A meta-analysis method based on simulated individual patient data

Yusuke Yamaguchi, Wataru Sakamoto, Shingo Shirahata
Division of Mathematical Science, Graduate School of Engineering Science, Osaka University
1-3, Machikaneyama-cho, Toyonaka. Osaka, 560-8531, Japan
E-mail: yamaguti@sigmath.es.osaka-u.ac.jp

Masashi Goto
Biostatistical Research Association, NPO
2-22-10-A411, Kamishinden, Toyonaka, Osaka, 560-0085, Japan

1 Introduction

In clinical evaluation processes, meta-analysis is carried out to synthesis results of several trials. However, most of meta-analysis methods build models on summary statistics reported from each trial, and therefore a pooled effect size is estimated with ignoring scheme of sampling individual patient data (IPD), which should have been measured in each trial. Above all, meta-regression (MR) models, which are techniques for modeling relationship between an effect size and trial-level covariates with intending to search characteristic factors, have been often subjected to criticism. The MR models incorporate as covariates summary statistics on background factors of patients for each trial, such as a mean age and a proportion of male patients. This means that characteristics of patients are evaluated expediently, with unavailable patient-specific covariates replaced by trial-specific covariates. It often involves a technical issue that is referred to as ecological bias, and leads to limitation in interpretation. Especially, it is well known that the treatment-covariate interaction effect estimated by fitting MR models has seriously lower statistical power in comparison with those estimated by fitting models to IPD, where we refer to these models as IPD models. Berlin *et al.* (2002) conducted analyses of both individual patient-level and group-level data from five trials in their clinical research, and showed that the group-level analyses failed to detect interaction between treatment and a patient characteristic factor. Some meta-analysis methods based on IPD models have been discussed among many researchers as alternative solutions to this kind of problems; however, they cannot always be applied to all situations due to difficulties in obtaining IPD.

First, we discuss limitation underlying MR models as the following sources of above problems: (a) MR models can essentially estimate only between-trial interaction, (b) MR models cannot incorporate within-trial variability of covariates. Then, based on these discussion, we suggest a meta-analysis method using simulated IPD, in which parameters of an IPD model are estimated from trial-level summary statistics and pseudo-IPD are then reconstructed by statistical simulation from the estimated IPD models. It is easy to extend this method to combine additional IPD from some other trials, if available. Once pseudo-IPD are generated, more flexible and comprehensive statistical methods can be applied to the reconstructed IPD, and difficulties in IPD collection would be cleared out.

1.1 IPD and MR models

Suppose that we observe one continuous outcome response and one continuous covariate of interest for each patient, and that patients are assigned to either treatment group (T) or a control group (C) in each trial ($i = 1, \ldots, I$), with $n_{i\mathrm{T}}$ and $n_{i\mathrm{C}}$ patients respectively. Let y_{ij} and z_{ij} be a patient-level response and a covariate observed for the j-th patient ($j = 1, \ldots, n_i$) in the i-th trial, and let x_{ij} be coded 0/1 to denote control/treatment group. Given IPD in each trial, a common IPD model

$$(1) \quad y_{ij} = \phi_i + \theta x_{ij} + \mu z_{ij} + \gamma_{\mathrm{B}} x_{ij} \bar{z}_i + \gamma_{\mathrm{W}} x_{ij}(z_{ij} - \bar{z}_i) + \epsilon_{ij}, \quad \epsilon_{ij} \sim \mathrm{N}(0, \sigma_{yi}^2)$$

is fitted to each observation (y_{ij}, x_{ij}, z_{ij}), where ϕ_i is a fixed trial effect, θ is the mean treatment effect, μ is the mean change in control group response for a one-unit increase in z_{ij}, γ_{B} and γ_{W} are the between-trial and within-trial effect parameters of treatment-covariate interaction. $\bar{z}_i = n_i^{-1} \sum_{i=1}^{I} z_{ij}$

denotes the mean covariate value in i-th trial. Note that IPD models (1) separates between-trial and within-trial effect of the treatment-covariate interaction. This kind of modeling framework for the hierarchical data is recommended in some literatures (e.g. Neuhaus & Kalbfleisch (1998)), and a related issue in meta-analysis is discussed in detail by Riley *et al.* (2008).

On the other hand, if available summary statistics in each trial include the mean response difference between groups $d_i = n_{i\mathrm{T}}^{-1}\sum_{j\in\mathrm{T}} y_{ij} - n_{i\mathrm{C}}^{-1}\sum_{j\in\mathrm{C}} y_{ij}$, its variance $\mathrm{Var}(d_i)$, and the mean covariate $\bar{z}_i$, an MR model

$$(2) \quad d_i = \alpha + \beta\bar{z}_i + \epsilon_i, \quad \epsilon_i \sim \mathrm{N}(0, \sigma_{di}^2)$$

is fitted to the statistics $(d_i, \bar{z}_i)$, where $\sigma_{di}^2 = \mathrm{Var}(d_i)$ is assumed to be known.

2 Limitation underlying MR models

2.1 Source (a)

Taking into account an assumption in the MR model (2), we encounter an apparent problem due to source (a). If one assumes $z_{ij} = \bar{z}_i$ in the IPD model (1), the same form as the representation of the MR model (2) is derived through a simple development. Thus, α and β in the MR model (2) are equivalent to θ and γ_{B}, respectively, in the IPD model (1). However, we have more interest in the parameter γ_{W}, increase in treatment effect according to one-unit increase in a patient-level covariate z_{ij}. If we intend to estimate γ_{W} using the estimate of γ_{B} expediently, this might lead to an incorrect conclusion. In particular, as is well known in epidemiological study, identifying characteristics of patients with aggregated data by such MR models is subject to bias or confounding, which is known as ecological bias (Morgenstern, 1982). Riley *et al.* (2008) advocated that it is the only solution to this problem to collect additional IPD from some trials.

2.2 Source (b)

For simplicity, we assume that it is valid to fit an IPD model under the assumption of $\gamma_{\mathrm{B}} = \gamma_{\mathrm{W}} = \gamma$,

$$(3) \quad y_{ij} = \phi_i + \theta x_{ij} + \mu z_{ij} + \gamma x_{ij} z_{ij} + \epsilon_{ij}, \quad \epsilon_i \sim \mathrm{N}(0, \sigma_{yi}^2)$$

to each observation (y_{ij}, x_{ij}, z_{ij}). This is the case where the above source (a) essentially causes no problem. Simmons & Higgins (2007) compared the power function of treatment-covariate interaction effect in an MR model with that in an IPD model under the following assumptions: (i) IPD distributes according to the model (3), where $\sigma_{y1}^2 = \cdots = \sigma_{yI}^2 = \sigma_y^2$, and (ii) all trials are balanced, so treatment and control groups have equal numbers of patients, $n_i/2$, (iii) both the mean and the variance of the covariate are the same in treatment and control groups within each trial. In the MR model (2), denoting $\bar{z}_i^* = \bar{z}_i - n^{-1}\sum_i \bar{z}_i n_i$, the power function of the hypothesis test for null hypothesis $\mathrm{H}_0 : \beta = 0$ against alternative hypothesis $\mathrm{H}_1 : \beta = \beta_1$ with the significance level 0.05 is given by

$$(4) \quad \Phi\left(-1.96 + \frac{\beta_1}{2\sigma_y}\sqrt{\textstyle\sum_i n_i \bar{z}_i^{*2}}\right) + \Phi\left(-1.96 - \frac{\beta_1}{2\sigma_y}\sqrt{\textstyle\sum_i n_i \bar{z}_i^{*2}}\right)$$

where $\Phi(\cdot)$ denotes the CDF of the standard normal distribution (Simmons & Higgins, 2007). On the other hand, in the IPD model (3), denoting $z_{ij}^* = z_{ij} - n^{-1}\sum_{ij} z_{ij}$ and supposing that the covariates z_{ij} in the i-th trial is normally distributed with mean m_{zi} and variance σ_{zi}^2 , the power function of the hypothesis test for null hypothesis $\mathrm{H}_0 : \gamma = 0$ against alternative hypothesis $\mathrm{H}_1 : \gamma = \gamma_1$ with the significance level 0.05 is given as follows (Simmons & Higgins, 2007).

$$(5) \quad \Phi\left(-1.96 + \frac{\gamma_1}{2\sigma_y}\sqrt{\textstyle\sum_i n_i(\sigma_{zi}^2 + \bar{z}_i^{*2})}\right) + \Phi\left(-1.96 - \frac{\gamma_1}{2\sigma_y}\sqrt{\textstyle\sum_i n_i(\sigma_{zi}^2 + \bar{z}_i^{*2})}\right).$$

The power functions (4) and (5) differ only in inclusion of σ_{zi}^2. Therefore, IPD models are always more powerful than MR models due to σ_{zi}^2. Actually, although we could use the sample variance of covariates in each trial, this information would be ignored in the MR model (2) because of the assumption $z_{ij} = \bar{z}_i$.

From the above consideration, if γ_{W} is estimated by the MR model (2), we should be concerned that bias should appear due to the source (a) and precision should decrease due to the source (b).

The sufficient statistics for the parameters in the IPD model (1) are obviously $\sum_{j\in \mathrm{T}} y_{ij}$, $\sum_{j\in \mathrm{C}} y_{ij}$, $\sum_{j\in \mathrm{T}} z_{ij}$, $\sum_{j\in \mathrm{C}} z_{ij}$, $\sum_{j\in \mathrm{T}} y_{ij}^2$, $\sum_{j\in \mathrm{C}} y_{ij}^2$, $\sum_{j\in \mathrm{T}} z_{ij}^2$, $\sum_{j\in \mathrm{C}} z_{ij}^2$, $\sum_{j\in \mathrm{T}} y_{ij}z_{ij}$ and $\sum_{j\in \mathrm{C}} y_{ij}z_{ij}$; however, $\sum_{j\in \mathrm{T}} y_{ij}z_{ij}$ and $\sum_{j\in \mathrm{C}} y_{ij}z_{ij}$ are not usually available in the case that the MR model is applied, and also $\sum_{j\in \mathrm{T}} z_{ij}^2$ and $\sum_{j\in \mathrm{C}} z_{ij}^2$ are ignored in the MR model. This means that unless informations such as the correlation between y_{ij} and z_{ij} are available, it is impossible to estimate individual-level relationships (e.g. γ_{W}). Therefore, we derive the likelifood function based on the marginal distribution of y_{ij} in the IPD model, obtained by marginalizing with respect to z_{ij}, treated as random variables. Once the correlation between y_{ij} and z_{ij} are estimated, we can generate IPD by simulation, and then estimate γ_{W} by fitting the IPD model to these pseudo-IPD with a standard method.

3 A method based on simulated IPD

In this section, a method based on simulated IPD is provided. This method, which has been inspired by multiple imputation applied in the analysis of incomplete data with missing (Rubin, 1987), takes the following simple procedure for inference of parameters: (i) by statistical simulation, pseudo IPD (Simulated IPD: SIPD) are generated repeatedly from a model estimated using the observed summary statistics (the mean and the variance of response and covariate), (ii) a standard IPD model is fitted to each SIPD, (iii) resulting estimates for each SIPD are suitably summarized. Here, we refer to these estimating process as SIPD method.

3.1 Simulation models

The most important step in above procedure is to identify the models for generating SIPD, which we call simulation models. Such as a meta-analysis, inference on the relationships between individual specific quantities using aggregated data is known as ecological inference. Wakefield & Salway (2001) presented a statistical framework for ecological inference, describing parametric models for binary response data that include within-aggregation variability of covariates, which is intended to reduce the ecological bias. Jackson *et al.* (2006) suggested that the ecological inference might be improved by supplementing aggregated information with some IPD from the other aggregations. In this subsection, we apply these modeling scheme in the case of continuous responses.

For simulation models describing the relationships among (y_{ij}, x_{ij}, z_{ij}), we consider the following IPD models with the assumption that z_{ij} is normally distributed ($i = 1, \ldots, I$, $j = 1, \ldots, n_i$).

$$y_{ij} = \phi_i + \theta x_{ij} + \mu z_{ij} + \gamma_{\mathrm{B}} x_{ij}\bar{z}_i + \gamma_{\mathrm{W}} x_{ij}(z_{ij} - \bar{z}_i) + \epsilon_{ij}, \quad \epsilon_{ij} \sim \mathrm{N}(0, \sigma_y^2), \tag{6}$$

where

$$x_{ij} = \begin{cases} 1, & j \in \mathrm{T} \\ 0, & j \in \mathrm{C} \end{cases}, \quad z_{ij} \sim \begin{cases} \mathrm{N}(m_{zi\mathrm{T}}, \sigma_{zi\mathrm{T}}^2), & j \in \mathrm{T} \\ \mathrm{N}(m_{zi\mathrm{C}}, \sigma_{zi\mathrm{C}}^2), & j \in \mathrm{C} \end{cases},$$

and $\bar{z}_i$ is a constant. Assuming that z_{ij} and ϵ_{ij} are independenty distributed, we have the joint distribution of (y_{ij}, z_{ij}) as a bivariate normal distirbution in each trial and group, that is,

$$\begin{bmatrix} y_{ij} \\ z_{ij} \end{bmatrix} \sim \begin{cases} \mathrm{N}_2\left(\begin{bmatrix} m_{yi\mathrm{T}} \\ m_{zi\mathrm{T}} \end{bmatrix}, \begin{bmatrix} (\mu+\gamma_{\mathrm{W}})^2\sigma_{zi\mathrm{T}}^2 + \sigma_y^2 & (\mu+\gamma_{\mathrm{W}})\sigma_{zi\mathrm{T}}^2 \\ (\mu+\gamma_{\mathrm{W}})\sigma_{zi\mathrm{T}}^2 & \sigma_{zi\mathrm{T}}^2 \end{bmatrix}\right), & j \in \mathrm{T} \\ \mathrm{N}_2\left(\begin{bmatrix} m_{yi\mathrm{C}} \\ m_{zi\mathrm{C}} \end{bmatrix}, \begin{bmatrix} \mu^2\sigma_{zi\mathrm{C}}^2 + \sigma_y^2 & \mu\sigma_{zi\mathrm{C}}^2 \\ \mu\sigma_{zi\mathrm{C}}^2 & \sigma_{zi\mathrm{C}}^2 \end{bmatrix}\right), & j \in \mathrm{C} \end{cases}, \tag{7}$$

where $m_{yi\mathrm{T}} = \phi_i + \theta + (\mu + \gamma_{\mathrm{W}})m_{zi\mathrm{T}} + (\gamma_{\mathrm{B}} - \gamma_{\mathrm{W}})\bar{z}_i$ and $m_{yi\mathrm{C}} = \phi_i + \mu m_{zi\mathrm{C}}$. Now, let $Y_{\mathrm{SUM}} = \{(\bar{y}_{i\mathrm{T}}, s_{yi\mathrm{T}}^2, \bar{y}_{i\mathrm{C}}, s_{yi\mathrm{C}}^2, \bar{z}_{i\mathrm{T}}, s_{zi\mathrm{T}}^2, \bar{z}_{i\mathrm{C}}, s_{zi\mathrm{C}}^2), i = 1, \ldots, I\}$ be observed variables, where $\bar{y}_{i\mathrm{T}} = n_{i\mathrm{T}}^{-1}\sum_{j\in \mathrm{T}} y_{ij}$, $s_{yi\mathrm{T}}^2 = n_{i\mathrm{T}}^{-1}\sum_{j\in \mathrm{T}}(y_{ij} - \bar{y}_{\mathrm{T}})^2$ and other summary statistics are also similarly defined. As described previously, it is impossible to directly estimate parameters $\eta = (\phi_1, \ldots, \phi_I, \theta, \mu, \gamma_{\mathrm{B}}, \gamma_{\mathrm{W}}, \sigma_y^2)$ from the model (6) because the sufficient statistics for η in the model (6) include not only Y_{SUM} but also $\sum_{j\in \mathrm{T}} y_{ij}z_{ij}$ and $\sum_{j\in \mathrm{C}} y_{ij}z_{ij}$. So, we consider the marginal distribution of y_{ij}, which is obtained by integrating the bivariate normal distribution (7) with respect to z_{ij}, so that

$$y_{ij} \sim \begin{cases} \mathrm{N}(m_{yi\mathrm{T}}, (\mu+\gamma_{\mathrm{W}})^2\sigma_{zi\mathrm{T}}^2 + \sigma_y^2), & j \in \mathrm{T} \\ \mathrm{N}(m_{yi\mathrm{C}}, \mu^2\sigma_{zi\mathrm{C}}^2 + \sigma_y^2), & j \in \mathrm{C} \end{cases}. \tag{8}$$

Estimating parameters $(m_{zi\mathrm{T}}, \sigma^2_{zi\mathrm{T}}, m_{zi\mathrm{C}}, \sigma^2_{zi\mathrm{C}})$ of the covariate distribution by the moment method, i.e. $\hat{m}_{zi\mathrm{T}} = \bar{z}_{i\mathrm{T}}$, $\hat{\sigma}^2_{zi\mathrm{T}} = s^2_{zi\mathrm{T}}$, $\hat{m}_{zi\mathrm{C}} = \bar{z}_{i\mathrm{C}}$, $\hat{\sigma}^2_{zi\mathrm{C}} = s^2_{zi\mathrm{C}}$, we obtain the log likelihood function from (8) as follows.

$$(9)\quad l_{\mathrm{SUM}}(\eta) = \sum_{i=1}^{I}\left[-\frac{n_{i\mathrm{T}}((\bar{y}_{i\mathrm{T}} - \phi_i - \theta - (\mu+\gamma_{\mathrm{W}})\bar{z}_{i\mathrm{T}} - (\gamma_{\mathrm{B}}-\gamma_{\mathrm{W}})\bar{z}_i)^2 + s^2_{yi\mathrm{T}})}{(\mu+\gamma_{\mathrm{W}})^2 s^2_{zi\mathrm{T}} + \sigma^2_y}\right.$$
$$\left. -\frac{n_{i\mathrm{C}}((\bar{y}_{i\mathrm{C}} - \phi_i - \mu\bar{z}_{i\mathrm{C}})^2 + s^2_{yi\mathrm{C}})}{\mu^2 s^2_{zi\mathrm{C}} + \sigma^2_y} - n_{i\mathrm{T}}\log((\mu+\gamma_{\mathrm{W}})^2 s^2_{zi\mathrm{T}} + \sigma^2_y) - n_{i\mathrm{C}}\log(\mu^2 s^2_{zi\mathrm{C}} + \sigma^2_y)\right].$$

It is obvious from expression (9) that the sufficient statistics reduce to Y_{SUM}, thus the parameters η are estimable and we get their maximum likelihood estimates (MLEs) $\hat{\eta}$. A remarkable aspect of these estimating process is that the correlation of (y_{ij}, z_{ij}) are replaced with that of $(\bar{y}_{i\mathrm{T}}, \bar{z}_{i\mathrm{T}})$ or $(\bar{y}_{i\mathrm{C}}, \bar{z}_{i\mathrm{C}})$. Moreover $\sigma^2_{zi\mathrm{T}}$ and $\sigma^2_{zi\mathrm{C}}$ ignored in the MR model (2) contribute to estimating η.

It is easy to extend to combine IPD from some trials if they are available. Let $Y_{\mathrm{IPD}} = \{(y_{ij}, x_{ij}, z_{ij}), i = I+1, \ldots, I', j = 1, \ldots, n_i\}$ be IPD observed actually in i-th trial $(i = I+1, \ldots, I')$. In this case, the total log likelihood function becomes $l_{\mathrm{COMB}}(\eta) = l_{\mathrm{SUM}}(\eta) + l_{\mathrm{IPD}}(\eta)$ where $l_{\mathrm{IPD}}(\eta)$ is obtained by fitting the IPD model (3) to Y_{IPD}, and $l_{\mathrm{SUM}}(\eta)$ is the log likelihood for Y_{SUM}. Thus, the MLEs $\hat{\eta}$ are obtained by maximizing $l_{\mathrm{COMB}}(\eta)$ with respect to η.

3.2 A procedure of implementation

Regarding the model (6) as simulation models, we generate SIPD by sampling from the bivariate normal distribution with the MLEs $\hat{\eta}$ as their parameters. Let $Y^*_{\mathrm{IPD}} = \{(y_{ij}, x_{ij}, z_{ij}), i = 1, \ldots, I, j = 1, \ldots, n_i\}$ be the original IPD from which summary statistics Y_{SUM} are actually observed. The SIPD method corresponds to random sampling from the conditional distribution $p(Y^*_{\mathrm{IPD}}|Y_{\mathrm{SUM}}, \hat{\eta})$ given Y_{SUM} and the MLEs $\hat{\eta}$, where $p(Y^*_{\mathrm{IPD}}|Y_{\mathrm{SUM}}, \hat{\eta})$ is the conditional density of Y^*_{IPD} given Y_{SUM} in the bivariate normal distribution (7). Let K sets of pseudo Y^*_{IPD} which are simulated by random sampling from $p(Y^*_{\mathrm{IPD}}|Y_{\mathrm{SUM}}, \hat{\eta})$ be $Y^{[k]}_{\mathrm{SIPD}} = \{(y^{[k]}_{ij}, x^{[k]}_{ij}, z^{[k]}_{ij}), i = 1, \ldots, I, j = 1, \ldots, n_i, k = 1, \ldots, K\}$. Once $Y^{[k]}_{\mathrm{SIPD}}$ are generated, one can estimate the parameters of interest, say γ_{W}, by fitting more standard IPD models to these data-set.

Note that inference of interesting parameters based on $Y^{[k]}_{\mathrm{SIPD}}$ sampled from $p(Y^*_{\mathrm{IPD}}|Y_{\mathrm{SUM}}, \hat{\eta})$ is similar to conditional parametric bootstrap method (Efron, 1994). It is well known that in the analysis of the incomplete data this method tends to underestimate the precision of resulting estimates. An estimating procedure of γ_{W} by SIPD method is as follows.

S1. The MLEs $\hat{\eta}$ are computed by maximizing $l_{\mathrm{SUM}}(\eta)$ with respect to η.

S2. K sets of $Y^{[k]}_{\mathrm{SIPD}}, k = 1, \ldots, K$ in each trial or group are generated by sampling from the bivariate normal distribution (7) with $\hat{\eta}$ as their parameters.

S3. The IPD model (1) are fitted to $Y^{[k]}_{\mathrm{SIPD}}$, and then the MLE $\hat{\gamma}^{[k]}_{\mathrm{W}}$ of γ_{W} is obtained.

S4. The mean of $\hat{\gamma}_{\mathrm{W}}$ is computed by $\mathrm{E}(\hat{\gamma}_{\mathrm{W}}) = K^{-1}\sum_{k=1}^{K}\hat{\gamma}^{[k]}_{\mathrm{W}}$, and a confidence interval is constructed (or a p-value is computed) with the percentile method.

If $Y_{\mathrm{IPD}} = \{(y_{ij}, x_{ij}, z_{ij}), i = I+1, \ldots, I', j = 1, \ldots, n_i\}$ as well as Y_{SUM} are observed, η is obtained by maximizing $l_{\mathrm{COMB}}(\eta)$, and then $Y^{[k]}_{\mathrm{SIPD}}, k = 1, \ldots, K$ on i-th trial $(i = 1, \ldots, I)$ are generated similarly with the above procedure. Thus, the parameters of interest, say γ_{W}, are estimated by fitting the IPD model (1) to $(Y^{[k]}_{\mathrm{SIPD}}, Y_{\mathrm{IPD}})$ in the same way.

4 Simulation study

By using artificial data, we show the difference on the evaluation of the treatment-covariate interaction effect among three kinds of methods (fitting models to the original IPD, fitting MR models and the SIPD method).

Table 1. Statistical power estimated by three methods.

		$(I, n_i) = (6, 200)$			$(I, n_i) = (12, 100)$		
σ_z^2	σ_{zi}^2	MR	IPD	SIPD	MR	IPD	SIPD
5	5	0.265	0.518	0.475	0.330	0.580	0.498
	10	0.292	0.748	0.626	0.299	0.768	0.633
	20	0.265	0.921	0.773	0.337	0.939	0.793
10	5	0.461	0.691	0.601	0.532	0.726	0.619
	10	0.474	0.834	0.690	0.527	0.852	0.711
	20	0.462	0.957	0.837	0.510	0.963	0.857
20	5	0.728	0.849	0.767	0.769	0.878	0.799
	10	0.698	0.915	0.816	0.775	0.942	0.864
	20	0.687	0.974	0.890	0.796	0.982	0.931

Table 2. Bias and variance of the estimators by three methods.

σ_z^2	σ_{zi}^2	Bias.MR	Bias.IPD	Bias.SIPD	Var.MR	Var.IPD	Var.SIPD
5	5	−0.0543	−0.0016	−0.0530	0.0223	0.0178	0.0185
	10	−0.0408	−0.0001	−0.0350	0.0215	0.0085	0.0133
	20	−0.0465	−0.0020	−0.0193	0.0261	0.0040	0.0074
10	5	−0.0481	0.0005	−0.0451	0.0137	0.0169	0.0092
	10	−0.0488	−0.0006	−0.0405	0.0108	0.0084	0.0079
	20	−0.0427	0.0022	−0.0203	0.0123	0.0045	0.0056
20	5	−0.0542	−0.0001	−0.0529	0.0054	0.0173	0.0050
	10	−0.0466	−0.0002	−0.0430	0.0053	0.0083	0.0044
	20	−0.0433	−0.0029	−0.0212	0.0061	0.0038	0.0035

Simulation 1 The model for generating artificial data was as follows.

$$y_{ij} = 50 + 2x_{ij} + 0.3z_{ij} + 0.2x_{ij}z_{ij} + \epsilon_{ij}, \quad \epsilon_{ij} \sim \mathrm{N}(0, 25).$$

We considered two scenarios of the number of trials and patients in each trial $(I, n_i) \in \{(6, 200), (12, 100)\}$, where $n_1 = \cdots = n_I$ and $n_{i\mathrm{T}} = n_{i\mathrm{C}} = n_i/2$. The covariates in each trial are simple random sequences from $z_{ij} \sim \mathrm{N}(m_{zi}, \sigma_{zi}^2)$, $m_{zi} \sim \mathrm{N}(30, \sigma_z^2)$. Moreover, we controlled the covariate distribution both between-trials and within-trial by nine scenario of $\sigma_z^2 \in \{5, 10, 20\}$ and $\sigma_{zi}^2 \in \{5, 10, 20\}$, where $\sigma_{z1}^2 = \cdots = \sigma_{zI}^2$. The settings of each parameter was motivated to suppose that the theoretic values of statistical power computed by expressions (4) and (5) differ. First, we generated IPD (y_{ij}, x_{ij}, z_{ij}) and then fit the model (3) to the IPD to estimate γ. Next, we obtained summary statistics Y_{SUM} from the IPD and then fit the MR model (2). Moreover, we generated $K = 100$ bootstrap samples of SIPD $Y_{\mathrm{SIPD}}^{[k]}$ from Y_{SUM} in the way described in Section 3, and then fit the model (3) to each $Y_{\mathrm{SIPD}}^{[k]}$ to get $\hat{\gamma}^{[k]}$. The purpose of Simulation 1 was to verify that how the variation of σ_z^2 and σ_{zi}^2 would affect statistical power estimated by three methods. Here, we tested the null hypothesis $\mathrm{H}_0 : \gamma = 0$ (or $\mathrm{H}_0 : \beta = 0$) against $\mathrm{H}_1 : \gamma \neq 0$ (or $\beta \neq 0$) by the three methods for 1000 sets of artificial data following the above model, and then the power was estimated by (the number of rejected tests)/1000. Table 1 shows the resulting power. The SIPD method provided remarkably higher power of interaction effect than those obtained by fitting MR models in all the scenarios. Even in the case of small size of σ_z^2, SIPD method could retain the high power with σ_{zi}^2, which was only slightly less than those obtained by using the original IPD. Moreover, the test with more number of trials was more powerful.

Simulation 2 The model for generating artificial data was as follows.

$$y_{ij} = 50 + 2x_{ij} + 0.3z_{ij} + 0.2x_{ij}\bar{z}_i + 0.25x_{ij}(z_{ij} - \bar{z}_i) + \epsilon_{ij}, \quad \epsilon_{ij} \sim \mathrm{N}(0, 25).$$

The number of trials and patients in each trial is $(I, n_i) = (12, 100)$, where $n_1 = \cdots = n_I$ and $n_{i\mathrm{T}} = n_{i\mathrm{C}} = n_i/2$. The setting for covariates in each trial was equivalent to those in Simulation 1. Note that we fit the model (1) to IPD or SIPD to estimate γ_{W}. In SIPD method, we generated $K = 100$ bootstrap samples of SIPD. The purpose of Simulation 2 was to verify that how the difference between γ_{B} and γ_{W} would affect the estimates obtained by the three methods. Firstly, we tested the null hypothesis $\mathrm{H}_0 : \gamma_{\mathrm{W}} = 0$ against $\mathrm{H}_1 : \gamma_{\mathrm{W}} \neq 0$ by two methods fitting the IPD model (to original

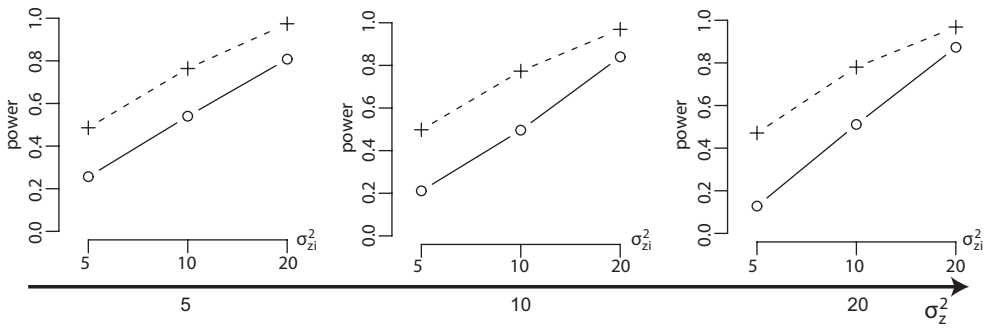

Figure 1. Statistical power estimated by two methods (+− IPD; ◯− SIPD).

IPD and SIPD) for 1000 sets of artificial data following above model, and then the power is estimated by (the number of rejected tests)/1000. Note that the power of the test of $\mathrm{H}_0 : \beta = 0$ in fitting the MR model (2) cannot be directly compared with the power of the test of $\mathrm{H}_0 : \gamma_{\mathrm{W}} = 0$ becouse they should give very different interpretation. Secondly, we compute the bias and the variance of the estimators for γ_{W} and β by the three methods as follows: $\mathrm{Bias.IPD} = R^{-1}\sum_{r=1}^{R}(\hat{\gamma}^{*r}_{\mathrm{W.IPD}} - \gamma_{\mathrm{W}})$, $\mathrm{Var.IPD} = R^{-1}\sum_{r=1}^{R}(\hat{\gamma}^{*r}_{\mathrm{W.IPD}} - \hat{\gamma}_{\mathrm{W.IPD}})^2$, $\mathrm{Bias.MR} = R^{-1}\sum_{r=1}^{R}(\hat{\beta}^{*r}_{\mathrm{MR}} - \gamma_{\mathrm{W}})$, $\mathrm{Var.MR} = R^{-1}\sum_{r=1}^{R}(\hat{\beta}^{*r}_{\mathrm{MR}} - \hat{\beta}_{\mathrm{MR}})^2$, $\mathrm{Bias.SIPD} = R^{-1}\sum_{r=1}^{R}(\hat{\gamma}^{*r}_{\mathrm{W.SIPD}} - \gamma_{\mathrm{W}})$, $\mathrm{Var.SIPD} = R^{-1}\sum_{r=1}^{R}(\hat{\gamma}^{*r}_{\mathrm{W.SIPD}} - \hat{\gamma}_{\mathrm{W.SIPD}})^2$, where $\hat{\gamma}^{*r}_{\mathrm{W.IPD}}$, $\hat{\beta}^{*r}_{\mathrm{MR}}$ and $\hat{\gamma}^{*r}_{\mathrm{W.SIPD}}$ denote the estimates of γ_{W} or β from the r-th data set ($r = 1, \ldots, R$), which are given by fitting the IPD model to original IPD, fitting the MR model and the SIPD method, respectively, where $\hat{\gamma}^{*r}_{\mathrm{W.SIPD}}$ is the mean values of K bootstrap estimates, so that $\hat{\gamma}^{*r}_{\mathrm{W.SIPD}} = K^{-1}\sum_{k=1}^{K}(\hat{\gamma}^{[k]}_{\mathrm{W.SIPD}})^{*r}$. Also, $\hat{\gamma}_{\mathrm{W.IPD}} = R^{-1}\sum_{r=1}^{R}\hat{\gamma}^{*r}_{\mathrm{W.IPD}}$, $\hat{\beta}_{\mathrm{MR}} = R^{-1}\sum_{r=1}^{R}\hat{\beta}^{*r}_{\mathrm{MR}}$, $\hat{\gamma}_{\mathrm{W.SIPD}} = R^{-1}\sum_{r=1}^{R}\hat{\gamma}^{*r}_{\mathrm{W.SIPD}}$. Figure 1 shows the resulting power, and Table 2 shows the bias and the variance. Although the power obtained by the SIPD method became extremely lower, it was close to those obtained by fitting the IPD model for bigger σ^2_{zi} and σ^2_z. One reason for this was thought that the downward bias and the variance increase of $\hat{\gamma}_{\mathrm{W}}$ by SIPD method might reflect the resulting power, that is the size of σ^2_{zi} and σ^2_z affected the bias and the variance of $\hat{\gamma}_{\mathrm{W}}$ respectively. Actually, although the bias and the variance by SIPD method increased when $\sigma^2_{zi} = 5$ and $\sigma^2_z = 5$ respectively, they were much superior to those by the MR model.

5 Conclusion

In this article, we have discussed technical issues on MR models applied to the evaluation on characteristics of patients in meta-analysis. Especially, the treatment covariate interaction effect estimated by fitting the MR model has seriously lower statistical power due to limitation in their structure. Therefore, we have presented the SIPD method that was intended to improve power. From the result of two kinds of simulation, it was shown that the SIPD method provided remarkably higher power of interaction effect than those obtained by fitting the MR model. An evaluation on the bias and the variance of the estimator for the parameter of interest also showed that SIPD method would be useful.

For future problems, although we generated multiple sets of SIPD based on conditional parametric bootstrap, SIPD with nonparametric bootstrap is expected to be more proper in terms of the essential principle of multiple imputation (Little & Rubin, 2002). Therefore, it would be considerable to improve our method by incorporating Bayesian approaches, such as data augmentation. Moreover, a meta-analysis combining summary statistics and IPD is enormously appealing as shown by Jackson *et al.* (2006) and Riley *et al.* (2008), so we should also consider verifying the efficiency and the performance of these analysis by SIPD method.

REFERENCES

Berlin J.A., Santanna J., Scmid C.H., Szczech L.A. & Feldman H.I. (2002). Individual patient versus group-level data meta-regression for the investigation of treatment effect modifiers: Ecological bias rears its ugly head. *Statistics in Medicine*, 21, 371-387.

Efron B. (1994). Missing data, imputation, and the bootstrap. *Journal of the American Statistical Association*, 89, 436 -475.

Jackson C., Best N. & Richardson S. (2006). Improving ecological inference using individual-level data. *Statistics in Medicine*, 25, 2136-2159.

Little R.J.A. & Rubin D.B. (2002). *Statistical Analysis with Missing Data, 2nd edition.* New York: John Wiley & Sons.

Morgenstern H. (1982). Uses of ecological analysis in epidemiologic research. *American Journal of Public Health*, 72, 1336-1334.

Neuhaus L.A. & Kalbfleisch J.D. (1998). Between- and within-cluster covariate effects in the analysis of clustered data. *Biometrics*, 54, 638-645.

Riley R.D., Lambert P.C., Staessen J.A., Wang J., Gueyffier F., Thijs L. & Boutitie F. (2008). Meta-analysis of continuous outcomes combining individual patient data and aggregate data. *Statistics in Medicine*, 27, 1870-1893.

Rubin D.B. (1987). *Multiple Imputation for Nonresponse in Surveys.* New York: John Wiley & Sons.

Simmonds M.C. & Higgins J.P.T. (2007). Covariate heterogeneity in meta-analysis: criteria for deciding between meta-regression and individual patient data. *Statistics in Medicine*, 26, 2982-2999.

Wakefield J. & Salway R. (2001). A statistical framework for ecological and aggregate studies. *Journal of the Royal Statistical Society, Series A: Statistics in Society*, 164, 119-137.