Supporting Information

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2 Search Query

- General search query used for MedLine and EMBASE on Jan 27th 2014:

  ("individual patient" OR "individual participant" OR "IPD" OR "patient level data" OR "missing data") AND ("meta-analysis" OR "meta-analyses" OR "evidence synthesis" OR "systematic review" OR "subgroup analysis" OR "subgroup analyses")

- For Journal of Research Synthesis Methods, we used a simplified query as most articles in this journal consider meta-analytical topics:

  "individual patient" in Abstract OR "individual participant" in Abstract OR "IPD" in Abstract OR "patient level data" in Abstract OR "missing data" in Abstract in Research Synthesis Methods

- For Journal of the Royal Statistical Society: Series A (Statistics in Society), Journal of the Royal Statistical Society: Series B (Statistical Methodology) and Journal of the Royal Statistical Society: Series C (Applied Statistics) the following simplified query was used:

  "meta-analysis" in Abstract OR "meta-analyses" in Abstract OR "evidence synthesis" in Abstract OR "systematic review" in Abstract OR "subgroup analysis" in Abstract OR "subgroup analyses" in Abstract

3 Technical background

As we discussed in Section 3.1 of the review, two alternate approaches exist for conducting an Individual Participant Data meta-analysis (IPD-MA). Below, we illustrate the implementation these approaches in the R software (http://www.R-project.org/). We begin by generating an example IPD-MA dataset that can subsequently be used to fit the different models. Afterwards, we illustrate how to implement statistical models that estimate an overall summary of treatment effect. Finally, we illustrate how to investigate heterogeneity in treatment effect.

3.1 Example IPD-MA dataset

Let x be a subject-level variable that indicates treatment group (0=control, 1=treatment) and let y represent the developed (continuous) outcome. Furthermore, let z be a subject-level effect modifier that follows a different distribution across trials. Finally, let *trialid* be a numeric variable indicating to which study each subject belongs. We can generate an example IPD-MA dataset (called *ds*) consisting of 6 trials:

```
> set.seed(1115)
> N <- 1000 #number of patients per trial
> N.trials <- 6 #number of trials
> alpha <- c(11, 8, 10.5, 9.6, 12.9, 15.8) #study effects
> beta <- c(-2.95, -2.97, -2.89, -2.91, -2.93, -2.90) #treatment effects
> gamma <- c(0.24, 0.21, 0.20, 0.18, 0.25, 0.22)  #prognostic effects of z
> theta <- c(-0.9, -0.5, -0.6, -0.7, -0.1, -0.3) #interaction effects of z
> trialid <- c(1:6)
> ds <- as.data.frame(array(NA, dim=c(N*6, 4)))
> colnames(ds) <- c("trialid", "x", "z", "y")
>
> for (i in 1:N.trials) {
+     x <- rbinom(N,1,0.5)
+     z <- rnorm(N, mean=rnorm(1, mean=0, sd=0.5), sd=1)
+     y <- round(alpha[i] + beta[i]*x + gamma[i]*z + theta[i]*x*z)
+     ds[(((i-1)*N)+1):(i*N), ] <- cbind(trialid[i], x, z, y)
+ }
> ds$trialid <- as.factor(ds$trialid)
> head(ds)
```

```
   trialid x          z  y
1        1 0  1.5583089 11
2        1 1  0.7058709  8
3        1 1  0.2981992  8
4        1 1 -0.4659147  8
5        1 0 -0.2223901 11
6        1 0  1.7232484 11
```

3.2 Statistical models to estimate an overall summary of treatment effect

Two-stage IPD-MA

In a two-stage meta-analysis, the IPD are first analyzed separately in each study to produce study-specific estimates of relative treatment effect. This implies that for our generated dataset (where we have a continuous outcome y), the following model can be estimated for each trial:

$$y_k \sim \mathcal{N}(\mu_k, \sigma^2)$$
$$\mu_k = \alpha + \beta x_k$$

(model 1, stage 1)

This stage then yields estimates of β for each trial (further denoted as $\hat{\beta}_i$) can be achieved in R as follows:

```
> results <- as.data.frame(array(NA, dim=c(N.trials,2)))
> colnames(results) <- c("betai", "var_betai")
> for (i in 1:N.trials) {
+   dsi <- as.data.frame(ds[which(ds$trialid==i),])
+   fit <- glm(y~x, data=dsi)
+   results[i,] <- c(coefficients(fit)[2], vcov(fit)[2,2])
+ }
```

A combined estimate of the relative treatment effect is then obtained by calculating a weighted average of the individual estimates $\hat{\beta}_i$.

$$\hat{\beta}_i \sim \mathcal{N}\left(\beta, \tau_\beta^2 + \mathrm{var}(\hat{\beta}_i)\right)$$

(model 1, stage 2)

The second stage of the IPD-MA can be implemented as follows in R:

```
> library(mvmeta)
> fit <- mvmeta(betai~1, S=var_betai, data=results, method="reml")
> summary(fit)
```

Results indicate that the pooled treatment effect is -2.87 (SE $= 0.11$) and that the standard deviation of the between-study heterogeneity (τ_β) is 0.27. Results from *mvmeta* also show that the I^2 statistic, which indicates the percentage of variation across studies that cannot be explained by chance, is very large: 99%.

One-stage IPD-MA

In the so-called *one-stage approach*, the IPD from all studies are analyzed simultaneously by adopting a single statistical model. It is common to stratify the study effects, and to assume a Normal distribution for the treatment effects:

$$\begin{aligned} y_{ik} &\sim& \mathcal{N}(\mu_{ik}, \sigma^2) \\ \mu_{ik} &=& \alpha_i + \beta_i x_{ik} \\ \beta_i &\sim& \mathcal{N}\left(\beta, \tau_\beta^2\right) \end{aligned}$$

(model 2)

The model can be implemented in R:

```
> library(lme4)
> lmer(y ~ 0 + trialid + x + (x-1|trialid), data=ds)
```

Results are very similar to estimates obtained by two-stage IPD-MA and indicate that the pooled treatment effect is -2.87 (SE $= 0.11$) with $\tau_\beta = 0.28$.

3.3 Statistical models to investigate heterogeneity in treatment effect

Two-stage IPD-MA

We can investigate sources of treatment effect heterogeneity by exploring the presence of effect modification due to z. In a two-stage IPD-MA, we then need to include treatment-covariate interactions in the first stage of the meta-analysis model:

$$
\begin{aligned}
y_k &\sim \mathcal{N}(\mu_k, \sigma^2) \\
\mu_k &= \alpha + \beta x_k + \gamma z_k + \theta z_k x_k
\end{aligned}
\qquad \text{(model 3, stage 1)}
$$

This can be achieved in R as follows:

```
> results <- as.data.frame(array(NA, dim=c(N.trials,2)))
> colnames(results) <- c("betai", "var_betai")
> for (i in 1:N.trials) {
+    dsi <- as.data.frame(ds[which(ds$trialid==i),])
+    fit <- glm(y~x+z+x:z, data=dsi)
+    results[i,] <- c(coefficients(fit)["x"], vcov(fit)["x", "x"])
+ }
```

The second stage of the IPD-MA can again use the equations from model 1, stage 2, and yields a pooled treatment effect of -2.95 (SE $= 0.02$). The degree of between-study heterogeneity τ_β has decreased from 0.27 to 0.06, and the I^2 statistic has decreased from 99% to 90%.

One-stage IPD-MA

It is possible investigate heterogeneity in treatment effect by adjusting model 2 to account for effect modification by z. Although it is common to assume common interaction terms across studies, we here allow interaction terms to be heterogeneous across studies:

$$
\begin{aligned}
y_{ik} &\sim \mathcal{N}(\mu_{ik}, \sigma^2) \\
\mu_{ik} &= \alpha_i + \beta_i x_{ik} + \gamma_i z_{ik} + \theta_i z_{ik} x_{ik} \\
\beta_i &\sim \mathcal{N}\left(\beta, \tau_\beta^2\right)
\end{aligned}
\qquad \text{(model 4)}
$$

We can estimate this model in R as follows:

```
> library(lme4)
> lmer(y ~ 0 + trialid + x + (x-1|trialid) + z:trialid + z:x:trialid, data=ds)
```

Results are again very similar to the two-stage approach: $\hat{\beta} = -2.95$ (SE $= 0.02$) with $\tau_\beta = 0.06$ and suggest that heterogeneity in treatment effect can partially be explained by the presence of effect modification.

4 Overview of included articles

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