Comparative role of various methods of estimating between study variance for meta-analysis using random effect method

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ABSTRACT

Methods of synthesizing the effect size is guided by observed heterogeneity. As a convention, fixed effect method (FEM) is used for low/no heterogeneity. However, random effect method (REM) is used for substantial heterogeneity. But, synthesized (i.e., pooled) effect size under REM also relies on the method used to estimate between study variance along with within study variance. There are various methods to assess between study variance to be used under REM. Accordingly, present study compared existing methods of estimating between study variance on the basis of coverage probability and precision in order to find preferred method of assessing between study variance. Data from a systematic review and meta-analysis for various outcomes involving varying extent of sample size and heterogeneity was used. Hunter and Schmidt method and DerSimonian & Laird method were found as preferred methods to estimate between study variance.

1. Introduction

Meta-analysis involves statistical techniques to synthesize the effect size of the considered outcome from various comparative studies.¹ Comparative studies too have some degree of heterogeneity because of variation in population, intervention, comparator and outcome characteristics. Further, choice of meta-analysis method depends on prevailing heterogeneity. As a convention, fixed effect method (FEM) is used in case of no heterogeneity as it assumes that all the studies are measuring a single true effect size and variation in the study level effect size is due to sampling alone. But, fixed effect method assumes that between studies variation is zero. On the other hand, random effect method (REM) assumes that study level effect size is a random sample out of the infinite studies following the same inclusion criteria for meta-analysis. Pooled effect estimate under fixed effect method is weighted average of study level effect sizes considering within study variance as weights. Also, instead of considering within study variance, other forms of weights can also be considered like sample size, study quality or a function of such parameters. On the other hand, REM accounts for the between study heterogeneity considering both within as well as between study variance. However, various methods exist to assess the between study variance. Accordingly, the pooled effect estimate may rely on the estimated between study variance. Therefore, present study compared the performance of various methods to estimate between

study variance under meta-analysis using random effect method(REM).

2. Materials & methods

2.1. Data

For the present article, data of a systematic review of randomized controlled trials comparing neoadjuvant chemotherapy with adjuvant chemotherapy for oncological and functional outcomes were considered. The detail methodology, definition of outcomes and result of the systematic review is published elsewhere.²

2.2. Random effect method

The individual study effect size under random effect method can be modeled as:

$$y_i = \mu + \theta_i + \varepsilon_i \quad (1)$$

Where θ_i is deviation between individual level study effect size (y_i) and the true effect (μ) which exceeds due to sampling variation (ε_i) alone. Further, θ_i depends on between study variance (τ^2) while ε_i depends on the within study variance (σ_i^2) alone. Hence y_i is distributed as $y_i \sim N(\mu, \sigma_i^2 + \tau^2)$.

As random effect method considers random sample of the effect sizes, the mean of the deviation in effect size will obviously be zero. As

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such, random effect method assumes that θ_i is distributed normally with mean zero and variance (τ^2) as $\theta_i \sim N(0, \tau^2)$, and sampling error is also distributed normally as $\varepsilon_i \sim N(0, \sigma_i^2)$. Since random effect method considers two sources of variation, between study variance as well as within study variance, the weights (w_i) associated with individual studies are inverse of this total variation:

$$w_i = 1/(\sigma_i^2 + \tau^2) \quad (2)$$

The pooled effect estimate of y_i may be given as below:

$$\hat{\mu} = \sum y_i w_i / \sum w_i \quad (3)$$

Further, the variance of this estimated effect size may be represented as:

$$V(\hat{\mu}) = 1 / \sum w_i \quad (4)$$

The random effect method rely depend on the estimated value of between study variance. This between study variance i.e., τ^2 , may however be estimated using various methods.

The methods to estimate between study variance are categorized in two parts as non-iterative methods and iterative methods.³ Non-iterative methods of variance estimation are formula based methods which do not require iterative algorithm. On the other hand, iterative methods may not converse always. Hence, present study chose to compare non-iterative methods of estimating variance. These methods are given as follows:

2.3. Method of moments⁴

In case of k studies, let us assume that $s_1^2, \dots, s_k^2$ and t^2 are respective estimates of within study variances ($\sigma_1^2, \dots, \sigma_k^2$) and between study variance (τ^2). Estimate of pooled effect estimate is $\bar{T} = \frac{\sum m_i T_i}{\sum m_i}$, where $m_1, \dots, m_k$ are study level considered weights (any positive constants). For variance estimation, the expected value of the expression $Q = \sum m_i (T_i - \bar{T})^2$ is:

$$E \left[\sum m_i (T_i - \bar{T})^2 \right] = \sum m_i (\tau^2 + \sigma_i^2) - \sum m_i (\tau^2 + \sigma_i^2) / \sum m_i \quad (5)$$

This can be expressed as:

$$E \left[\sum m_i (T_i - \bar{T})^2 \right] = \tau^2 \left[\sum m_i - \frac{\sum m_i^2}{\sum m_i} \right] + \left[\sum m_i \sigma_i^2 - \frac{\sum m_i \sigma_i^2}{\sum m_i} \right] \quad (6)$$

By equating the $\sum m_i (T_i - \bar{T})^2$ to its expected value in equation (6), and substituting $s_1^2, \dots, s_k^2$ for $\sigma_1^2, \dots, \sigma_k^2$, the value of τ^2 using method of moments (MM) can be estimated^{4,5}:

$$\tau^2(MM) = \frac{[\sum m_i (T_i - \bar{T})^2] - [\sum m_i s_i^2 / \sum m_i]}{\left[\sum m_i - \frac{\sum m_i^2}{\sum m_i} \right]} \quad (7)$$

In case, if $\tau^2(MM)$ is negative, it is truncated at zero. Most of the methods to estimate τ^2 were derived from the method of moments by specifying varying values of weight m_i .

2.4. Cochran ANOVA method^{5,6}

Cochran ANOVA method assumes that each study provides equal information and is of equal size.^{5,6} Accordingly, by substituting $a_i = \frac{1}{k}$ in equation (7) yields the Cochran ANOVA (CA) estimate of τ^2 .

$$\tau^2(CA) = \max \left\{ 0, \frac{1}{k-1} \sum_i (T_i - \bar{T}_{CA})^2 - \frac{1}{k} \sum_i s_i^2 \right\} \quad (8)$$

$$\bar{T}_{CA} = \frac{\sum_i T_i}{k} \quad (9)$$

2.5. DerSimonian and Liard method⁷

DerSimonian and Liard (1986) proposed another method to estimate τ^2 by taking precision of each study as weight. Under this method, substituting $a_i = \frac{1}{s_i^2}$ in equation (7) yields the DerSimonian and Liard estimate (DL) of τ^2 .

$$\tau^2(DL) = \max \left\{ 0, \frac{[\sum_i w_{iDL} (T_i - \bar{T}_{DL})^2] - (k-1)}{\left[\sum_i w_{iDL} - \frac{\sum_i w_{iDL}^2}{\sum_i w_{iDL}} \right]} \right\} \quad (10)$$

$$\bar{T}_{DL} = \frac{\sum_i w_{iDL} T_i}{\sum_i w_{iDL}} \text{ and } w_{iDL} = 1/s_i^2 \quad (11)$$

DerSimonian and Liard method is most common method of used under random effect analysis. So it is widely available in the software facilitating meta-analysis.

2.6. Two step DerSimonian and Liard method⁵

DerSimonian and Kacker⁵ proposed a two steps estimator. It is also based on the method of moment estimator by substituting τ^2 with τ_{DL}^2 in equation $m_i = \frac{1}{s_i^2 + \tau_{DL}^2}$ and with $\bar{T}$ with $\bar{\mu}_{DL}$ (Pooled effect estimate under DerSimonian & Liard method) in equation (7). The two steps DerSimonian and Laird Method (DL2) of between study variance can be calculated as:

$$\tau^2(DL2) = \begin{cases} 0, & \frac{[\sum_i w_{iDL2} (T_i - \bar{\mu}_{DL})^2] - [\sum_i w_{iDL2} s_i^2 - \sum_i w_{iDL2}^2 s_i^2 / \sum_i w_{iDL2}]}{\left[\sum_i w_{iDL2} - \frac{\sum_i w_{iDL2}^2}{\sum_i w_{iDL2}} \right]} \end{cases} \quad (12)$$

Where

$$w_{iDL2} = 1/(\tau^2(DL) + s_i^2) \quad (13)$$

2.7. Two step cochrane ANOVA method⁵

DerSimonian and Kacker⁵ also proposed another two steps estimator. In first step τ_{CA}^2 and $\bar{\mu}_{CA}$ is estimated by using Cochran ANOVA methods. In the second step, between study variance using two step Cochran ANOVA method (CA2) is estimated by substituting $m_i = \frac{1}{s_i^2 + \tau_{CA}^2}$ and $\bar{T}$ with $\bar{T}_{CA}$ in equation (7).

$$\tau^2(CA2) = \begin{cases} 0, & \frac{[\sum_i w_{iCA2} (T_i - \bar{\mu}_{CA})^2] - [\sum_i w_{iCA2} s_i^2 - \sum_i w_{iCA2}^2 s_i^2 / \sum_i w_{iCA2}]}{\left[\sum_i w_{iCA2} - \frac{\sum_i w_{iCA2}^2}{\sum_i w_{iCA2}} \right]} \end{cases} \quad (14)$$

Where,

$$w_{iCA2} = 1/(\tau^2(CA) + s_i^2) \quad (15)$$

2.8. Hartung and Makambi Method^{8,9}

The method proposed by Hartung and Makambi^{8,9} is a modification of the method proposed by DerSimonian and Liard method.⁷ Unlike other methods to estimate between study variance, it does not require truncation to zero.

Table 1
Estimated Between Study Variance using Each of Variance Estimation Methods.

Method	Overall Survival	Disease Free Survival	Relapse Free Survival	Loco-Regional Recurrence	Local Recurrence	Distant Metastasis	Breast Conserving Surgery
No of RCTs	15	6	14	15	10	13	9
I ² Statistics	0.0%	26.3%	47.2%	0.0%	0.0%	43.5%	90.1%
DerSimonian & Liard	0.0000	0.0121	0.0336	0.0000	0.0000	0.0345	0.0439
Two Step DerSimonian & Liard	0.0000	0.0173	0.0677	0.0000	0.0000	0.0562	0.1339
Cochrane ANOVA	0.0000	0.0910	0.1883	0.0000	0.0000	0.1627	2.3130
Two step Cochrane ANOVA	0.0000	0.0396	0.1260	0.0000	0.0000	0.0910	1.4804
Hartung & Makambi	0.0108	0.0185	0.0346	0.0279	0.0226	0.0372	0.0408
Hunter and Schmidt	0.0000	0.0025	0.0249	0.0000	0.0000	0.0242	0.0358
Sidik & Jonkman	0.0393	0.1072	0.1789	0.0872	0.0390	0.1617	1.4388

$$\frac{\sum w_{i,F} (T_i - \hat{\mu}_F)^2}{\sum w_{i,F} - \frac{\sum w_{i,F}^2}{\sum T_{i,F}}} = \frac{Q}{\sum w_{i,F} - \frac{\sum w_{i,F}^2}{\sum T_{i,F}}} \quad (16)$$

where $w_{i,F}$ is weights under fixed effect method, i.e., inverse of within study variance only; y_i and $\hat{\mu}_F$ are individual study effect size and pooled effect estimate (weighted average) under fixed effect method respectively. Under Hartung & Makambi method, the quadratic form above is multiplied by the factor $Q/(2(k-1) + Q)$ to ensure positivity.³ The estimator is given as:

$$\hat{\tau}_{HM}^2 = \frac{Q^2}{2(k-1) + Q} \left(\sum w_{i,F} - \frac{\sum w_{i,F}^2}{\sum T_{i,F}} \right) \quad (17)$$

2.9. Hunter and Schmidt Method¹⁰

Another method proposed by Hunter and Schmidt¹⁰ is given by

$$\hat{\tau}_{HS}^2 = \left\{ 0, \frac{Q - k}{\sum w_{i,F}} \right\} \quad (18)$$

2.10. Sidik and Jonkman method^{11,12}

To calculate between study variance by Sidik and Jonkman method^{11,12}, initial estimator of between study variance is calculated as $\hat{\tau}_0^2 = \sum_i (T_i - \bar{T})^2/k$. Then estimate of between study variance using Sidik and Jonkman method (SJ) may be obtained as:

$$\hat{\tau}_{SJ}^2 = \frac{1}{k-1} \sum w_{iSJ} (T_i - \hat{T}_{SJ})^2 \quad (19)$$

Where

$$\hat{T}_{SJ} = \sum w_{iSJ} y_i / \sum w_{iSJ} \quad (20)$$

Where

$$w_{iSJ} = \frac{\hat{\tau}_0^2}{s_i^2 + \hat{\tau}_0^2}$$

All the above discussed methods was used to estimate the between study variance (τ^2). The estimated value of between study variance was used to calculate the total variance, i.e., sum of within as well as between study variance. Pooled effect estimate under random effects method is weighted average of study level effect sizes considering this total variance as weight.

2.11. Comparison of meta-analysis methods

For each of the considered outcomes, the performance of random effects method using each of the method to estimate between study variance was compared using the following statistics:

2.12. Coverage probability

It measures the actual probability of the true value being included in the 95% CI of pooled effect estimate. It is measured as proportion of how many times the confidence interval contains the true population parameter. The coverage probability of interval estimate synthesized by random effects method using a particular method of between study variance was calculated using 10000 bootstrap samples of individual studies. The pooled effect estimate by random effect method with that particular method of estimating between study variance was calculated for each of these 10000 samples. Further, the proportion of these effect estimates under each of the bootstrap sample lying within the 95% CI of μ was considered as coverage probability.

2.13. Width of confidence interval

Along with coverage probability, the width of confidence interval also matters, so width of the confidence interval of pooled effect estimates was also considered while comparing difference variance estimation methods.

3. Results

Present study involved 18 RCTs comparing at least one of the considered outcomes. Various outcomes involved variable sample size, and variable extent of heterogeneity. The existing non-iterative methods of calculating between study variance were used to estimate between study variance for each of the outcomes. The estimates of between study variance (τ^2) by various methods are listed in Table 1 and pooled hazard ratio for all the outcomes except breast conserving surgery, for which it is risk ratio, are listed in Table 2 calculated by each of the considered methods. All methods estimated $\tau^2 = 0$ in case of no heterogeneity, i.e., $I^2 = 0\%$, in case of overall survival, local recurrence and loco-regional recurrence, except Hartung & Makambi Method and Sidik & Jonkman method. These two methods overestimated the τ^2 . As evident from Table 2, in case of no heterogeneity, all the methods gave exactly same results except in case of Hartung & Makambi method and Sidik & Jonkman method. These two methods overestimated the τ^2 and hence lead to wider confidence interval of effect size. With increasing heterogeneity, the magnitude of difference between the estimated values of τ^2 by different methods also increased. With very high heterogeneity like in case of breast conserving surgery, differences in estimated value of τ^2 also increased from 0.0358 by Hunter & Schmidt method to 2.313 by Cochrane ANOVA method.

As obvious, the width of confidence interval increases with increased heterogeneity as evident from case of breast conserving surgery. Random effect method using Hunter and Schmidt, and DerSimonian & Laird method of estimating between study variance had most precise confidence intervals in comparison to other methods.

Variance estimation methods were also compared on the basis of coverage probability of interval estimate of hazard ratio calculated

Table 2
Hazard Ratio/Risk Ratio for Various Outcomes using Random Effect Method with Varying Between Study Variance Estimation Methods.

Outcome	Overall Survival	Disease free Survival	Relapse Free Survival	Loco-Regional Recurrence	Local Recurrence	Distant Metastasis	Breast Conserving Surgery ^a
No of RCTs	15	6	14	15	10	13	9
I ² Statistics	0.0%	26.3%	47.2%	0.0%	0.0%	43.5%	90.1%
DerSimonian & Liard	0.98 (0.89–1.08)	0.99 (0.83–1.19)	1.01 (0.86–1.18)	1.23 (1.06–1.43)	1.31 (1.11–1.56)	0.97 (0.82–1.16)	1.21 (1.04–1.41)
Two Step DerSimonian & Liard	0.98 (0.89–1.08)	0.99 (0.82–1.21)	0.98 (0.81–1.19)	1.23 (1.06–1.43)	1.31 (1.11–1.56)	0.96 (0.79–1.17)	1.24 (0.97–1.60)
Cochrane ANOVA	0.98 (0.89–1.08)	0.98 (0.70–1.37)	0.93 (0.70–1.23)	1.23 (1.06–1.43)	1.31 (1.11–1.56)	0.93 (0.71–1.23)	1.59 (0.60–4.18)
Two step Cochrane ANOVA	0.98 (0.89–1.08)	0.99 (0.77–1.28)	0.95 (0.75–1.21)	1.23 (1.06–1.43)	1.31 (1.11–1.56)	0.95 (0.76–1.19)	1.50 (0.69–3.28)
Hartung & Makambi	0.97 (0.86–1.10)	0.99 (0.81–1.22)	1.01 (0.86–1.18)	1.24 (1.02–1.51)	1.32 (1.08–1.62)	0.97 (0.81–1.16)	1.21 (1.04–1.40)
Hunter and Schmidt	0.98 (0.89–1.08)	0.99 (0.86–1.12)	1.02 (0.88–1.18)	1.23 (1.06–1.43)	1.31 (1.11–1.56)	0.98 (0.83–1.15)	1.20 (1.05–1.38)
Sidik & Jonkman	0.96 (0.81–1.13)	0.97 (0.68–1.39)	0.93 (0.71–1.23)	1.23 (0.96–1.57)	1.32 (1.06–1.65)	0.93 (0.71–1.23)	1.50 (0.69–3.23)

^a For Breast Conserving Surgery, effect size is Risk Ratio.

Table 3
Coverage probability of pooled effect interval estimate calculated using random effect method with various variance estimation methods.

Method	Overall Survival	Disease Free Survival	Relapse Free Survival	Loco Regional Recurrence	Local Recurrence	Distant Metastasis	Breast Conservation
DerSimonian & Liard	0.9446	0.9246	0.9302	0.9489	0.9626	0.9460	0.8924
Two Step DerSimonian & Liard	0.9410	0.9191	0.9321	0.9492	0.9626	0.9536	0.9279
Cochrane ANOVA	0.9600	0.9852	0.9855	0.9518	0.9626	0.9934	0.9786
Two step Cochrane ANOVA	0.9413	0.9332	0.9589	0.9499	0.9626	0.9724	0.9284
Hartung & Makambi	0.9700	0.9319	0.9339	0.9815	0.9744	0.9585	0.8822
Hunter and Schmidt	0.9529	0.8683	0.9220	0.9480	0.9626	0.9391	0.8645
Sidik & Jonkman	0.9903	0.9795	0.9740	0.9972	0.9830	0.9865	0.9284

under random effect method using various between study variance estimation methods. The coverage probabilities under each of the considered methods for each of the considered outcomes are listed in Table 3. In the case of no heterogeneity, as obvious, the point as well as interval estimates under each method coincided except two methods, i.e., Hartung & Makambi method and Sidik & Jonkman method, where between studies variance was overestimated. But, in the presence of heterogeneity, difference in terms of coverage probability was observed among the variance estimation methods. Further, wide confidence interval retained higher coverage probability. However, DerSimonian & Laird and Hunter & Schmidt methods had coverage probability of 95% confidence interval around nominal level with precise confidence interval.

4. Discussion

It is a global consensus that method of meta-analysis should be guided by the extent of heterogeneity, fixed effect method for lower extent of heterogeneity and random effect method for substantial heterogeneity.^{13,14} But pooled effect size calculated under random effect method also relies on the method used to estimate between study variance. Apart from the non-iterative methods of estimating τ^2 discussed in present study, iterative methods, viz. maximum likelihood method^{15,16}, restricted maximum likelihood method¹⁷, approximate maximum likelihood method³, Paule and Mandel's method^{5,18} and Empirical Bayes method^{15,19} also exist. However, these iterative methods involve τ^2 itself for calculating τ^2 . Hence, these methods may not converge all the times. As observed in present study, REM is sensitive to the estimation of between study variance.

Keeping in view of three considered measures of comparing the estimation methods regarding between study variance, Hunter and Schmidt and DerSimonian & Laird methods may be preferred. Simulation studies had found that Hunter and Schmidt method produces negatively biased results²⁰, but it was not observed in the present study. The pooled effect estimate under REM using these two methods had precise confidence intervals in comparison to other methods. Although coverage probability was found higher under some of the other

methods as well, considering precision these two methods with optimal coverage probability are preferred choice.

Among these methods of estimating between study variance, DerSimonian & Laird Method is widely popular method and available in most of the statistical software facilitating meta-analysis. Although Hunter & Schmidt method is less popular but it was found to be equally proficient with DerSimonian & Laird method. Use of these two variance estimation methods over other such methods will provide reliable estimate of various epidemiological questions.

Conflicts of interest

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Author's contribution

All the three authors conceived & designed the study. Dr. Mona Pathak did statistical analysis. All authors interpreted the results. The final manuscript of the research work was prepared by Dr. Mona Pathak. All the authors read and provided their inputs to finalize the manuscript.

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Appendix A. Supplementary data

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