An Empirical Assessment of Meta-Analysis Estimates from Multi-level Studies

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Introduction

Meta-analysis is a statistical technique for integrating quantitative results from several sources. The main aim is to provide conclusions based on the whole body of research. A traditional meta-analysis involves integration of aggregate data (AD) which is extracted from the individual study publications [1]. Typical AD includes a mean difference for continuous outcomes or the number of events and participants for binary outcomes. The overall treatment effect is computed by taking the weighted average of the effects across the trials using methods such as the inverse variance method [2] or the Mantel-Haenszel method [3] for the binary data. Alternatively, meta-analysis may be performed based on individual patient data (IPD), where raw data from individual study is obtained and synthesized directly. Although it has numerous advantages compared to the traditional meta-analysis, particularly in terms of type of analyses that can be done, IPD meta-analysis is usually relatively costly and time consuming [4][5]. Another potential problem for IPD analysis is that IPD should always be included in a conventional meta-analysis using summary level data as significant statistical benefit is gained by pooling the two levels of data.

A conventional meta-analysis may be performed using studies which are available at individual patient level (IPD) or aggregate level (AD). Presently however, meta-analysis that combine the two levels of studies is increasingly common. The implications of utilizing different levels of data on the overall estimates have not been fully explored. Objective: This study examined the efficacy of the estimates of overall treatment effect from AD, IPD and the mixed AD:IPD studies, and investigated how they differ from the true treatment effect. Additionally, this study investigated the influence of the ratio of AD: IPD on the precision of the overall treatment effects estimates. The bias, root mean-square-error (RMSE) and coverage probability were used to assess the efficiency of the overall estimates. Results: The results showed that the IPD meta-analysis produced better estimates in terms of RMSE compared to AD meta-analysis and the mixed AD:IPD meta-analysis. For the cases where both the AD and IPD studies were available, our findings showed that the combined AD : IPD data produced better estimates, in terms of precision, than utilising the AD alone. Conclusion: It is therefore recommended that available IPD should always be included in a conventional meta-analysis using summary level data as significant statistical benefit is gained by pooling the two levels of data.

Keywords: Meta-analysis; Combine data; Individual patient data; Aggregate data; Simulation; Bias

Reference

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The present study extended this part of the work by Riley et al. We used simulated meta-analysis to empirically assess and compare statistical properties of estimates based on all AD, all IPD and the combination of both IPD and AD (which will be referred to as the mixed data, MD). We examined how some statistical properties of the estimates extracted from these three sets of data differ from the true effect estimates. Additionally, for the scenarios involving combined IPD and AD studies, we attempted to establish the influence of the ratio of AD: IPD on the accuracy and precision of the overall treatment effects estimates. The use of simulated meta-analysis had allowed us to make this comparison as the true effect was manually assigned when generating the data.

Meta-Analysis Model:
In this section we present briefly the theoretical basis and steps for performing conventional AD meta-analysis, followed by IPD and MD meta-analysis using one-step and two-step approach. The model considered is the general form of random effect model which is more applicable in practice.

2.1. Conventional AD Meta-Analysis:
A conventional meta-analysis combines study estimates of treatment effect from each individual study. The random effect estimate of the treatment effect for study \( i \), \( \hat{\theta}_i \), is given by

\[
\hat{\theta}_i = \theta_i + e_i
\]

(1)

\[
\theta_i = \theta + v_i
\]

\[
v_i \sim N(0, \tau^2)
\]

\[
e_i \sim N(0, \sigma^2)
\]

(2)

Where \( \theta \) is the true effect of study \( i \), and the sampling error term \( e_i \) are realizations of normally distributed random variables with expected value 0 and variance \( \sigma^2 \), which is assumed to be known. \( v_i \) is the random error term of study \( i \) which is assumed to be normally distributed with mean 0 and between-study variance \( \tau^2 \). Thus \( \tau^2 \) represents the unexplained heterogeneity in treatment effect across studies while \( \sigma^2 \) is the variance of the sampling error terms for study \( i \) after accounting for the treatment effect. As \( v_i \) and \( e_i \) are assumed to be independent, it follows that \( \hat{\theta}_i \sim N(\theta, \sigma^2 + \tau^2) \). The general form of the random effect estimate of the overall treatment effect based on \( N \) studies, denoted \( \hat{\theta} \) is the weighted average of study specific \( \hat{\theta}_i \), with study weights \( w_i \) equals to the inverse of \( V(\hat{\theta}_i) \), and the variance of \( \hat{\theta} \) is the inverse of the sum of the study weights,

\[
\hat{\theta} = \frac{\sum w_i \hat{\theta}_i}{\sum w_i}
\]

\[
V(\hat{\theta}) = \frac{1}{\sum_{i=1}^{N} w_i}
\]

(3)

2.2. IPD meta-analysis:
Studies available at IPD level may be meta-analysed using either one-step or two-step approach.

2.2.1. One-Step Approach:
Suppose \( y_{ij} \) be a response from patient \( j \) from study \( i \). Then \( y_{ij} \) may be modelled using a mixed effect model as follows:

\[
y_{ij} = \psi_i + \theta_i x_{ij} + e_{ij}
\]

\[
\theta_i = \theta + v_i
\]

(4)

where \( \psi_i \) is a fixed study effect; \( x_{ij} \) is the dummy covariate which takes the value 0 for control and 1 for treatment. As in the case of AD meta-analysis, a study specific treatment effect in the \( i \)th study, \( \theta_i \), is normally
distributed about a pooled treatment effect, $\theta$, with between-study variance, $\tau^2$. This model estimates the $\tau^2$, $\sigma_i^2$ and, $\theta$ simultaneously.

2.2.1. Two-Step Approach:

A more common approach for IPD meta-analysis is a two-step method [5]. Using this approach, a common IPD model (Eq. 4) is first fit to each of the IPD study separately. The study estimates $\hat{\theta}_i$ and its variance $\nu(\hat{\theta}_i)$ are then extracted from each study and then combined using the method for conventional AD meta-analysis (Eq. 3) as described earlier.

All the models in this paper can be estimated using restricted maximum likelihood (REML) within the suitable packages from R software [11] for mixed models such as the lme or the nlme.

2.3 Meta-analysis Combining AD and IPD:

Meta-analysis using both the available AD and IPD may be integrated using either a two-staged or one-stage approach. For one-staged method, the IPD and AD studies may be combined simultaneously using an extended version of (Eq. 4). Interested readers are referred to Goldstein et al [12][13] for detailed procedures. In this paper we will combine the IPD and AD using the most commonly used approach, namely the two-stage approach.

The two-staged method is more commonly used in practice [8, 14] whenever both levels of data are utilized. Suppose a total number of studies $N$, is given by $N = N_{AD} + N_{IPD}$, where $N_{AD}$ and $N_{IPD}$ are the number of studies which provides IPD and AD, respectively. In this approach, the $\theta_i$ estimates are first obtained from each of the individual IPD studies, $N_{AD}$, using the method described earlier. These estimates are then integrated with $\theta_i$ estimates from the AD studies using the standard meta-analysis method (Eq.3) to obtain the overall estimates $\hat{\theta}$ and the corresponding standard error. This method is more appropriate as the subject of interest is the overall pool (treatment) effect where the covariates are assumed to be identical for each patient in the study.

Method:

3.1 Generation of data:

Simulation approach was used to generate individual patient level response, $y_{ij}$, representing patient $j$ from study $i$, under known conditions. The following model was used

$$y_{ij} = \beta_{ui} + \beta_{t}t_{ij} + \varepsilon_{ij}$$

where $\beta_{ui}$ is the random study effect, $t_{ij}$ represents a dummy covariate for treatment which takes two values, namely 0 for the control and 1 for the treatment arm, $\beta_{t}$ is the random treatment effect, and $\varepsilon_{ij}$ are the sampling random error terms for the response from patient $j$ within study $i$. We assumed that $\beta_{ui}, \beta_{t}$ and $\varepsilon_{ij}$ are independent and normally distributed, with $\varepsilon_{ij} \sim N(0, \sigma_{\varepsilon}^2)$, $\beta_{ui} \sim N(\beta_{ui}, \sigma_{ui}^2)$, and $\beta_{t} \sim N(\beta_{t}, \sigma_{\beta}^2)$. For simplicity, each study was assumed to have an equal number of patients in each treatment arm, i.e. $n_{ui} = n_{t} = \frac{1}{2}n$ for $i = 1, 2, ..., N$. Summary level data, AD, were created by taking the differences of the means of each treatment arms in each individual study.

Basing on scenarios commonly occurred in clinical trials, the following values were assigned to the fixed and random effects; $\beta_{ui} = 0$ and $\beta_{t} = 3$ for the fixed effects and $\sigma_{\varepsilon}^2 = 1$, $\sigma_{ui}^2 = 1$ and $\tau^2 = 2$ for the random effects. Factors that were varied in this simulation study were the ratio of AD: IPD studies in a meta-analysis, namely, 0:100, 20:80, 30:70, 40:60, 50:50, 60:40, 80:20, 100:0 the number of studies, $N$, included in meta-analysis, ($N = 10, 20, 30$) while the size of the samples $n$ was fixed ($n = 60$). These specifications generated 24 meta-analyses of different scenarios. For each scenario examined, 500 meta-analyses were replicated and the mean bias, RMSE and coverage probability recorded.

3.2. Assessments:

The relative goodness of the overall estimates from each meta-analysis were evaluated in terms of their bias and the root mean squared error (RMSE).
3.2.1 Absolute Bias:
The bias was computed as the absolute mean differences between the true treatment effects and the estimated treatment effects from each meta-analysis over the number of simulations, computed as follows;

$$\text{Absolute bias, } (\hat{\delta}) = |\hat{\theta} - \hat{\theta}|$$

where $\hat{\theta}$ is the estimate of the treatment effect and $\theta$ is the true treatment effect.

3.2.2 Root Mean Square Error:
The RMSE is the root of mean-squared-error for overall estimate of treatment effect, where the MSE is given by

$$MSE = \frac{\sum_{t}[bias(\hat{\theta}_t)^2 + SE(\hat{\theta}_t)^2]}{K}$$

where $bias(\hat{\theta}_t)$ is the observed bias for $\hat{\theta}_t$ and $SE(\hat{\theta}_t)$ is the standard error corresponds to overall estimate from meta-analysis $t$, incorporating the uncertainty due to imputation[15].

3.2.3 Coverage:
Coverage probability is some procedure for constructing a confidence interval leading to the interval $X_c \pm c$. In words, this is the frequency over many replications that the interval contains the target value. A confidence interval should have the same coverage probability regardless of the sample size.

Results:
Table 1: The estimates and SE for AD, IPD and combinations of AD:IPD (MD).

<table>
<thead>
<tr>
<th>N</th>
<th>Ratio AD:IPD Name</th>
<th>10</th>
<th>20</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0:100</td>
<td>3.038271 (0.147293)</td>
<td>3.041161 (0.105258)</td>
<td>3.013203 (0.086445)</td>
</tr>
<tr>
<td>20:80</td>
<td>IPD</td>
<td>3.037662 (0.154314)</td>
<td>3.041603 (0.110726)</td>
<td>3.01328 (0.091051)</td>
</tr>
<tr>
<td>30:70</td>
<td>MD1</td>
<td>3.03669 (0.158457)</td>
<td>3.041871 (0.113847)</td>
<td>3.013453 (0.093666)</td>
</tr>
<tr>
<td>40:60</td>
<td>MD2</td>
<td>3.037392 (0.16305)</td>
<td>3.04053 (0.117319)</td>
<td>3.01359 (0.096522)</td>
</tr>
<tr>
<td>50:50</td>
<td>MD3</td>
<td>3.036876 (0.168109)</td>
<td>3.042031 (0.121142)</td>
<td>3.012863 (0.099665)</td>
</tr>
<tr>
<td>60:40</td>
<td>MD4</td>
<td>3.037796 (0.173721)</td>
<td>3.042218 (0.125381)</td>
<td>3.01309 (0.10314)</td>
</tr>
<tr>
<td>80:20</td>
<td>MD5</td>
<td>3.039548 (0.187233)</td>
<td>3.041538 (0.135409)</td>
<td>3.013124 (0.111397)</td>
</tr>
<tr>
<td>100:0</td>
<td>MD6</td>
<td>3.03823 (0.204907)</td>
<td>3.04117 (0.148347)</td>
<td>3.013194 (0.122043)</td>
</tr>
</tbody>
</table>

Table 1 gives the treatment effect estimates together with their corresponding SE for the three types of data, namely, the IPD studies, AD studies and the combinations of AD and IPD studies. The IPD refers to data in which all studies were available at IPD level, the AD refers to a data in which all studies were available at AD level, while the MD is the combination of AD and IPD studies at six different ratios. The true effect, $\theta$ was assigned at 3. The effect estimates from all studies did not differ very much. However as N is increased the SE is reduced (see Fig.1).

From Fig. 1, we can see that IPD has the lowest SE and AD has the highest SE. If IPD comprised of 20% of studies within combination of AD:IPD, the SE would be smaller than those from AD studies alone. And the inclusion of 80% of IPD in AD studies, the SE are the closest with SE of all IPD study used.

In Fig. 2 above showed negative biases from all studies, suggesting overestimation of effect estimates. From the graph, it appeared to be very little differences in the bias between all three types of data. However, upon closer inspection of the data(refer Table 2), we noted that the bias were slightly lower from the AD:IPD data compared to those from the AD. The effect of the number of studies, N, included in meta-analysis were notable, namely increasing N resulted in reducing biases. The effects of the ratio of AD:IPD on the overall estimates in this case were similarly not very markedly different.

The distribution of the root-mean-square errors (RMSE) is presented in Fig. 3a shows that the distribution of the root-mean-square errors (RMSE) for IPD is slightly lower than AD. This is expected since the SE of the IPD is lower than AD.
Fig. 1: The SE for AD, IPD and combinations of AD:IPD (MD).

4.1 Absolute Bias:
Table 2: The absolute bias of estimates from IPD, MD and AD studies.

<table>
<thead>
<tr>
<th>Ratio</th>
<th>N</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>20</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>AD:IPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD</td>
<td>-0.03827</td>
<td>-0.04116</td>
<td>-0.0132</td>
<td></td>
</tr>
<tr>
<td>MD1</td>
<td>-0.03766</td>
<td>-0.0416</td>
<td>-0.01328</td>
<td></td>
</tr>
<tr>
<td>MD2</td>
<td>-0.03669</td>
<td>-0.04187</td>
<td>-0.01345</td>
<td></td>
</tr>
<tr>
<td>MD3</td>
<td>-0.03739</td>
<td>-0.04053</td>
<td>-0.01359</td>
<td></td>
</tr>
<tr>
<td>MD4</td>
<td>-0.03688</td>
<td>-0.04203</td>
<td>-0.01386</td>
<td></td>
</tr>
<tr>
<td>MD5</td>
<td>-0.0378</td>
<td>-0.04222</td>
<td>-0.01309</td>
<td></td>
</tr>
<tr>
<td>MD6</td>
<td>-0.03955</td>
<td>-0.04154</td>
<td>-0.01312</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>-0.03823</td>
<td>-0.04117</td>
<td>-0.01319</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2:

4.2 Root-Mean-Squared Error (RMSE):

Fig. 3a: Distribution of RMSE of estimates from IPD and AD studies.
Fig. 3b: Distribution of RMSE of estimates for MD and AD studies.

Fig. 3b shows that the distribution of RMSE between AD and MD is similar. The estimates for RMSE seemed to be not much different for the different level of studies. But RMSE is decreased as the number of studies increase (given that N=10, 20, 30).

4.2 Coverage:

Fig 4: Distribution of coverage of estimates from IPD, MD and AD studies.

The distributions of coverage probability of estimates are shown in Fig. 4 with 95% CI. Generally, the coverage is low with range between 0.192 and 0.31. IPD had the lowest coverage while AD meta-analysis provided the highest coverage, averaging at around 31%. In addition, the coverage from the mixed AD:IPD studies ranges between those from AD and IPD meta-analysis and the coverage is increasing as number of studies in meta-analysis,N is increased.

Discussion:

We examined scenarios where studies included in meta-analysis were available at IPD, AD and both AD and IPD level. The results revealed IPD produced the lowest SE among the three type of data, followed by the combinations of AD:IPD and AD. However, there were not much difference in terms of the bias from IPD, AD and MD. Similarly, the RMSE for the three levels of data were very close, nonetheless, estimates from IPD studies showed slightly lower RMSE than those from the AD studies. This is expected since the SE from the IPD meta-analysis was lower. However, AD provided better coverage than the IPD meta-analysis. This is expected as the SE from estimates based on AD studies were higher, thus resulting in a wider interval band which affects the coverage probability. However, we noted that the coverage probability is too low than expected.

Our results showed that estimates based on combination of AD:IPD were better than those from AD alone, in terms of both SE and RMSE, albeit at very small differences. Overall, the small differences of estimates produced by generation of data may be attributed by the homogeneous individual responses, resulting in SE that was smaller than they should be. We noted that when a more heterogeneous data were generated, the differences between these three levels of data were more significant. However, the results showed notable influence of the number of studies, N included in a meta-analysis on the examined statistical properties within the assigned value of N.

In a conventional meta-analysis where studies are typically in AD form, available IPD data should be included in the analysis, as it will improve the statistical properties of the estimates. We acknowledge a number of limitations in this study. We only considered one value for the sample size n, namely n=60 for each studies. Currently, we are experimenting with different values of n, to gauge the sensitivity of the results. In addition, our results may be influence by homogeneous individual response that we used which may not necessarily be realistic.
in practice, because it removes all external factor which might exist in real life. Next, we planned to make a realistic simulation which can include all the external factors.

Conclusion:
Inclusion of some IPD studies into AD meta-analysis appears to have reduce the bias and RMSE. IPD studies could thus serve as moderating effect on the biasness and RMSE of the AD-meta analysis. It is therefore recommended that available IPD should always be included in a conventional meta-analysis using summary level data as significant statistical benefit is gained by pooling the two levels of data.

REFERENCES