reference. Table 3 summarizes all the available data from the 11 studies to perform fixed-effect meta-analyses.

We applied Theorem 4 to examine the consistency of the estimator $\hat{\mu}_n$ for this data example. We first fitted the model $\sigma_i^2 = ci^\alpha$, where $c > 0$ and $-\infty < \alpha < \infty$. Figure 4 displays the observed value σ_i^2 against the fitted value $\hat{c}i^{\hat{\alpha}}$, where $(\hat{c}, \hat{\alpha}) = (1.69, -1.91)$ were obtained by the LSE for the decreasing sequence $\{\log(\sigma_i^2)\}_{i=1}^{11}$ against $\{\log(i)\}_{i=1}^{11}$.

We observe that the LSE is fitted very well since the coefficient of determination (R-squared) is 0.94. That is, 94% of $\{\sigma_i^2\}_{i=1}^{11}$ is explained by the model $\hat{c}i^{\hat{\alpha}}$. Since $\hat{\alpha} = -1.91$ is less than one, by Theorem 4, the estimator $\hat{\mu}_n$ is consistent.

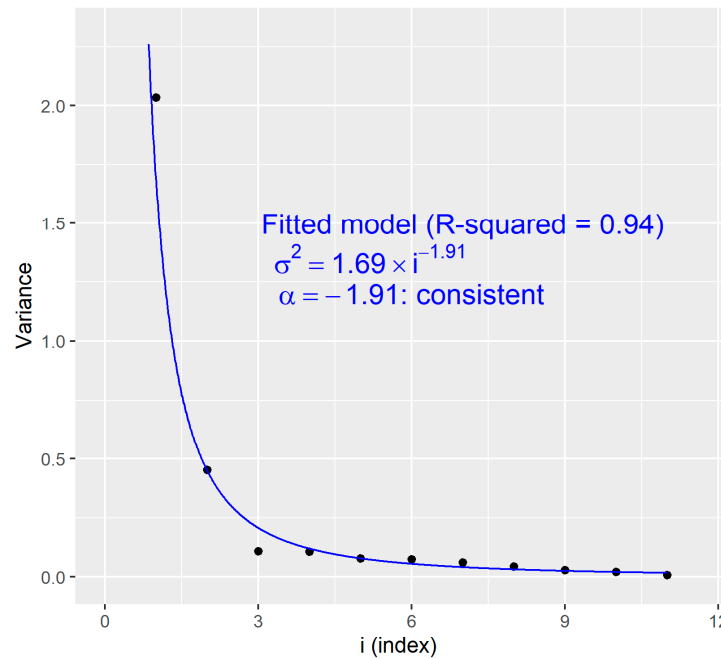


Figure 4. Observed value σ_i^2 vs. fitted value $\hat{c}i^{\hat{\alpha}}$ based on the COVID-19 data. The LSE $(\hat{c}, \hat{\alpha}) = (1.69, -1.91)$ were obtained for the decreasing sequence $\{\log(\sigma_i^2)\}_{i=1}^{11}$ against $\{\log(i)\}_{i=1}^{11}$.

5. Extension to Unknown Variances

This section extends our theory (Section 3) to the case of unknown variances. Recall that we observe a random variable Y_i having the common mean $\mu = E(Y_i)$ and variance $\sigma_i^2 = V(Y_i) > 0, i = 1, 2, \dots, n$. In this section, we assume that both μ and σ_i^2 are unknown, where σ_i^2 is estimated by $\hat{\sigma}_i^2$ (see Appendix A for an example for the estimator) and μ is estimated by

$$\hat{\mu}_n^* = \frac{\sum_{i=1}^n (\hat{\sigma}_i^2)^{-1} Y_i}{\sum_{i=1}^n (\hat{\sigma}_i^2)^{-1}}$$

Unlike $\hat{\mu}_n$, the estimator $\hat{\mu}_n^*$ entails additional variations by a random variable $\hat{\sigma}_i^2$. Appendix A provides an example in which $\hat{\sigma}_i^2 \sim \sigma_i^2 \chi_{v_i}^2 / v_i$, where v_i is the degree of freedom. This example corresponds to a meta-analysis, where Y_i is a mean difference and hence $\hat{\sigma}_i^2$ the pooled variance (Section 4.1). In this case, $E(\hat{\sigma}_i^2) = \sigma_i^2$, and $\hat{\sigma}_i^2$ is independent of Y_i . The estimator $\hat{\mu}_n^*$ is known as the Graybill-Deal estimator [25,26].

To show the consistency of $\hat{\mu}_n^*$, we apply Chebychev’s inequality conditional on the sequence $\hat{\sigma}_1^2, \hat{\sigma}_2^2, \dots$ so that

$$P_{\mu, \sigma_1, \sigma_2, \dots} (|\hat{\mu}_n^* - \mu| > \varepsilon) = E_{\sigma_1, \sigma_2, \dots} [P_{\mu} (|\hat{\mu}_n^* - \mu| > \varepsilon | \hat{\sigma}_1^2, \hat{\sigma}_2^2, \dots)] \leq \frac{1}{\varepsilon^2} E_{\sigma_1, \sigma_2, \dots} \left[\frac{1}{\sum_{i=1}^n (\hat{\sigma}_i^2)^{-1}} \right].$$

Therefore, $P_{\mu, \sigma_1, \sigma_2, \dots} (|\hat{\mu}_n^* - \mu| > \varepsilon) \rightarrow 0$ if the right-hand side goes to zero. The following theorem arises:

Theorem 5: *The common mean estimator $\hat{\mu}_n^*$ is consistent if*

$$\lim_{n \rightarrow \infty} E_{\sigma_1, \sigma_2, \dots} \left[\frac{1}{\sum_{i=1}^n (\hat{\sigma}_i^2)^{-1}} \right] = 0.$$

An example of applying Theorem 5 is the case of a bounded sequence so that here there exists a number $M > 0$ such that $\hat{\sigma}_i^2 \leq M \forall i$. Then, $(\hat{\sigma}_i^2)^{-1} \geq M^{-1} \forall i$. Thus,

$$\frac{1}{\sum_{i=1}^n (\hat{\sigma}_i^2)^{-1}} \leq \frac{M}{n} \rightarrow 0$$

as $n \rightarrow \infty$. Indeed, this type of bounded sequence condition was imposed for some simulation studies [13,14,20].

6. Conclusions and Discussion

The literature has not explained regularity conditions for the consistency of estimating a common mean in fixed-effect meta-analyses, even though they provide a theoretical basis for meta-analyses. In this article, we provide five versions of regularity conditions (in Theorems 1–5) for making the common mean estimator to be consistent in fixed-effect meta-analyses. We conclude that, by well-regularizing the variances of studies, consistency can be achieved. On the other hand, we also reveal the conditions to make the estimator inconsistent, where the variances of studies fail to be regularized. These findings actually mean that readers better check the consistency when performing fixed-effect meta-analyses. For a more practical level, our findings facilitate the well-regularized variances by avoiding extremely small variances in studies.

We analyzed three real datasets to illustrate the main theorem (Theorem 4) that can determine the consistency or inconsistency of the common mean estimator via a simple linear model. The first and third datasets supported the consistency of the common mean estimator. On the other hand, the second data did not support the consistency of the estimator since the variances of the individual studies increased toward infinity too fast. The first dataset also exhibited increasing variances, yet its speed was slow enough to justify the consistency. The problem with the second data is that the meta-analysis accumulates more and more inaccurate studies. However, this inconsistency of the second example was stated solely for $n = 11$ studies. Here, an implicit assumption is that the variances of the studies keep growing with $n \rightarrow \infty$. Unfortunately, this assumption cannot be checked only by a finite number of observed studies. Hence, our conclusion of the inconsistency becomes speculative.

An important future work is an extension of the consistency properties to bivariate, trivariate, and multivariate meta-analyses [13,14,27–29]. Our current results on a univariate meta-analysis may not directly carry over to these multivariate settings since the estimator of the multivariate common means is no longer expressed as the weighted sum of the independent variables unless the multivariate normal distribution is imposed as in [29]. Instead, the estimator takes the form of the numerical maximization of the likelihood function [13,14,27,28]. The estimator becomes an even more complex form under some parameter restrictions [30,31]. Furthermore, the choice of parametric copulas is a key element in determining the form of the likelihood, such as the FGM copula [13], the Clayton copula [14], the Gaussian copula [28], and vine copulas [27], all of which were already adopted in meta-analyses. Other newly developed copulas not yet applied to meta-analysis can also be tried, such as the trigonometric copulas [32], generalized FGM copula [33], and Celebioglu–Cuadras copula [34]. More efforts are necessary to work on multivariate

meta-analysis in order to establish the conditions/assumptions of the consistency of the multivariate common means.

Another important future work is an extension to fixed-effect meta-regression models, including fixed-effect structural equation models [1,5,27,35,36]. In the presence of explanatory variables, the common mean parameter could be written as a linear predictor. In these meta-regression models, regularity conditions for the consistency of regression coefficients were largely unexplored and, thus, should be clarified as we have in Theorems 1–5.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/axioms12050503/s1>, the R code for the simulation and data analyses.

Author Contributions: Conceptualization, T.E.; formal analysis, N.T. and T.E.; funding acquisition, T.E.; methodology, N.T. and T.E.; supervision, T.E.; writing—original draft, N.T. and T.E. All authors have read and agreed to the published version of the manuscript.

Funding: This work was financially supported by JSPS KAKENHI (22K11948).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All the results in this article are reproducible by the R code available in Supplementary Materials.

Acknowledgments: We thank the three reviewers for their helpful comments. We also thank Yoshiko Konno (Department of Mathematics, Osaka Metropolitan University, Japan) for his helpful comments on theoretical properties and English corrections. We also thank Mihoko Mori (School of Medicine, Kurume University, Japan) for providing us with the allergic reaction data (Section 4.1).

Conflicts of Interest: The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Appendix A. Pooled Variance Estimator

Recall that the mean difference is defined as $Y_i = \bar{Y}_{i1} - \bar{Y}_{i2} = \sum_{j=1}^{n_{i1}} Y_{ij1}/n_{i1} - \sum_{j=1}^{n_{i2}} Y_{ij2}/n_{i2}$, where Y_{ijk} is the j -th individual observation and n_{ik} is the sample size from the k -th group in the i -th study. We assume that $V(Y_{ij1}) = V(Y_{ij2}) = \tau^2$. Then, $\sigma_i^2 = V(Y_i) = \tau^2(1/n_{i1} + 1/n_{i2})$, where τ^2 is unbiasedly estimated by the pooled variance

$$\hat{\tau}_i^2 = \frac{1}{n_{i1} + n_{i2} - 2} \left\{ \sum_{j=1}^{n_{i1}} (Y_{ij1} - \bar{Y}_{i1})^2 + \sum_{j=1}^{n_{i2}} (Y_{ij2} - \bar{Y}_{i2})^2 \right\} \sim \tau^2 \frac{\chi_{n_{i1}+n_{i2}-2}^2}{n_{i1} + n_{i2} - 2}.$$

Thus,

$$\hat{\sigma}_i^2 = \hat{\tau}_i^2 \left(\frac{1}{n_{i1}} + \frac{1}{n_{i2}} \right) \sim \sigma_i^2 \frac{\chi_{n_{i1}+n_{i2}-2}^2}{n_{i1} + n_{i2} - 2}.$$

Appendix B.

Proof of Theorem 3. It can be shown that

$$\lim_{n \rightarrow \infty} P(|\hat{\mu}_n - \mu| > \varepsilon) = 2 \lim_{n \rightarrow \infty} \Phi \left(-\varepsilon \sqrt{\sum_{i=1}^n (\sigma_i^2)^{-1}} \right) \tag{A1}$$

where

$$\Phi(z) = \int_{-\infty}^z \frac{1}{\sqrt{2\pi}} \exp \left(-\frac{u^2}{2} \right) du$$

is the distribution function of the standardized normal distribution. Therefore, the left-hand side of Equation (A1) is zero if $\lim_{n \rightarrow \infty} \sum_{i=1}^n (\sigma_i^2)^{-1} = \infty$. If $\lim_{n \rightarrow \infty} \sum_{i=1}^n (\sigma_i^2)^{-1} < \infty$, by the completeness axiom for an increasing and bounded sequence, $\lim_{n \rightarrow \infty} \sum_{i=1}^n (\sigma_i^2)^{-1} = c$ for a real number $c > 0$. Therefore, the left-hand side of Equation (A1) is nonzero. □

Appendix C.

Proof of Theorem 4. Under the assumption of Theorem 4,

$$\lim_{n \rightarrow \infty} \sum_{i=1}^n (\sigma_i^2)^{-1} = c^{-1} \lim_{n \rightarrow \infty} \sum_{i=1}^n \frac{1}{i^\alpha} = c^{-1} \zeta(\alpha),$$

where $\zeta(\alpha)$ is the Riemann zeta function. It is known that $\zeta(\alpha) = \infty$ if and only if $\alpha \leq 1$. Additionally, $\zeta(\alpha)$ converges to a real number if $\alpha > 1$. This completes the proof. \square

References

- Borenstein, M.; Hedges, L.V.; Higgins, J.P.; Rothstein, H.R. *Introduction to Meta-Analysis*; John Wiley & Sons: Hoboken, NJ, USA, 2011.
- Kaiser, T.; Menkhoff, L. Financial Education in Schools: A Meta-analysis of Experimental Studies. *Econ. Educ. Rev.* **2020**, *78*, 101930. [[CrossRef](#)]
- Leung, Y.; Oates, J.; Chan, S.P. Voice, Articulation, and Prosody Contribute to Listener Perceptions of Speaker Gender: A Systematic Review and Meta-analysis. *J. Speech Lang. Hear. Res.* **2018**, *61*, 266–297. [[CrossRef](#)]
- DerSimonian, R.; Laird, N. Meta-analysis in Clinical Trials Revisited. *Contemp. Clin. Trials* **2015**, *45*, 139–145. [[CrossRef](#)]
- Fleiss, J.L. The Statistical Basis of Meta-analysis. *Stat. Methods Med. Res.* **1993**, *2*, 121–145. [[CrossRef](#)]
- Reyna-Villasmil, E.; Caponcello, M.G.; Maldonado, N.; Olivares, P.; Caroccia, N.; Bonazzetti, C.; Tazza, B.; Carrara, E.; Giannella, M.; Tacconelli, E.; et al. Association of Patients' Epidemiological Characteristics and Comorbidities with Severity and Related Mortality Risk of SARS-CoV-2 Infection: Results of an Umbrella Systematic Review and Meta-Analysis. *Biomedicines* **2022**, *10*, 2437. [[CrossRef](#)]
- Pranata, R.; Lim, M.A.; Huang, I.; Raharjo, S.B.; Lukito, A.A. Hypertension is Associated with Increased Mortality and Severity of Disease in COVID-19 Pneumonia: A Systematic Review, Meta-analysis and Meta-regression. *J. Renin-Angiotensin-Aldosterone Syst.* **2020**, *21*, 1470320320926899. [[CrossRef](#)] [[PubMed](#)]
- Wang, Y.; Kala, M.P.; Jafar, T.H. Factors Associated with Psychological Distress During the Coronavirus Disease 2019 (COVID-19) Pandemic on the Predominantly General Population: A Systematic Review and Meta-analysis. *PLoS ONE* **2020**, *15*, e0244630. [[CrossRef](#)]
- Rice, K.; Higgins, J.P.; Lumley, T. A Re-evaluation of Fixed Effect (s) Meta-analysis. *J. R. Stat. Soc. Ser. A* **2018**, *181*, 205–227. [[CrossRef](#)]
- Lehmann, E.L. *Elements of Large-Sample Theory*; Springer Science & Business Media: Berlin, Germany, 2010.
- Serfling, R.J. *Approximation Theorems of Mathematical Statistics*; John Wiley & Sons: Hoboken, NY, USA, 1980.
- Shao, J. *Mathematical Statistics*; Springer Science & Business Media: New York, NY, USA, 2003.
- Shih, J.H.; Konno, Y.; Chang, Y.-T.; Emura, T. Estimation of a Common Mean Vector in Bivariate Meta-Analysis under the FGM copula. *Statistics* **2019**, *53*, 673–695. [[CrossRef](#)]
- Shih, J.H.; Konno, Y.; Chang, Y.T.; Emura, T. Copula-based Estimation Methods for a Common Mean Vector for Bivariate Meta-analyses. *Symmetry* **2002**, *14*, 186. [[CrossRef](#)]
- Shinozaki, N.; Chang, Y.T. Minimality of Empirical Bayes Estimators Shrinking Toward the Grand Mean when Variances are Unequal. *Commun. Stat.-Theor. Methods* **1996**, *25*, 183–199. [[CrossRef](#)]
- Singh, H.P.; Vishwakarma, G.K. A Family of Estimators of Population Mean Using Auxiliary Information in Stratified Sampling. *Commun. Stat.-Theor. Methods* **2008**, *37*, 1038–1050. [[CrossRef](#)]
- Malekzadeh, A.; Kharrati-Kopaei, M. Inferences on the Common Mean of Several Normal Populations under Hetero-scedasticity. *Comput. Stat.* **2018**, *33*, 1367–1384. [[CrossRef](#)]
- Bradley, R.A.; Gart, J.J. The Asymptotic Properties of ML Estimators when Sampling from Associated Populations. *Biometrika* **1962**, *49*, 205–214. [[CrossRef](#)]
- Emura, T.; Hu, Y.H.; Konno, Y. Asymptotic Inference for Maximum Likelihood Estimators under the Special Exponential Family with Double-truncation. *Stat. Pap.* **2017**, *58*, 877–909. [[CrossRef](#)]
- Kontopantelis, E.; Reeves, D. Performance of Statistical Methods for Meta-analysis when True Study Effects are Non-normally Distributed: A Simulation Study. *Stat. Methods Med. Res.* **2010**, *21*, 409–426. [[CrossRef](#)]
- Taketomi, N.; Konno, Y.; Chang, Y.T.; Emura, T. A Meta-analysis for Simultaneously Estimating Individual Means with Shrinkage, Isotonic Regression and Pretests. *Axioms* **2021**, *10*, 267. [[CrossRef](#)]
- Taketomi, N.; Michimae, H.; Chang, Y.T.; Emura, T. meta. Shrinkage: An R Package for Meta-analyses for Simultaneously Estimating Individual Means. *Algorithms* **2022**, *15*, 26. [[CrossRef](#)]
- Mori, M.; Kakuma, T. Development of a Prediction Model for Subjective Physical Symptoms Induced during Systematic Anatomy Practice among Medical Students. *Kurume Med. J.* **2023**; in press.
- Dingena, C.F.; Arofikina, D.; Campbell, M.D.; Holmes, M.J.; Scott, E.M.; Zulyniak, M.A. Nutritional and Exercise-Focused Lifestyle Interventions and Glycemic Control in Women with Diabetes in Pregnancy: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Nutrients* **2023**, *15*, 323. [[CrossRef](#)]

25. Pal, N.; Lin, J.J.; Chang, C.H.; Kumar, S. A revisit to the common mean problem: Comparing the maximum likelihood estimator with the Graybill–Deal estimator. *Comput. Stat. Data Anal.* **2007**, *51*, 5673–5681. [[CrossRef](#)]
26. Sinha, B.K.; Hartung, J.; Knapp, G. *Statistical Meta-Analysis with Applications*; John Wiley & Sons: Hoboken, NJ, USA, 2011.
27. Nikoloulopoulos, A.K. A Multinomial Quadrivariate D-vine Copula Mixed Model for Meta-analysis of Diagnostic Studies in the Presence of Non-evaluable Subjects. *Stat. Methods Med. Res.* **2020**, *29*, 2988–3005. [[CrossRef](#)] [[PubMed](#)]
28. Yamaguchi, Y.; Maruo, K. Bivariate Beta-binomial Model using Gaussian Copula for Bivariate Meta-analysis of Two Binary Outcomes with Low incidence. *Jpn. J. Stat. Data. Sci.* **2019**, *2*, 347–373. [[CrossRef](#)]
29. Mavridis, D.; Salanti, G. A Practical Introduction to Multivariate Meta-analysis. *Stat. Methods Med. Res.* **2013**, *22*, 133–158. [[CrossRef](#)] [[PubMed](#)]
30. Garg, N.; Misra, N. Estimation of Order Restricted Location/scale Parameters of a General Bivariate Distribution under General Loss Function: Some Unified Results. *Jpn. J. Stat. Data. Sci.* **2022**, *5*, 553–576. [[CrossRef](#)]
31. Jena, P.; Ranjan Tripathy, M. Estimating Positive Powers of the Scale Parameters under Order Restriction for Two Normal Populations with a Common Mean. *Statistics* **2022**, *56*, 598–630. [[CrossRef](#)]
32. Chesneau, C. Theoretical Study of Some Angle Parameter Trigonometric Copulas. *Modelling* **2022**, *3*, 140–163. [[CrossRef](#)]
33. Susam, S.O. A multi-parameter Generalized Farlie-Gumbel-Morgenstern Bivariate Copula Family via Bernstein Polynomial. *Hacet. J. Math. Stat.* **2022**, *51*, 618–631. [[CrossRef](#)]
34. Chesneau, C. Theoretical Contributions to Three Generalized Versions of the Celebioglu–Cuadras Copula. *Analytics* **2023**, *2*, 31–54. [[CrossRef](#)]
35. Cheung, M.W.L.; Chan, W. Meta-analytic Structural Equation Modeling: A Two-stage Approach. *Psychol. Methods* **2005**, *10*, 40. [[CrossRef](#)]
36. Standsyah, R.E.; Otok, B.W.; Suharsono, A. Fixed Effect Meta-Analytic Structural Equation Modeling (MASEM) Estimation Using Generalized Method of Moments (GMM). *Symmetry* **2021**, *13*, 2273. [[CrossRef](#)]

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