Alternative Test Procedures and Confidence Intervals on the Common Mean in the Fixed Effects Model for Meta–Analysis

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ABSTRACT *The best linear unbiased estimator of the common mean in heteroscedastic one–way fixed effects model exists only if the values of the variance components are known. In practice this does not hold and so far there exists no consensus on the most suitable test for the common mean parameter. With respect to the attained significance levels, the $t-$test proposed by Meier (1953) makes significant improvements when the sample sizes are large. In this paper, alternative tests and confidence intervals are proposed which use either the normal distribution or the $F-$distribution as reference distributions. Using analytical and simulation results, it is demonstrated that the tests proposed attain significance levels (confidence coefficients) closer to the prescribed value compared to some selected classical tests. An example on the effectiveness of a drug in the treatment of angina is given to demonstrate the application of the tests.*

1 Introduction

Testing hypothesis on the overall effect parameter, also known as the common mean parameter, μ, in meta–analysis is usually addressed in the context of either the fixed effects approach or the random effects approach. In the commonly used method for meta–analysis which goes back to Cochran (1937, 1954), to draw inference on the

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overall treatment effect, the normal distribution is taken as the reference distribution. However, Li, Shi and Roth (1994), Boeckenhoff and Hartung (1998) have demonstrated that the variance of the estimated overall effect is underestimated leading to too many significant results.
For estimators of μ, Cochran (1937) considered the unweighted mean, the weighted and the semi-weighted mean and the maximum likelihood estimator when the number of observations in each group is constant. Other authors who have investigated inference on μ in fixed effects models include: Cochran and Carroll (1953), Meier (1953), Norwood and Hinkelmann (1977), and Whitehead and Whitehead (1991).

In this article we present some tests and confidence intervals on the common mean, μ, in the unbalanced heteroscedastic one-way fixed effects model. A simulation study is conducted to judge the performance of the tests with regard to the attained significance levels. Further, the simulation study demonstrates that the commonly used test is liberal and the $t-$test proposed by Meier (1953) is liberal for small samples but performs well for relatively large samples. An example from Li et al. (1994) on the effectiveness of a drug named amlodipine in the treatment of angina is given to illustrate the application of the test procedures.

2 Model

Consider a situation where K studies are available, with y_i being a summary statistic from the ith study with associated degrees of freedom ν_i, $i = 1, \ldots, K$. For the fixed effects model, we shall assume that

$$y_i = \mu + e_i, \ i = 1, \ldots, K \geq 2, \tag{1}$$

where $e_1, \ldots, e_K$ are mutually independent and normally distributed random variables such that $e_i \sim (0, \theta_i), \ \theta_i > 0$, and μ is the common mean for all the K studies. In a typical meta–analysis, independent estimates of μ from the individual studies $\hat{\mu}_i = y_i$ are available and unbiased estimates of the error variances, ξ_i, are provided, where $\nu_i \cdot \xi_i/\theta_i \overset{approx}{\sim} \chi^2_{\nu_i}$, and using Patnaik (1949), $\nu_i = 2 \cdot \{E(\xi_i)\}^2/var(\xi_i)$, $i = 1, \ldots, K$, cf: the example in section 4. In studies with normally distributed outcomes, ξ_i are independent of y_i and if the ith study consists of a single arm (as in the one-way ANOVA model) then the ξ_i have an exact $\chi^2_{\nu_i}-$distribution, $i = 1, \ldots, K$. Define now $b_i = \omega_i/\omega_\Sigma$ with $\omega_\Sigma = \sum_{i=1}^K \omega_i, \ \omega_i = 1/\xi_i, \ i = 1, \ldots, K$. The estimate of

μ is $\hat{\mu}^* = \sum_{i=1}^{K} b_i\, y_i$ and for testing the hypothesis of no treatment effect, the test statistic

$$T = \hat{\mu}^* / \sqrt{1/\omega_\Sigma} \overset{approx}{\sim} N(0,1)$$

or the confidence interval

$$CI_T(\mu) : \left[\hat{\mu}^* - u_{1-\alpha/2}\sqrt{1/\omega_\Sigma},\, \hat{\mu}^* + u_{1-\alpha/2}\sqrt{1/\omega_\Sigma}\right],$$

is used, where $u_{1-\alpha/2}$ is the $(1-\alpha/2)-$quantile of a standard normal distribution. Under the normal distribution as the reference distribution, this test has been shown to be liberal, cf: for instance, Boeckenhoff and Hartung (1998).

If θ_i's are known, the best estimator of the common mean is $\hat{\mu} = \sum_{i=1}^{K} \beta_i\, y_i/\beta_\Sigma$, where $\beta_\Sigma = \sum_{i=1}^{K} \beta_i$ and $\beta_i = 1/\theta_i$, with variance $1/\beta_\Sigma$ which is usually estimated by $1/\omega_\Sigma$. Let the actual variance of $\hat{\mu}^*$ be denoted by $\mathcal{F}_{\hat{\mu}^*}(\theta)$. In simply using $1/\omega_\Sigma$ in the denominator of T, that is, to act as the variance of $\hat{\mu}^*$, two factors are overlooked: First, that $1/\beta_\Sigma$ is not the true variance of $\hat{\mu}^*$ and secondly, that $E(1/\omega_\Sigma) \leq 1/\beta_\Sigma$, cf: Meier (1953), Li et al. (1994), Boeckenhoff and Hartung (1998). Therefore, to obtain more justified tests on μ, there is need to obtain more reliable estimates of $\mathcal{F}_{\hat{\mu}^*}(\theta)$, the true variance of $\hat{\mu}^*$.

3. Proposed Tests

3.1. Normal Distribution Based Tests

First consider the best linear unbiased estimator, $\hat{\mu}$, of μ and the Graybill and Deal (1959) estimator $\hat{\mu}^*$. Proceeding as in Kackar and Harville (1984), the estimation error in estimating μ by $\hat{\mu}^*$ can be partitioned into two parts, namely, $\hat{\mu}^* - \mu = (\hat{\mu} - \mu) + (\hat{\mu}^* - \hat{\mu})$. Due to the independence of $y = (y_1, \ldots, y_K)'$ and $\xi = (\xi_1, \ldots, \xi_K)'$, it is clear that $\hat{\mu} - \mu$ and $\hat{\mu}^* - \hat{\mu}$ are also statistically independent. Therefore,

$$E(\hat{\mu}^* - \mu)^2 \;=\; E(\hat{\mu} - \mu)^2 + E(\hat{\mu}^* - \hat{\mu})^2 = \frac{1}{\beta_\Sigma} + E(\hat{\mu}^* - \hat{\mu})^2 . \qquad (2)$$

Clearly $1/\beta_\Sigma$ underestimates $\mathcal{F}_{\hat{\mu}^*}(\vartheta)$ by an amount $E(\hat{\mu}^* - \hat{\mu})^2$. Expanding $\hat{\mu}^*$ in a Taylor series in ξ about θ gives

$$\hat{\mu}^* = \hat{\mu} + \sum_{i=1}^{p} (\xi_i - \theta_i) \cdot \frac{\partial \hat{\mu}}{\partial \theta_i} + \frac{1}{2} \cdot \sum_{i=1}^{p} (\xi_i - \theta_i)^2 \cdot \frac{\partial^2 \hat{\mu}}{\partial \theta_i^2} + \cdots$$

Retaining only up to the linear term in the expansion above, and on rearranging, squaring and taking expectations, we obtain the following approximation:

$$E(\hat{\mu}^* - \hat{\mu})^2 \approx E\left\{\sum_{i=1}^{p}(\xi_i - \theta_i)\cdot\frac{\partial\hat{\mu}}{\partial\theta_i}\right\}^2 .$$

It can be shown that

$$\frac{\partial\hat{\mu}}{\partial\theta_i} = \frac{\beta_i^2}{\beta_\Sigma}\cdot(\hat{\mu} - y_i), \quad \text{and} \quad E(\partial\hat{\mu}/\partial\theta_i)^2 = \frac{\beta_i^4}{\beta_\Sigma^2}\cdot\left(\theta_i - \frac{1}{\beta_\Sigma}\right) .$$

Due to the independence of all the elements of ξ and y,

$$E(\hat{\mu}^* - \hat{\mu})^2 \;=\; \sum_{i=1}^{K} E(\xi_i - \theta_i)^2 \cdot E\left(\frac{\partial\hat{\mu}}{\partial\theta_i}\right)^2 \approx \sum_{i=1}^{K} var(\xi_i)\cdot\frac{\beta_i^4}{\beta_\Sigma^2}\cdot\left(\theta_i - \frac{1}{\beta_\Sigma}\right). \quad (3)$$

In other words, we can express $\mathcal{F}_{\hat{\mu}^*}(\theta) = E(\hat{\mu}^* - \mu)^2$ as

$$\mathcal{F}_{\hat{\mu}^*}(\vartheta) \;\approx\; \frac{1}{\beta_\Sigma} + \sum_{i=1}^{K} var(\xi_i)\cdot\frac{\beta_i^4}{\beta_\Sigma^2}\left(\theta_i - \frac{1}{\beta_\Sigma}\right), \quad (4)$$

with a natural estimate given by

$$\mathcal{F}_{\hat{\mu}^*}(\xi) \;\approx\; \frac{1}{\omega_\Sigma} + \sum_{i=1}^{K} \widehat{var}(\xi_i)\cdot\frac{\omega_i^4}{\omega_\Sigma^2}\left(\xi_i - \frac{1}{\omega_\Sigma}\right). \quad (5)$$

Now, for testing the hypothesis of the nullity of the overall treatment efficacy, there exists a test T_1 such that when $\mu = 0$,

$$T_1 = \frac{\hat{\mu}^*}{\sqrt{\mathcal{F}_{\hat{\mu}^*,HK}(\xi)}} \overset{approx}{\sim} N(0,1)\,, \quad (6)$$

with the corresponding confidence interval given by

$$CI_1(\mu) : \left[\hat{\mu}^* - u_{1-\alpha/2}\sqrt{\mathcal{F}_{\hat{\mu}^*,HK}(\xi)},\; \hat{\mu}^* + u_{1-\alpha/2}\sqrt{\mathcal{F}_{\hat{\mu}^*,HK}(\xi)}\right],$$

where

$$\mathcal{F}_{\hat{\mu}^*,HK}(\xi) = \frac{1}{\omega_{\Sigma,c}} + \sum_{i=1}^{K} \widehat{var}(\xi_i)\cdot\frac{\omega_i^4}{\omega_\Sigma^2}\cdot\left(\xi_i - \frac{1}{\omega_\Sigma}\right), \quad (7)$$

and $\omega_{\Sigma,c} = \sum_{i=1}^{K}\omega_{i,c}$, with $\omega_{i,c} = (c_i\cdot\xi_i)^{-1}$, $c_i = \nu_i/(\nu_i - 2), i = 1,\ldots,K$, cf: equation (2.3) and Theorem (3.3) of Boeckenhoff and Hartung (1998). The estimator $1/\omega_{\Sigma,c}$ is considered as a bias adjusted estimator of $1/\beta_\Sigma$.

Another alternative is to proceed along the lines of Kenward and Roger (1997). A series expansion of $1/\omega_\Sigma$ in ξ about θ yields

$$\frac{1}{\omega_\Sigma} \approx \frac{1}{\beta_\Sigma} + \sum_{i=}^{K}(\xi_i - \theta_i)\frac{\partial(1/\omega_\Sigma)}{\partial\theta_i} + \frac{1}{2}\cdot\sum_{i=}^{K}(\xi_i - \theta_i)^2 \cdot \frac{\partial^2(1/\omega_\Sigma)}{\partial\theta_i^2}\,.$$

So that

$$\begin{aligned} E\left(\frac{1}{\omega_\Sigma}\right) &\approx \frac{1}{\beta_\Sigma} + \frac{1}{2}\cdot\sum_{i=}^{K} var(\xi_i)\cdot\frac{\partial^2(1/\omega_\Sigma)}{\partial\theta_i^2} \\ &= \frac{1}{\beta_\Sigma} + \sum_{i=}^{K} var(\xi_i)\cdot\frac{\beta_i^4}{\beta_\Sigma^2}\left(\frac{1}{\beta_\Sigma} - \theta_i\right). \end{aligned}$$

It is then obvious that to obtain an estimate of $\mathcal{F}_{\hat{\mu}^*}(\vartheta)$ we have to add to (4) another term which is equal to its correction term. That is, we now have

$$\mathcal{F}_{\hat{\mu}^*,KR}(\xi) = \frac{1}{\omega_\Sigma} + 2\cdot\sum_{i=}^{K}\widehat{var}(\xi_i)\cdot\frac{\omega_i^4}{\omega_\Sigma^2}\left(\xi_i - \frac{1}{\omega_\Sigma}\right), \tag{8}$$

so that to test $H_0 : \mu = 0$ versus $H_1 : \mu \neq 0$, we can also use the statistic

$$T_2 = \frac{\hat{\mu}^*}{\sqrt{\mathcal{F}_{\hat{\mu}^*,KR}(\xi)}} \overset{approx}{\sim} N(0,1), \tag{9}$$

or the confidence interval

$$CI_2(\mu) : \left[\hat{\mu}^* - u_{1-\alpha/2}\sqrt{\mathcal{F}_{\hat{\mu}^*,KR}(\xi)},\ \hat{\mu}^* + u_{1-\alpha/2}\sqrt{\mathcal{F}_{\hat{\mu}^*,KR}(\xi)}\right],$$

This was the idea of Kackar and Harville (1984) of estimating standard errors of estimators which was later used by Kenward and Roger (1997) in estimating fixed effects parameters in mixed models. Our idea, which led to $\mathcal{F}_{\hat{\mu}^*,HK}(\xi)$, is slightly different in that instead of making a second series expansion to obtain a bias corrected estimate of $1/\beta_\Sigma$, the first component in the expression for $\mathcal{F}_{\hat{\mu}^*}(\vartheta)$, we invoke the convexity arguments in Boeckenhoff and Hartung (1998) to obtain a bias corrected estimator of $1/\beta_\Sigma$, namely, $1/\omega_{\Sigma,c}$.

Table 1: Sample designs for $K = 3$ for the simulation results in Table 2 and 3.

	Sample sizes			Error variances		
	Study (Group)			Study (Group)		
Plan	1	2	3	1	2	3
A11	10	10	10	4	4	4
A12	10	10	10	1	3	5
A21	20	20	20	4	4	4
A22	20	20	20	1	3	5
B11	5	10	15	4	4	4
B12	5	10	15	1	3	5
B13	5	10	15	5	3	1
B21	10	20	30	4	4	4
B22	10	20	30	1	3	5
B23	10	20	30	5	3	1

To obtain $K = 6$ and $K = 9$, we make, respectively, one and two independent replications of $K = 3$. For example, for plan $B12$ the sample sizes for $K = 6$ are (5, 10, 15, 5, 10, 15) and the corresponding error variances (1, 3, 5, 1, 3, 5).

Remark 1

If we define

$$V_M = \frac{1}{\omega_\Sigma}\left\{1 + 4\sum_{i=1}^{K} \frac{\omega_i}{\hat{\nu}_i \cdot \omega_\Sigma}\left(1 - \frac{\omega_i}{\omega_\Sigma}\right)\right\},$$

to test $H_0 : \mu = 0$ against $H_1 : \mu \neq 0$, Meier's (1953) proposed the test

$$T_M = \frac{\hat{\mu}^*}{\sqrt{V_M}} \overset{approx}{\sim} t_{\hat{\nu}_M}, \tag{10}$$

where

$$\hat{\nu}_M = \frac{\omega_\Sigma^2}{\sum_{i=1}^{K} \omega_i^2 / \hat{\nu}_i},$$

and t_m is a t-distribution with m degrees of freedom. A confidence interval corresponding to this test is given by

$$CI_{T_M}(\mu) : \left[\hat{\mu}^* - t_{\hat{\nu}_M;1-\alpha/2}\sqrt{V_M},\ \hat{\mu}^* + t_{\hat{\nu}_M;1-\alpha/2}\sqrt{V_M}\right],$$

where $t_{m;1-\alpha/2}$ is the $(1-\alpha/2)-$quantile of a $t-$distribution with m degrees of freedom.

Attained significance levels by using T, T_M, T_1 and T_2 and patterns given in Table 1 for $K = 3$, 6 and 9 at nominal level $\alpha = 0.05$ are reported in Table 2 below. The attained confidence coefficients for the confidence intervals corresponding to the given test statistics can be obtained by taking $1 - \hat{\alpha}$, where $\hat{\alpha}$ is the attained significance level (this will also be true thereafter).

Table 2: Simulated significance levels (10 000 runs) for $K = 3$, 6, 9 at $\alpha = 0.05$ using test statistics T, T_M, T_1 and T_2.

Attained type I error rates, $\hat{\alpha}\%$												
	$K=3$				$K=6$				$K=9$			
Plan	T	T_M	T_1	T_2	T	T_M	T_1	T_2	T	T_M	T_1	T_2
A11	10.6	5.8	5.8	6.6	11.9	6.4	6.1	6.9	12.6	7.0	6.6	7.5
A12	9.9	5.5	5.6	7.2	11.7	6.5	6.4	7.4	11.9	6.6	6.3	7.3
A21	7.7	5.4	5.4	5.9	7.4	5.3	5.2	5.5	7.5	5.1	5.0	5.2
A22	7.4	5.4	5.5	6.2	7.5	5.1	5.0	5.4	7.8	5.2	5.1	5.5
B11	12.2	7.2	7.0	8.6	14.3	7.6	7.2	8.4	16.0	9.3	8.9	9.9
B12	13.4	6.7	6.6	9.3	16.2	8.2	7.8	10.2	17.4	8.6	7.8	10.1
B13	10.1	6.5	6.6	7.8	11.2	7.0	6.9	7.8	11.9	7.4	7.2	8.3
B21	7.4	5.2	5.2	5.8	8.2	5.5	5.4	5.7	8.9	6.1	6.0	6.3
B22	8.3	5.5	5.6	6.5	8.8	5.6	5.6	5.9	9.4	5.8	5.7	6.2
B23	7.2	5.2	5.3	5.8	6.8	5.2	5.2	5.4	7.1	5.4	5.3	5.5

From Table 2, for $K = 3$, 6, 9, the commonly used test in meta-analysis, T, always overstates the significance level. The other tests, T_M, T_1, and T_2 lead to some improvements in the attained significance levels. However, for patterns A11, A12, B11, B12 and B13, there is still unacceptable liberality, using [4%, 6%] as the bounds for acceptable attained significance levels (see for example, De Beuckelaer, 1996), which increases with K.

3.2. $F-$Distribution Based Tests

The unacceptable levels attained by the test statistics in section 2.1 require that better alternatives test be sort. Alternative and more conservative procedures can be obtained by tackling the problem along the lines of Kenward and Roger (1997) and Meier (1953).

Let us consider the function $g(\hat{\mu}^*) = \hat{\mu}^{*2}/(1/\omega_\Sigma)$, that is when $H_0 : \mu = 0$ is true. Using a Taylor series expansion of $1/(1/\omega_\Sigma) = \omega_\Sigma$, it can be shown

$$E(\omega_\Sigma) \approx \beta_\Sigma + \frac{1}{2} \cdot E\left\{\sum_{i=1}^{K} (\xi_i - \theta_i)^2 \frac{\partial^2 \beta_\Sigma}{\partial \theta_i^2}\right\} .$$

On using the relationship $E(X) = E_Y\{E(X|Y)\}$, expanding and ignoring the dependence between $\hat{\mu}^*$ and $1/\omega_\Sigma$ gives

$$E\{g(\hat{\mu}^*)\} = 1 + \frac{1}{\beta_\Sigma} \cdot \sum_{i=1}^{p} var(\xi_i) \cdot \frac{1}{\theta_i^3} . \tag{11}$$

The statistic $g(\hat{\mu}^*)$ is distributed as a $F-$variable with 1 and $\nu_{g(\hat{\mu}^*)}$ degrees of freedom. Which implies that we only have to estimate the denominator degrees of freedom , $\nu_{g(\hat{\mu}^*)}$, from the data. Equating the expected value of $g(\hat{\mu}^*)$ to the corresponding moment of the $F_{1,\nu_{g(\hat{\mu}^*)}}$ and solving, we obtain

$$\nu_{g(\hat{\mu}^*)} = 2 \cdot \frac{E\{g(\hat{\mu}^*)\}}{E\{g(\hat{\mu}^*)\} - 1}, \tag{12}$$

which can be estimated by $\hat{\nu}_{g(\hat{\mu}^*)} = 2 \cdot f(\hat{\mu}^*)/\{f(\hat{\mu}^*) - 1\}$, where

$$f(\hat{\mu}^*) \approx 1 + \frac{1}{\omega_{\Sigma,c}} \cdot \sum_{i=1}^{K} \widehat{var}(\xi_i) \cdot \frac{1}{\xi_i^3} .$$

So that for testing $H_0 : \mu = 0$ against $H_1 : \mu \neq 0$ we can use the test statistic

$$T_3 = g(\hat{\mu}^*) = \frac{\hat{\mu}^{*2}}{(1/\omega_\Sigma)} \overset{approx}{\sim} F_{1,\hat{\nu}_{g(\hat{\mu}^*)}} . \tag{13}$$

or the confidence interval

$$CI_3(\mu) : \left[\hat{\mu}^* - \sqrt{F_{1,\hat{\nu}_{g(\hat{\mu}^*)};1-\alpha} \cdot (1/\omega_\Sigma)},\ \hat{\mu}^* + \sqrt{F_{1,\hat{\nu}_{g(\hat{\mu}^*)};1-\alpha} \cdot (1/\omega_\Sigma)}\right],$$

where $F_{m_1,m_2;\kappa}$ is the $\kappa-$quantile of an $F-$distribution with m_1 and m_2 degrees of freedom.

We can also obtain another variant of the test above by applying the following theorem which is equivalent to that of Meier (1953, p. 64):

Theorem 1

If $x_1, \cdots, x_p$ are independently distributed with density functions

$$h_{\nu_i}(x_i) = \frac{\left(\frac{\nu_i}{2}\right)^{\nu_i/2}}{\Gamma\left(\frac{\nu_i}{2}\right)} \cdot x_i^{\frac{\nu_i}{2}-1} exp\left(-\frac{\nu_i x_i}{2}\right), \quad x_i > 0,$$

ν_i being the associated degrees of freedom, and $q(x_1, \cdots, x_p)$ is a rational function with no singularities for $x_i > 0$, then $E\{q(x_1, \cdots, x_p)\}$ can be expanded in a asymptotic series in $1/\nu_i$. Specifically,

$$E\{q(x_1, \cdots, x_p)\} = q(1, \cdots, 1) + \sum_{i=1}^{p} \frac{1}{\nu_i} \frac{\partial^2 q}{\partial x_i^2}|_{(1,\cdots,1)} + O\left(\sum_{i=1}^{p} \frac{1}{\nu_i^2}\right). \tag{14}$$

Consider now the function

$$g(\hat{\mu}^*) = \frac{\hat{\mu}^{*2}}{\omega_\Sigma^{-1}} = \frac{\left(\sum_{i=1}^p y_i/\xi_i\right)^2}{\sum_{i=1}^K 1/\xi_i}.$$

It is easy to notice that $x_i = \xi_i/\theta_i$ has the density $h_{\nu_i}(x_i)$ given above. Therefore, we have

$$g(\hat{\mu}^*) = \frac{\left\{\sum_{i=1}^K y_i/(\theta_i x_i)\right\}^2}{\sum_{i=1}^K 1/(\theta_i x_i)}.$$

By the independence of y_i and ξ_i, we can take the expectation of $g(\hat{\mu}^*)$ first with respect to y_i holding x_i fixed, and then with respect to x_i. Thus,

$$\begin{aligned} E\{g(\hat{\mu}^*)|x_i\} &= \frac{\sum_{i=1}^K E(y_i^2)/(\theta_i x_i)^2}{\sum_{i=1}^K 1/(\theta_i x_i)} \\ &= \frac{\sum_{i=1}^K 1/(\theta_i x_i^2)}{\sum_{i=1}^K 1/(\theta_i x_i)}. \end{aligned} \tag{15}$$

To the order $O\left(\sum_{i=1}^p \nu_i^{-2}\right)$, the expected value of the $g(\hat{\mu}^*)$ can now be written as

$$\begin{aligned} E\{g(\hat{\mu}^*)\} &= E\{g(\hat{\mu}^*)|1, \cdots, 1\} + \sum_{i=1}^K \frac{1}{\nu_i} \frac{\partial^2 E\{g(\hat{\mu}^*)|x_i\}}{\partial x_i^2}|_{(1,\cdots,1)} \\ &= 1 + \sum_{i=1}^K \frac{1}{\nu_i} \frac{\partial}{\partial x_i} \left[\frac{1}{\left(\sum_{i=1}^K 1/\theta_i x_i\right)^2} \left\{ \frac{1}{\theta_i x_i^2} \sum_{i=1}^K \frac{1}{\theta_i x_i^2} - \frac{2}{\theta_i x_i^3} \sum_{i=1}^K \frac{1}{\theta_i x_i} \right\} \right]_{(1,\cdots,1)} \end{aligned}$$

$$= \quad 1 + \frac{2}{\beta_\Sigma^2} \cdot \sum_{i=1}^{K} \frac{\beta_i}{\nu_i} \left(2\beta_\Sigma - \beta_i\right). \tag{16}$$

With these results we can now construct a test statistic to test $H_0 : \mu = 0$ against $H_1 : \mu \neq 0$, namely,

$$T_4 = \frac{\hat{\mu}^{*2}}{1/\omega_\Sigma} \overset{approx}{\sim} F_{1,\hat{\nu}_{g^*(\mu^*)}} \tag{17}$$

or a confidence interval

$$CI_4(\mu) : \left[\hat{\mu}^* - \sqrt{F_{1,\hat{\nu}_{g^*(\hat{\mu}^*)};1-\alpha} \cdot (1/\omega_\Sigma)},\ \hat{\mu}^* + \sqrt{F_{1,\hat{\nu}_{g^*(\hat{\mu}^*)};1-\alpha} \cdot (1/\omega_\Sigma)}\right].$$

where $\hat{\nu}_{g^*(\mu^*)} = 2 \cdot f^*(\hat{\mu}^*)/\{f^*(\hat{\mu}^*) - 1\}$, with

$$f^*(\hat{\mu}^*) = 1 + \frac{2}{\omega_{\Sigma,c}^2} \cdot \sum_{i=1}^{K} \frac{\omega_i}{\hat{\nu}_i} \left(2\omega_\Sigma - \omega_i\right).$$

3.3. Scaled $F-$Distribution Based Tests

Given that the estimate $1/\omega_\Sigma$ underestimates the variance of $\hat{\mu}^*$, the immediate implication is that $g(\hat{\mu}^*)$ would take larger values than expected and this partly explains why the statistic $g(\hat{\mu}^*)$ would exhibits unacceptable liberality. Therefore, a scaled version of $g(\hat{\mu}^*)$, say, $g_S(\hat{\mu}^*) = \varepsilon \cdot g(\hat{\mu}^*)$, where we will let the value of ε be determined by the data itself, could deliver acceptable levels. In other words, we now have

$$g_S(\hat{\mu}^*) = \varepsilon \cdot g(\hat{\mu}^*) \sim F_{1,\nu_\varepsilon};$$

where ε and ν_ε have to be determined from the data. The approach now would be to determine the first and second central moments of the approximating statistic $g_S(\hat{\mu}^*)$ using theorem 1 and equating them to the corresponding moments of an $F-$distribution with 1 and ν_ε degrees of freedom. Consequently,

$$E\{g_S(\hat{\mu}^*)\} = \varepsilon \cdot E\{g(\hat{\mu}^*)\} = \frac{\nu_\varepsilon}{\nu_\varepsilon - 2}.$$

That is,

$$\varepsilon = \frac{\nu_\varepsilon}{(\nu_\varepsilon - 2) \cdot E\{g(\hat{\mu}^*)\}}, \tag{18}$$

which can be estimated by

$$\hat{\varepsilon} = \frac{\hat{\nu}_\varepsilon}{(\hat{\nu}_\varepsilon - 2) \cdot f^*(\hat{\mu}^*)}$$

Next,

$$var\{g_S(\hat{\mu}^*)\} = \varepsilon^2 \cdot var\{g(\hat{\mu}^*)\} = \frac{2 \cdot \nu_\varepsilon^2(\nu_\varepsilon - 1)}{(\nu_\varepsilon - 4)(\nu_\varepsilon - 2)^2}.$$

Solving for ν_ε, we obtain

$$\nu_\varepsilon = \frac{6 \cdot [E\{g(\hat{\mu}^*)\}]^2}{var\{g(\hat{\mu}^*)\} - 2 \cdot [E\{g(\hat{\mu}^*)\}]^2} + 4. \tag{19}$$

Using again theorem 1, we get

$$\begin{aligned} var\{g(\hat{\mu}^*)|x_i\} &= \frac{1}{\left(\sum_{i=1}^K 1/\theta_i x_i\right)^2} \cdot var\left(\sum_{i=1}^K \frac{y_i}{\theta_i x_i}\right)^2 \\ &= \frac{2}{\left(\sum_{i=1}^K 1/\theta_i x_i\right)^2} \cdot \sum_{i=1}^K \frac{1}{\theta_i^2 x_i^4}. \end{aligned} \tag{20}$$

With now

$$var\{g(\hat{\mu}^*)|(1,\cdots,1)\} = \frac{2}{\beta_\Sigma^2} \cdot \sum_{i=1}^K \frac{1}{\theta_i^2},$$

and

$$\begin{aligned} \frac{\partial}{\partial x_i}[var\{g(\hat{\mu}^*)|x_i\}] &= \frac{2}{\left(\sum_{i=1}^p 1/\theta_i\right)^4} \cdot \left\{ \frac{2}{\theta_i x_i^2} \cdot \left(\sum_{i=1}^p \frac{1}{\theta_i x_i}\right) \cdot \left(\sum_{i=1}^p \frac{1}{\theta_i^2 x_i^4}\right) \right. \\ &\quad \left. - \frac{4}{\theta_i^2 x_i^5} \cdot \left(\sum_{i=1}^p \frac{1}{\theta_i x_i}\right)^2 \right\}, \end{aligned}$$

(see the appendix for the evaluation of $\partial[var\{g(\hat{\mu}^*)|x_i\}]/\partial x_i|_{(1,\cdots,1)}$), we get

$$\begin{aligned} var\{g(\hat{\mu}^*)\} &\approx var\{g(\hat{\mu}^*)|(1,\cdots,1)\} + \sum_{i=1}^K \frac{1}{\nu_i} \cdot \frac{\partial^2}{\partial x_i^2}[var\{g(\hat{\mu}^*)|x_i\}]|_{(1,\cdots,1)} \\ &= 2 \cdot \frac{1}{\beta_\Sigma^2} \left\{ \sum_{i=1}^K \beta_i^2 + 2 \cdot \frac{1}{\beta_\Sigma^2} \cdot \sum_{i=1}^K \frac{1}{\nu_i \cdot \theta_i^3} \left(10\theta_i \cdot \beta_\Sigma^2 \right.\right. \\ &\quad \left.\left. +3\ \theta_i \cdot \sum_{i=1}^K \beta_i^2 - 2\theta_i^2 \cdot \beta_\Sigma \cdot \sum_{i=1}^K \beta_i^2 - 8\beta_\Sigma \right)\right\}. \end{aligned} \tag{21}$$

A natural estimate of $var\{g(\hat{\mu}^*)\}$ is

$$\begin{aligned} \widehat{var}\{g(\hat{\mu}^*)\} &= \frac{2}{\omega_\Sigma^2} \left\{ \sum_{i=1}^K \omega_i^2 + \frac{2}{\omega_\Sigma^2} \cdot \sum_{i=1}^K \frac{\omega_i^3}{\nu_i} \left(10\xi_i \cdot \omega_\Sigma^2 \right.\right. \\ &\quad \left.\left. + 3\xi_i \cdot \sum_{i=1}^K \omega_i^2 - 2\xi_i^2 \cdot \omega_\Sigma \cdot \sum_{i=1}^K \omega_i^2 - 8\omega_\Sigma \right)\right\}. \end{aligned} \tag{22}$$

However, this estimate is expected to be biased and a bias correction of some sort is necessary. First, we propose to use the bias corrected estimate of $1/\beta_\Sigma$ wherever it appears in the expression for $var\{g(\hat{\mu}^*)\}$. Therefore, we get

$$\begin{aligned} V_1^* &= \frac{2}{\omega_{\Sigma,c}^2}\left\{\sum_{i=1}^K \omega_i^2 + \frac{2}{\omega_{\Sigma,c}^2}\cdot\sum_{i=1}^K \frac{\omega^3}{\hat{\nu}_i}\left(10\xi_i\cdot\omega_\Sigma^2\right.\right. \\ &\quad \left.\left. +\ 3\xi_i\cdot\sum_{i=1}^K\omega_i^2 -\ 2\xi_i^2\cdot\omega_\Sigma\cdot\sum_{i=1}^K\omega_i^2 - 8\omega_\Sigma\right)\right\}. \end{aligned} \tag{23}$$

Secondly, we can make a bias correction to the order of our expansions. Thus, let's consider the first term of $var\{g(\hat{\mu}^*)\}$, namely, $M(\xi) = 2\cdot\sum_{i=1}^K \omega_i^2/\omega_\Sigma^2$. Applying again theorem 1 yields

$$\begin{aligned} E\{M(\xi)|1,\cdots,1\} &= \frac{2}{\beta_\Sigma^2}\cdot\sum_{i=1}^K\beta_i^2, \\ \frac{\partial^2}{\partial x_i^2}E\{M(\xi)|1,\cdots,1\} &= \frac{4}{\theta_i^3}\cdot\frac{1}{\beta_\Sigma^4}\left(3\theta_i\cdot\beta_\Sigma^2 + 3\theta_i\cdot\sum_{i=1}^K\beta_i^2\right. \\ &\quad \left. -2\theta_i^2\beta_\Sigma\cdot\sum_{i=1}^K\beta_i^2 - 4\beta_\Sigma\right) \end{aligned}$$

So that

$$\begin{aligned} E\{M(\xi)\} &\approx \frac{2}{\beta_\Sigma^2}\left\{\sum_{i=1}^K\beta_i^2 + \frac{2}{\beta_\Sigma^2}\sum_{i=1}^K\frac{1}{\nu_i\cdot\theta_i^3}\left(3\theta_i\cdot\beta_\Sigma^2\right.\right. \\ &\quad \left.\left. +3\ \theta_i\cdot\sum_{i=1}^K\beta_i^2 - 2\theta_i^2\cdot\beta_\Sigma\cdot\sum_{i=1}^K\beta_i^2 - 4\beta_\Sigma\right)\right\}. \end{aligned}$$

Therefore, with a bias of order $O(\sum_{i=1}^K \nu_i^{-1})$, a bias corrected estimate of $var\{g(\hat{\mu}^*)\}$ is

$$V_2^* = \frac{2}{\omega_\Sigma^2}\cdot\left\{\sum_{i=1}^p\omega_i^2 + \frac{2}{\omega_\Sigma^2}\cdot\sum_{i=1}^K\frac{\omega_i^3}{\hat{\nu}_i}\left(7\xi_i\cdot\omega_\Sigma^2 - 4\omega_\Sigma\right)\right\}. \tag{24}$$

So, to test $H_0 : \mu = 0$ we can use the scaled test statistics

$$\begin{aligned} T_5 &= g_S(\hat{\mu}^*) \sim F_{1,\hat{\nu}_{\varepsilon,1}^*}, \\ T_6 &= g_S(\hat{\mu}^*) \sim F_{1,\hat{\nu}_{\varepsilon,2}^*} \end{aligned} \tag{25}$$

or the respective confidence intervals

$$CI_5(\mu) : \left[\hat{\mu}^* - \sqrt{F_{1,\hat{\nu}^*_{\varepsilon,1};1-\alpha} \cdot (1/\omega_\Sigma)/\hat{\varepsilon}}\,,\ \hat{\mu}^* + \sqrt{F_{1,\hat{\nu}^*_{\varepsilon,1};1-\alpha} \cdot (1/\omega_\Sigma)/\hat{\varepsilon}}\,\right],$$

$$CI_6(\mu) : \left[\hat{\mu}^* - \sqrt{F_{1,\hat{\nu}^*_{\varepsilon,2};1-\alpha} \cdot (1/\omega_\Sigma)/\hat{\varepsilon}}\,,\ \hat{\mu}^* + \sqrt{F_{1,\hat{\nu}^*_{\varepsilon,2};1-\alpha} \cdot (1/\omega_\Sigma)/\hat{\varepsilon}}\,\right],$$

with

$$\hat{\nu}_{\varepsilon,1} = 4 + \frac{6 \cdot f^{*2}(\hat{\mu}^*)}{V_1^* - 2 \cdot f^{*2}(\hat{\mu}^*)}, \quad \hat{\nu}_{\varepsilon,2} = 4 + \frac{6 \cdot f^{*2}(\hat{\mu}^*)}{V_2^* - 2 \cdot f^{*2}(\hat{\mu}^*)}.$$

However, we notice that if $V_1^* < 2 \cdot f^{*2}(\hat{\mu}^*)$, then it is possible that $\hat{\nu}_\varepsilon \leq 0$. To guard against this eventuality we propose the use of

$$\hat{\nu}^*_{\varepsilon,1} = 4 + \frac{6 \cdot f^{*2}(\hat{\mu}^*)}{|V_1^* - 2 \cdot f^{*2}(\hat{\mu}^*)|}, \quad \hat{\nu}^*_{\varepsilon,2} = 4 + \frac{6 \cdot f^{*2}(\hat{\mu}^*)}{|V_2^* - 2 \cdot f^{*2}(\hat{\mu}^*)|},$$

where $|b|$ represents the absolute value of b.

Table 3: Simulated significance levels (10 000 runs) for $K = 3$, 6, 9 at $\alpha = 0.05$ using test statistics T_3, T_4 T_5 and T_6.

Attained type I error rates, $\hat{\alpha}$%												
	$K = 3$				$K = 6$				$K = 9$			
Plan	T_3	T_4	T_5	T_6	T_3	T_4	T_5	T_6	T_3	T_4	T_5	T_6
A11	6.6	4.1	4.5	4.2	7.8	4.7	4.7	4.7	8.4	5.2	5.1	5.1
A12	6.5	4.3	4.5	4.3	7.4	4.5	4.5	4.4	7.7	4.9	4.8	4.8
A21	5.8	4.5	4.5	4.5	6.2	4.7	4.6	4.6	6.0	4.8	4.7	4.6
A22	5.9	5.0	5.1	5.0	5.6	5.0	4.9	4.9	5.9	4.5	4.5	4.5
B11	7.5	4.9	4.8	4.7	9.2	5.7	5.5	5.4	10.2	5.8	5.6	5.6
B12	7.3	4.2	4.0	4.0	9.0	4.9	4.4	4.4	9.3	5.5	4.8	4.7
B13	6.9	4.9	5.0	4.9	8.0	5.3	5.4	5.4	8.4	5.7	5.7	5.7
B21	5.9	5.0	5.0	5.0	6.1	4.8	4.8	4.7	6.0	4.7	4.7	4.7
B22	6.5	4.6	4.8	4.7	6.7	5.0	5.1	5.1	6.3	4.6	4.5	4.6
B23	5.7	4.9	4.9	4.9	5.8	5.0	5.0	5.0	5.8	5.1	5.0	5.0

From Table 3, the test T_3 is liberal, especially when the sample sizes are relatively small, that is, patterns A11, A12, B11, B12 and B13. The tests T_4, T_5 and T_6 always attain acceptable levels for $K = 3$, 6 and 9.

It should be mentioned here that significant differences in the tests given above are expected for small sample cases, of say ≤ 10. However, with larger samples one would expect to arrive at almost same conclusion by using any of the above test procedures.

4 Example

Just for demonstrating the procedures discussed, we consider the following example of clinical trials on the effectiveness of amlodipine in the treatment of angina. The data we use are taken from Li et al. (1994). A total of eight randomized clinical trials compared the change in work capacity for patients who received either the drug (amlodipine) or a placebo. The change in work capacity, for each patient, is the ratio of the exercise time after the intervention (amlodipine or placebo) to before receiving the intervention. The logarithms of the observed changes are assumed to be approximately normally distributed. The data and some summaries are given in Table 4 below.

Table 4: Change in work capacity in the treatment of angina.

Study	Amlodipine			Placebo				
	Sample Size $n_{i,a}$	Mean $y_{i,a}$	Variance $n_{i,a}\xi_{i,a}$	Sample Size $n_{i,p}$	Mean $y_{i,p}$	Variance $n_{i,p}\xi_{i,p}$	Mean Difference y_i	Variance ξ_i
1	46	0.2316	0.2256	48	-0.0027	0.0007	0.2343	0.0049
2	30	0.2811	0.1441	26	0.0270	0.1139	0.2541	0.0092
3	75	0.1894	0.1981	72	0.0443	0.4972	0.1451	0.0095
4	12	0.0930	0.1389	12	0.2277	0.0488	-0.1347	0.0156
5	32	0.1622	0.0961	34	0.0056	0.0955	0.1566	0.0058
6	31	0.1837	0.1246	31	0.0943	0.1734	0.0894	0.0096
7	27	0.6612	0.7060	27	-0.0057	0.9891	0.6669	0.0628
8	46	0.1366	0.1211	47	-0.0057	0.1291	0.1423	0.0054

In our calculations we have $y_i = y_{i,a} - y_{i,p}$, $\xi_i = \xi_{i,a} + \xi_{i,p}$, $i = 1, \ldots, 8$. With $n_{i,a} \cdot \xi_{i,a} \sim \chi^2_{n_{i,a}-1}$ and $n_{i,p} \cdot \xi_{i,p} \sim \chi^2_{n_{i,p}-1}$, we have

$$\hat{\nu}_i = 2 \cdot \frac{(\xi_{i,a} + \xi_{i,p})^2}{\widehat{var}(\xi_{i,a} + \xi_{i,p})} = \frac{(\xi_{i,a} + \xi_{i,p})^2}{\xi_{i,a}^2/(n_{i,a} - 1) + \xi_{i,p}^2/(n_{i,p} - 1))},$$

cf: section 2 above, so that from the data above we obtain:
$\hat{\mu}^* = 0.1619,\ f(\hat{\mu}^*) = 1.0386,\ f^*(\hat{\mu}^*) = 1.0743,\ \hat{\nu}_{g(\hat{\mu}^*)} = 53.8536,$
$\hat{\nu}_{g^*(\hat{\mu}^*)} = 28.9269 \quad \hat{\nu}^*_{\varepsilon,1} =, 7.6763\ \hat{\nu}^*_{\varepsilon,2} = 7.5925.$

Suppose interest is in testing the hypothesis that there is no change in work capacity after use of amlodipine against a two sided alternative of a negative or positive effect at $\alpha = 0.05$. Table 5 gives the test statistics T, T_M, T_1, T_2, T_3, T_4, T_5, and T_6 with the corresponding computed values, critical values and the confidence intervals. Clearly, the decision reached by using all the test statistics is the same, that is, at level $\alpha = 0.05$, the data does provide enough evidence to reject the hypothesis of no change in work capacity after use of amlodipine. This is in line with the confidence intervals which also indicate that zero is outside the confidence limits. That all the test procedures (and the corresponding confidence intervals) give the same conclusion may not be surprising given that in more that one half of the eight studies the sample sizes, in both arms, are greater than 30.

Table 5: Value of the test statistics and corresponding critical values (level $\alpha = 5\%$) for the data in Table 4.

Test statistic	Computed value	Critical value	Confidence Interval
T	5.0134	1.9600	$CI_T(\mu) : [0.0986, 0.2252]$
T_M	4.8615	1.9664	$CI_{T_M}(\mu) : [0.0964, 0.2274]$
T_1	4.8460	1.9600	$CI_1(\mu) : [0.0964, 0.2274]$
T_2	4.8615	1.9600	$CI_2(\mu) : [0.0966, 0.2272]$
T_3	25.1340	4.0200	$CI_3(\mu) : [0.0971, 0.2266]$
T_4	25.1340	4.1839	$CI_4(\mu) : [0.0958, 0.2279]$
T_5	31.6397	5.3965	$CI_5(\mu) : [0.0950, 0.2288]$
T_6	31.7632	5.4183	$CI_6(\mu) : [0.0949, 0.2289]$

5 Conclusion

In the meta-analysis of, for example, randomized clinical trials, the most commonly used test is T, which, from results published elsewhere and also from our results, attains levels well above the prescribed levels, α. The practical implication is that in studies where this test is used, there is likely to be a tendency to mimic the true effect (usually no effect) of the factor under investigation (say, some drug). The test proposed by Meier (1953) leads to improvements in the attained significance levels only for reasonably large samples (say ≥ 20). For large samples, the proposed tests can be used as congruents of Meier's $t-$test and of course, they should be preferred to the commonly used test. When smaller samples are in question, we proposed the use of either T_4, T_5 or T_6. However, care should also be taken on the number of studies under consideration.

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Appendix

$$\begin{aligned}\frac{\partial}{\partial x_i}[var\{g(\hat{\mu}^*)|x_i\}] &= \frac{2}{(\sum_{i=1}^{p} 1/\theta_i)^4}\cdot\left\{\frac{2}{\theta_i x_i^2}\cdot\left(\sum_{i=1}^{p}\frac{1}{\theta_i x_i}\right)\cdot\left(\sum_{i=1}^{p}\frac{1}{\theta_i^2 x_i^4}\right)\right.\\ &\left. -\frac{4}{\theta_i^2 x_i^5}\cdot\left(\sum_{i=1}^{p}\frac{1}{\theta_i x_i}\right)^2\right\}.\end{aligned}$$

Set

$$S_1(x) = \frac{4}{(\sum_{i=1}^{p} 1/\theta_i x_i)^3}\cdot\frac{1}{\theta_i x_i^2}\cdot\left(\sum_{i=1}^{p}\frac{1}{\theta_i^2 x_i^4}\right),\quad S_2(x) = \frac{8}{(\sum_{i=1}^{p} 1/\theta_i x_i)^2}\cdot\frac{1}{\theta_i^2 x_i^5}.$$

Then

$$\begin{aligned}\frac{\partial S_1(x)}{\partial x_i} &= \frac{4}{\left(\sum_{i=1}^{K} 1/\theta_i x_i\right)^6}\cdot\left[\left(\sum_{i=1}^{K} 1/\theta_i x_i\right)^3\left\{\frac{-4}{\theta_i^3 x_i^7}-\frac{2}{\theta_i x_i^3}\left(\sum_{i=1}^{K} 1/\theta_i^2 x_i^4\right)\right\}\right.\\ &\left.+\frac{3}{\theta_i^2 x_i^4}\left(\sum_{i=1}^{K} 1/\theta_i^2 x_i^4\right)\cdot\left(\sum_{i=1}^{K} 1/\theta_i x_i\right)^2\right].\\ \frac{\partial S_1(x)}{\partial x_i}|_{(1,\ldots,1)} &= \frac{-16}{\theta_i^3}\cdot\frac{1}{\beta_\Sigma^3}-\frac{8}{\theta_i}\cdot\frac{1}{\beta_\Sigma^3}\cdot\sum_{i=1}^{K}\frac{1}{\theta_i^2}+\frac{12}{\theta_i^2}\cdot\frac{1}{\beta_\Sigma^4}\cdot\sum_{i=1}^{K}\frac{1}{\theta_i^2}.\\ \frac{\partial S_2(x)}{\partial x_i} &= \frac{8}{\left(\sum_{i=1}^{K} 1/\theta_i x_i\right)^4}\cdot\left\{\frac{2}{\theta_i^3 x_i^7}\left(\sum_{i=1}^{K} 1/\theta_i x_i\right)-\frac{5}{\theta_i^2 x_i^6}\left(\sum_{i=1}^{K} 1/\theta_i x_i\right)^2\right\}.\\ \frac{\partial S_2(x)}{\partial x_i}|_{(1,\ldots,1)} &= \frac{16}{\theta_i^3}\cdot\frac{1}{\beta_\Sigma^3}-\frac{40}{\theta_i^2}\cdot\frac{1}{\beta_\Sigma^2}.\end{aligned}$$