Exact inference on contrasts in means of intraclass correlation models with missing responses

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Abstract

Intraclass correlation models with missing data at random are considered. With a properly reduced model, a general method, which allows repeated observations with missing in non-monotone pattern, is proposed to construct exact test statistics and simultaneous confidence intervals for linear contrasts in the means. Simulation results are given to compare exact and asymptotic simultaneous confidence intervals. A real example is provided for illustration of the proposed method.

Keywords

Contrast; Exact test; Intraclass correlation model; Linear mixed model; Simultaneous confidence intervals

1 Introduction

Intraclass correlation models are popular choices to analyze data from block designs, or cluster sampling, or longitudinal studies with an individual random effect (Diggle et al., 2002, Verbeke and Molenberghs, 2000). Here we deal with such studies in which the repeated observations are missing at random and the nonmissing observations satisfy the two-component mixed linear model

$$x_{ij} = \mu_i + \alpha_j + \epsilon_{ij}, \quad i \in O_j = \{j_1, \cdots, j_{pj}\}, \quad j = 1, \cdots, n, \quad (1)$$

where $\mu_i$ is the mean value of the $i$th observation, $\alpha_j$ is the random effect of the $j$th subject, $1 \leq j_1 < \cdots < j_{pj} \leq p$. Here $p$, often pre-specified in the study design, is the number of repeated observations for each subject, $p_j$ is the number of available observations from the $j$th subject, $\alpha_j$ and $\epsilon_{ij}$ are assumed to be independent and normally distributed with mean 0 and variance $\sigma^2_{\alpha}$ and $\sigma^2_{\epsilon}$ respectively. Denote $x_j = (x_{j1}, \cdots, x_{jp_j})', \quad u_j = (\mu_{j1}, \cdots, \mu_{jp_j})'$. It is clear from the above assumption that $x_1, \cdots, x_n$ are independent, $E(x_j) = u_j$ and
\(\text{Cov}(x_j) = \sum_j \sigma^2(1 - \rho)I_{p_j} + \rho J_{p_j},\)

where \(\sigma^2 = \sigma^2_{\alpha} + \sigma^2_{\varepsilon} + \rho^2\sigma^2_{\alpha}/\sigma^2\), \(I_{p_j}\) is the \(p_j \times p_j\) identity matrix, \(1_{p_j} = (1, \cdots, 1)\)', and \(J_{p_j} = 1_{p_j}1_{p_j}'\).

Our interest lies in the inference on contrasts of the mean vector \(\mathbf{u} = (\mu_1, \mu_2, \cdots, \mu_p)'\) under model (1). For the case of all \(p_j = p\) (balanced data), a number of efficient inference procedures exist on hypothesis testing and estimation of the parameters in model (1). Indeed, one can find the uniformly minimum variance unbiased (UMVU) estimators, most powerful unbiased tests and exact simultaneous confidence intervals for all contrasts in means (Searle, et. al, 1992, Bhargava and Srivastava, 1973). However, when missing data occurs, these optimal properties do not hold, and we can not even construct exact inference on contrasts in means by the analysis of variance (ANOVA) method or the likelihood method. In this case, the asymptotic inference on parameters of intraclass correlation model based on likelihood method are usually considered in the literature. Srivastava and Carter (1986) discussed the maximum likelihood (ML) method for the intraclass correlation model with missing data. Based on their asymptotic theories, Seo and Srivastava (2000) gave the asymptotic simultaneous confidence interval for all contrasts in means. Note that the results of asymptotic inference are usually effected by sample size and missing pattern. Moreover, the ML method requires extensive numerical iterative computations since there does not exist explicit ML estimation of \((\mathbf{u}, \sigma^2_{\alpha}, \sigma^2_{\varepsilon})\) under model (1) with missing data; see Szatroski (1980). Thus simple and efficient exact tests and estimators are desirable in practice. By certain transformation, Seo and Srivastava (2000) gave an exact test statistic for the equality of the means and simultaneous confidence intervals for all contrasts in the means when the missing observations follow the monotone-type missingness, i.e. \(O_j = \{1, \cdots, p_j\}\) in model (1); see Little and Rubin (2002) for definitions of various types of missingness. However, when missing type is non-monotone, the problem of finding exact tests and estimation of contrasts in means has yet to be solved. The main difficulty lies in giving the expression of estimator for parameter of interest under a transformation model when missing data occur. This paper considers the exact inference on all contrasts of means under model (1) when the missing observations do not follow a monotone pattern. A simple method is given to construct exact confidence intervals and exact test statistics for contrasts in means. By defining index matrix of contrasts in the means for each subject, Section 2 introduces a reduced model. Based on this reduced model, Sections 3 and 4 provide a simple estimator, exact test statistic, and simultaneous confidence intervals for all contrasts in means. Finally, some simulation results and a real example are presented in Section 5 and 6, respectively.

2 Reduced model for contrasts in means

In this paper, contrasts in the mean vector \(\mathbf{u} = (\mu_1, \cdots, \mu_p)'\) are of primary interest. Denote \(\tilde{\xi}_i = \mu_i - \mu_{i+1}\) and \(\tilde{\xi} = (\tilde{\xi}_1, \cdots, \tilde{\xi}_{p-1})'\). It is easy to see that any contrast \(a'u\) can be transformed as a linear function of \(\tilde{\xi}\), where \(a = (a_1, \cdots, a_p)'\) is a non-null vector such that \(a'1_p = 0\). In fact, let \(b_i = \sum_{j=1}^i a_j\) and \(\mathbf{b} = (b_1, \cdots, b_{p-1})'\). Then

\[a'u = \sum_{i=1}^{p-1} b_i \tilde{\xi}_i = \mathbf{b}' \tilde{\xi} \quad \text{(3)}\]
Thus statistical inference on all contrasts in means can be reduced to the corresponding inference on the new parameter vector $\xi$, hereafter referred to as the contrast parameter.

We consider the transformation $y_j = C_{pj}x_j$, where

$$C_{pj} = \begin{bmatrix}
1 & -1 & 0 & \cdots & 0 \\
0 & 1 & -1 & 0 & \cdots \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & \cdots & \cdots & \cdots & 1 & -1
\end{bmatrix}_{(p_j-1)\times p_j}$$

(4)

for $p_j > 1$ and $C_1 = 0$. Clearly, $y_j = 0$ when $p_j = 1$. Without loss of generality, we assume that $p_j \geq 2$ for $j \leq n_0 \leq n$ and $p_j \leq 1$ otherwise. Note that

$$E(y_j) = C_{pj}u_j = (\mu_{j_1} - \mu_{j_1}, \cdots, \mu_{j_{p_j-1}} - \mu_{j_{p_j-1}})'$$

(5)

Hence there exists a $(p_j - 1) \times (p - 1)$ matrix $B_j$ such that

$$C_{pj}u_j = B_j\xi.$$ 

In fact, $B_j$ can be defined as follows.

**Definition 1**

$$B_j = (b_{kl}^{(j)})_{k,l=1}^{p_j-1}$$

$$b_{kl}^{(j)} = \begin{cases} 
1, & \text{if } j_k \leq l \leq j_{k+1} - 1, \\
0, & \text{otherwise},
\end{cases}$$

(6)

$k = 1, \cdots, p_j - 1$, $l = 1, \cdots, p - 1$. $B_j$ is called the index matrix of contrasts in the means for the $j$th subject.

Thus model (1) can be transformed into

$$y_j = B_j\xi + e_j, \quad \text{Cov}(e_j) = \sigma^2 G_{pj}, \quad j = 1, \cdots, n_0,$$

(7)

where $G_{pj} = C_{pj}C_{pj}' > 0$. The reduced model (7) is called the model for contrast parameter $\xi$. 

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Clearly, the reduced model is a linear regression model only on the parameter of interest $\xi$ and variance parameter $\sigma^2_e$. Thus the complicated issue of estimating $\rho$ and the mean vector with unbalanced data is avoided.

### 3 Estimation and exact test statistics

Note that $B_j$ is of full rank. Thus $\hat{\xi}$ is estimable under the reduced model (7). From the well-known least squares theory (e.g., Wang and Chow, 1994), the reduced model (7) yields unbiased estimator of $(\xi^*, \sigma^2_e)$:

\[
\begin{align*}
\hat{\xi} &= \left( \sum_{j=1}^{n_0} B' G_p^{-1} B_j \right)^{-1} \sum_{j=1}^{n_0} B' G_p^{-1} B_j y_j, \\
\hat{\sigma}^2_e &= \sum_{j=1}^{n_0} \left( y_j - B_j \hat{\xi} \right)' G_p^{-1} \left( y_j - B_j \hat{\xi} \right) / f,
\end{align*}
\]

and the following theorem.

**Theorem 1**

\[
\hat{\xi} \sim N(C_p u, \sigma^2_e \sum \xi), \ f \hat{\sigma}^2_e / \sigma^2_e \sim \chi^2_f, \ \hat{\xi} \text{ and } \hat{\sigma}^2_e \text{ are independent, where}
\]

\[
f = \sum_{j=1}^{n_0} p_j - n_0 - p + 1, \ \sum \xi = \left( \sum_{j=1}^{n_0} B' G_p^{-1} B_j \right)^{-1}.
\]

By Theorem 1, we can construct an exact test statistic for the null hypothesis $H_0 : B\xi = \delta_0$ for any $m \times (p - 1)$ matrix $B$ and $m \times 1$ vector $\delta_0$. The test statistic is given by

\[
F_0(B, \delta_0) = (B\hat{\xi} - \delta_0)' (B' \sum \xi B)^{-1} (B\hat{\xi} - \delta_0) / r \hat{\sigma}^2_e
\]

where $r = \text{rank}(B)$. Clearly, $F_0(B, \delta_0)$ follows an $F$-distribution with degrees of freedom $r$ and $f$ under $H_0$.

In particular, for the null hypothesis $H_0 : \mu_1 = \cdots = \mu_p$, that is, $H_0 : \xi = 0$, we have a test statistic

\[
F_0(I_{p-1}, 0) = \hat{\xi}' \sum \xi^{-1} \hat{\xi} / (p-1) \hat{\sigma}^2_e
\]

which has an $F$-distribution with degrees of freedom $p - 1$ and $f$ under the null hypothesis $H_0 : \xi = 0$.

Noting that under the null hypothesis $H_0 : \mu_1 = \cdots = \mu_p$,

\[
y_j = (C_p \hat{\xi})' C_p x_j \sim N(0, \sigma^2_p I_{p-1}), \ j = 1, \cdots, n_0,
\]

Seo and Srivastava (2000) obtained two exact test statistics for testing $H_0$. Let $y_j$ be a $(p - 1) \times 1$ vector with element $y_{ij} = \tilde{y}_{ij}$ if $i = j + 1 - 1$, and $y_{ij} = 0$, if otherwise, $i = 1, \cdots, p_j - 1$, where $j$ is defined in (1). Then the first test statistic in Seo and Srivastava (2000) can be written as
\[
F_{S&S1} = \frac{\sum_{i=1}^{p-1} n_i^* \tilde{y}_i / (p-1)}{\tilde{\gamma}^2},
\]

where \( \tilde{y}_i = \sum_{j=1}^{n_0} y_{ij} / n_i^* \), \( \tilde{\gamma}^2 = \sum_{i=1}^{p-1} \left\{ \sum_{j=1}^{n_0} (y_{ij} - \tilde{y}_i)^2 / f_1 \right\} / f_1 = \sum_{i=1}^{p-1} n_i^* - (p-1) \), and \( n_i^* \) is the number of non-zero elements in the set \( \{y_{i1}, \ldots, y_{in_0}\} \).

Without loss of generality, we assume that \( p_1 \leq p_2 \leq \ldots \leq p_{n_0} \). Rearranging \( y_j \) as \( (\tilde{y}_{1j}, \ldots, \tilde{y}_{(pj-1)j}, 0, \ldots, 0) \), the second test statistic by Seo and Srivastava (2000) is then

\[
F_{S&S2} = \frac{\sum_{i=1}^{p-1} n_i^* \tilde{y}_i / (p-1)}{\tilde{\gamma}^2},
\]

where \( \tilde{y}_i = \sum_{j=1}^{n_i^*} y_{ij} / n_i^* \), \( \tilde{\gamma}^2 = \sum_{i=1}^{p-1} \left\{ \sum_{j=1}^{n_i^*} (y_{ij} - \tilde{y}_i)^2 / f_2 \right\} / f_2 = \sum_{i=1}^{p-1} n_i^* - (p-1) \), and \( n_i^* \) is the number of non-zero elements in the set \( \{y_{i1}, \ldots, y_{in_0}\} \).

Clearly, \( f_1 = f_2 = f \). Furthermore, \( F_{S&S1} \) and \( F_{S&S2} \) have the same null distribution as \( F_0(I_{p-1}, 0) \) in (10). However, the distributions of \( F_{S&S1} \) and \( F_{S&S2} \) become very complicated under the alternative hypotheses (i.e. when the means are not equal). A comparison of the three test statistics is presented in Section 5.

Another special case of (9) is \( B = b \), in which the test statistic \( F_0(b, \delta_0) \) is usually replaced by the \( t \)-statistic

\[
t_0 = (b' \tilde{\xi} - \delta_0) / \sqrt{b' \Sigma_b} \]

which has a \( t \)-distribution with \( f \) degrees of freedom under \( H_0 : b' \tilde{\xi} = \delta_0 \).

Alternative expressions can be obtained to relax the complexity of computation of (8) which includes computing the inverse matrix for each \( G_{pj} \). Indeed, we have

\[
\left\{ \begin{array}{l}
\tilde{\xi} = C \rho \tilde{\eta}, \\
\tilde{\eta}^2 = \sum_{j=1}^{m} \sum_{i=1}^{p_j} \left( x_{ij} - \tilde{x}_{ij} - \tilde{\eta}_{ij} + \tilde{z}_{ij} \right)^2 / f, 
\end{array} \right.
\]

(12)

where \( \eta = (\eta^1, \ldots, \eta^{p_j})' = (V - M)^{+} z \), \( \tilde{x}_{ij} = \sum_{j=1}^{p_j} \tilde{x}_{ij} / p_j \) and \( \tilde{\eta}_{ij} = \sum_{j=1}^{p_j} \tilde{\eta}_{ij} / p_j \). Here \((\cdot)^{+}\) denotes the Moore-Penrose generalized inverse of matrix \((\cdot)\), \( z = (z_1, \ldots, z_p)' \), \( V = \text{diag}(n_i) \) and \( M = (m_{ij}) \) with elements
\[ z_i = \sum_{j=1}^{n} (x_{ij} - \bar{x}_j) \delta_{ij}, \quad n_i = \sum_{j=1}^{n} \delta_{ij}, \quad m_i = \sum_{j=1}^{n} \delta_{ij} \bar{x}_{ij} / p_j, \]

where \( 1 \leq i, k, l \leq p \),

\[ \delta_{ij} = \begin{cases} 1, & \text{if} \ i \in O, \\ 0, & \text{otherwise}. \end{cases} \]

Moreover, we can simplify the computations of test statistics (9–11) by replacing \( \sum \xi \) with

\[ \sum \xi = C_p (V - M)^+ C_p', \quad (13) \]

For the proof of (12) and (13) see the Appendix.

Clearly, when all \( p_j = p \), expressions (12) are tantamount to

\[ \left\{ \begin{array}{l} \hat{\xi} = C_p \bar{x}, \\ \hat{\sigma}^2 = \frac{\sum_{j=1}^{n} \sum_{i=1}^{p} (x_{ij} - \bar{x}_j - \bar{x}_i + \bar{x})^2}{(n-1)(p-1)}, \end{array} \right. \]

where \( \bar{x} = \sum_{j=1}^{n} x_{ij} / n \), \( \bar{x}_i = \sum_{j=1}^{n} x_{ij} / n \) and \( \bar{x} = \sum_{i=1}^{p} \sum_{j=1}^{n} x_{ij} / pn \). Thus \( (\hat{\xi}, \hat{\sigma}^2) \) is the UMVU estimator of \( (C_p u, \sigma^2_p) \) and the test based on test statistic (9) is the most powerful unbiased test when there are no missing observations, see searle, et. al (1992).

### 4 Simultaneous confidence intervals

In this section, we consider simultaneous confidence intervals of contrasts \( a'u \) for any non-null vector \( a = (a_1, \cdots, a_p)' \) such that \( a'1 = 0 \). Using (10) and (11) we have the following exact confidence intervals.

(i) The Scheffé type of simultaneous confidence intervals for all contrasts are given by

\[ a'u \in \left[ b'\hat{\xi} \pm \hat{\sigma} \sqrt{(p-1)F_{p-1, f, \alpha}} b' \sum \xi b \right], \quad (14) \]

where \( b \) is defined in (3), \( F_{p-1, f, \alpha} \) is the upper 100\( \alpha \)% quantile of an \( F \) distribution with degrees of freedom \( p - 1 \) and \( f \).

(ii) The Bonferroni type of simultaneous confidence intervals for \( k \) contrasts are given by
where $b_i$ is defined similarly as (3), and $t_{f, a/(2k)}$ is the upper 100$a/(2k)$% quantile of a $t$ distribution with $f$ degrees of freedom.

Note that if $t_{f, a/(2k)} > \sqrt{(p - 1)F_{p-1, f, a}}$, then the Bonferroni type simultaneous confidence intervals can be replaced by Scheffé type of simultaneous confidence intervals.

(iii) Let $k = 1$ in (15). Then the exact confidence intervals for a contrast is given by

$$
a'u \in \left[ b_i' \hat{\Xi} \pm \hat{\sigma}_{e'f, f_{1/2}} \sqrt{b_i' \sum_{f_i} b_i} \right], \quad i = 1, \cdots, k,
$$

(15)

It follows from the asymptotic theory of maximum likelihood estimator (MLE) that

$$
T^2 = (C_p \hat{u})' \left[ C_p W(\hat{\sigma}^2, \hat{\rho}) C_p' \right]^{-1} C_p \hat{u}
$$

(17)

has asymptotically $\chi^2$ distribution with $p - 1$ degrees of freedom. Using this, Seo and Srivastava (2000) gave asymptotic simultaneous confidence intervals for linear contrasts $a'u$ by

$$
a'u \in \left[ a'u + \sqrt{\chi_{p-1, \alpha}^2} \left[ a'C_p W(\hat{\sigma}^2, \hat{\rho}) C_p' a \right]^{1/2} \right],
$$

(18)

where $(\hat{a}', \hat{\sigma}^2, \hat{\rho})$ are MLE of $(a, \sigma^2, \rho)$ in model (1).

Here $D_j$ is a $p_j \times p$ matrix with the $(l, j)$-element being one for $l = 1, \cdots, p_j$ and zero elsewhere.

To compare the exact and asymptotic simultaneous confidence intervals, it is noticed that the former always ensures the coverage probability equal to the specified confidence level $1 - \alpha$. However, the coverage probabilities of the latter is affected by the sample size and missing type. In fact, the coverage probabilities are usually much smaller than the nominal confidence level $1 - \alpha$ when the small sample size is small and data are severely missing; see simulation results below.

5 Simulation

In this section, firstly, we compare via Monte Carlo simulation the coverage probabilities and lengths of exact simultaneous confidence intervals (Scheffé type) with that of asymptotic simultaneous confidence intervals. Let $p = 3$, $\mu = (3, 3, 5)'$, $\sigma^2 = \sigma^2 (1 - \rho) = 1$ and $\alpha = 0.05$. 
Results are displayed for three different choices (0.1, 0.5, 0.9) of ρ, two different missing types (I, II), with 10000 replicates and n = 20, 40 subjects per replicate generated in each case. Here the two missing types are, respectively,

Type I: {11(0), 3(1), 3(2), 3(3)},

Type II: {2(0), 3(1), 9(2), 4(3), 2(2, 3)},

where k(i) = k(i, i), and k(i, j) means that there are k · (n/20) subjects missing only the ith and jth observations, i, j = 0, 1, 2, 3. Clearly, the data set in Type II are missing more severely than that in Type I.

Critical values of $F_{p-1,f,a}$ in the Scheffé type of simultaneous confidence intervals for n = 20, 40 are respectively given by $F_{2,29,0.05} = 3.33, F_{2,60,0.05} = 3.15$ under Type I; $F_{2,18,0.05} = 3.55, F_{2,38,0.05} = 3.24$ under Type II. Critical values of $F_{p-1,0.05}$ in the asymptotic simultaneous confidence intervals are $F_{2,0.05} = 5.99$ for all cases of n = 20, 40 and missing types I and II. The corresponding estimated coverage probabilities for the three choices (0.1, 0.5, 0.9) of ρ are given in Table 1. The table shows that the approximation of asymptotic simultaneous confidence intervals is not satisfactory with small sample size and the coverage probabilities are considerably below the specified confidence level as the data is severely missing. One the other hand, our proposed exact confidence intervals guarantee the correct coverage probability, but at a price of having longer lengths. When the sample size is relatively small, one may wish to make a compromise between the coverage probability and the length of the confidence intervals.

We further compare the widths of the Scheffé type simultaneous confidence intervals for $\mu_1 - \mu_2, \mu_1 - \mu_3, \mu_2 - \mu_3, 2\mu_1 - \mu_2 - \mu_3, \mu_1 - 2\mu_2 + \mu_3$ with that of asymptotic simultaneous confidence intervals by averaging the lengths of the simultaneous confidence intervals from the 10000 replicates. Table 2 shows that the differences in lengths between the two methods are larger with missing Type II than that with missing type I.

Therefore, with small sample size and severely missing data, the exact method is more appealing than the asymptotic method.

Tables 3 compares the power of our proposed test with the two exact tests by Seo and Srivastava (2000) for testing $H_0 : \mu_1 = \cdots = \mu_p$ all with the same level of significance of 0.05. Since all three test statistics are independent of ρ in model (1), we set ρ = 0.1. The table shows that in most cases the power of the test based on $F_{0(l_p-1)}$ is the highest for unequal means, and the power of $F_{SK\&S1}$ is the lowest. Moreover, the power of $F_{SK\&S1}$ and $F_{SK\&S2}$ is substantially adversely affected by the order of the $\mu_i$s. Though performing almost equally well if the values of $\{\mu_i\}$ are in monotonic order, they two exact tests $F_{SK\&S1}$ and $F_{SK\&S2}$ have much lower power under other alternatives than the proposed test in the present paper.

6 An example

In this section, we shall discuss a set of data from the Calcium for Preeclampsia Prevention (CPEP) Study (Levine, et.al, 1997) to illustrate the method developed in this paper. In this study, blood samples were collected during the trial from the study participants at various gestational age, and soluble fms-like tyrosine kinase 1 (sFlt1) level (pg/ml) were assayed from the blood samples of a subgroup of study participants, at six intervals of gestational age, 8–20, 21–24, 25–28, 29–32, 33–36, and 37–39 weeks. One interest of the trial is to investigate how the sFlt1 levels change over gestational age, especially among women who have preeclampsia.
During the trial 149 women were diagnosed as having preeclampsia. Among these, there are 22 women with only one observation each, the remaining 127 with two to four observations each during the six intervals of gestational age. Here $p = 6$, $n_0 = 127$, $n = 149$. Since the sFlt1 value is large, we consider the observations after logarithmic transformation. Denote by $\mu_i$ the mean level of ln sFlt1 in the $i$th gestational age interval, $i = 1, \ldots, 6$. By Calculating (12) and (13), we obtain $\hat{\xi} = (-0.248, 0.074, -0.187, -0.853, -0.278)'$, $\hat{\sigma}_x^2=0.196$

\[
\sum_{k=1}^{6} \frac{1}{\hat{\sigma}_x^2} \left[ \begin{array}{cccc}
0.205 & -0.202 & 0.005 & -0.001 \\
-0.202 & 0.218 & -0.021 & 0.006 \\
0.007 & -0.02 & 0.104 & -0.090 & 0.013 \\
-0.003 & 0.008 & -0.090 & 0.102 & -0.030 \\
-0.004 & 0.002 & 0.013 & -0.030 & 0.128 \\
\end{array} \right],
\]

and the value of test statistic in (10) $F_0 = \hat{\sigma}_x^2 \sum_{k=1}^{6} \frac{1}{\hat{\sigma}_x^2} \xi_i^2 = 87.64 > F_{5,207,0.001}$. Therefore, the hypothesis $H_0: \mu_1 = \mu_2 = \cdots = \mu_6$ is rejected. Using Scheffé type of simultaneous confidence intervals and the asymptotic simultaneous confidence intervals in (14), (18), simultaneous confidence intervals for $\mu_i - \mu_j$, $1 \leq i < j \leq 6$ with $1-\alpha = 0.95$ are given in Table 4.

From Table 4, it may be noted that Scheffé type of simultaneous confidence intervals are slightly longer than the asymptotic simultaneous confidence intervals. Both simultaneous confidence intervals can be adopted. Note that the data are severely missing in that, among these 149 women with preeclampsia, no women have more than four observations during the six intervals of gestational age. Here we recommend Scheffé type of simultaneous confidence intervals.

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Appendix

Proof of (12) and (13). Let $D_j$ be a $p_j \times p$ matrix with the $(l, j)$-element being one for $l = 1, \ldots, p_j$ and zero elsewhere. Then $u_j = D_j u$. Combining with the fact that $B_j \bar{\xi} = C_p u_j$ and $\bar{\xi} = C_p u$, we have $B_j C_p u = C_p D_j u$ for any $u \in \mathbb{R}^p$. Thus

$$B_j C_p = C_p D_j,$$

yielding

$$B_j = C_p D_j C_p'^{-1}$$

(A.1)

since $C_p$ is of full (row) rank. Furthermore, it is easy to verify that

$$C_p'^{-1} C_p = I - J_{p_j}, \quad \sum_{j=1}^{p_j} D_j' D_j = \text{diag}(n_i) = V, \quad \sum_{j=1}^{p_j} D_j' J_{p_j} D_j = (m_u) = M,$$

where $J_{p_j} = J_{p_j}/p_j$. Hence we have

$$\sum_{j=1}^{p_j} D_j' (I_{p_j} - J_{p_j}) x_j = z, \quad C_p D_j' I_p = 0,$$

we have

$$\bar{\xi} = C_p (V - M)' (I_p - J_p) \sum_{j=1}^{p_j} D_j' (I_{p_j} - J_{p_j}) x_j = C_p (V - M)' z = C_p \bar{x},$$

$$B_j \bar{\xi} = C_p D_j (I_p - J_p) \bar{x} = C_p D_j \bar{x},$$

and

$$B_j \bar{\xi} = C_p D_j (I_p - J_p) \bar{x} = C_p D_j \bar{x}.$$
\[ \hat{\sigma}_e^2 = \sum_{j=1}^{n_0} (x_j - D_j \hat{\eta})'(I_{p_j} - \hat{J}_{p_j})(x_j - D_j \hat{\eta}) / f. \]

Note that \( D_j \hat{\eta} = (^\eta_{j_1}, \ldots, ^\eta_{j_{p_j}})' \). The proof of (12) is complete.
### Table 1

Estimated coverage probabilities

<table>
<thead>
<tr>
<th>ρ</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scheffé</td>
<td>asymptotic</td>
</tr>
<tr>
<td>n = 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>0.9483</td>
<td>0.9189</td>
</tr>
<tr>
<td>0.5</td>
<td>0.9214</td>
<td>0.9052</td>
</tr>
<tr>
<td>0.9</td>
<td>0.9227</td>
<td>0.9023</td>
</tr>
<tr>
<td>n = 40</td>
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</tr>
<tr>
<td>0.1</td>
<td>0.9507</td>
<td>0.9408</td>
</tr>
<tr>
<td>0.5</td>
<td>0.9403</td>
<td>0.9187</td>
</tr>
<tr>
<td>0.9</td>
<td>0.9399</td>
<td>0.9141</td>
</tr>
</tbody>
</table>

*Nominal confidence level $1 - \alpha = 0.95$. 

* J Multivar Anal. Author manuscript; available in PMC 2010 February 1.
### Table 2

Average widths of simultaneous confidence intervals

<table>
<thead>
<tr>
<th>$a'$ type</th>
<th>Schefé (any $\rho$)</th>
<th>asymptotic $\rho = 0.1$</th>
<th>$\rho = 0.5$</th>
<th>$\rho = 0.9$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n = 20$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1, −1, 0)</td>
<td>I  1.840 1.606 1.661 1.684</td>
<td>II  2.580 1.925 2.095 2.216</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1, 0, −1)</td>
<td>I  1.840 1.606 1.661 1.684</td>
<td>II  2.094 1.661 1.756 1.808</td>
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<td></td>
</tr>
<tr>
<td>(0, 1, −1)</td>
<td>I  1.840 1.606 1.661 1.684</td>
<td>II  2.666 1.997 2.175 2.293</td>
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</tr>
<tr>
<td>(−2, 1, 1)</td>
<td>I  3.188 2.782 2.876 2.916</td>
<td>II  3.870 2.990 3.197 3.332</td>
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<td></td>
</tr>
<tr>
<td>(1, −2, 1)</td>
<td>I  3.188 2.782 2.876 2.916</td>
<td>II  4.811 3.553 3.893 4.131</td>
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</tr>
<tr>
<td>$n = 40$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1, −1, 0)</td>
<td>I  1.270 1.167 1.199 1.215</td>
<td>II  1.766 1.406 1.526 1.611</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1, 0, −1)</td>
<td>I  1.270 1.167 1.199 1.215</td>
<td>II  1.543 1.215 1.277 1.315</td>
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<td></td>
</tr>
<tr>
<td>(0, 1, −1)</td>
<td>I  1.270 1.167 1.199 1.215</td>
<td>II  1.835 1.489 1.585 1.668</td>
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</tr>
<tr>
<td>(−2, 1, 1)</td>
<td>I  2.199 2.021 2.076 2.104</td>
<td>II  2.763 2.186 2.326 2.424</td>
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<td></td>
</tr>
<tr>
<td>(1, −2, 1)</td>
<td>I  2.199 2.021 2.076 2.104</td>
<td>II  3.255 2.596 2.837 3.005</td>
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</tr>
</tbody>
</table>
### Table 3

The powers of three tests for equality of means (runs:5000)

<table>
<thead>
<tr>
<th>Type</th>
<th>n</th>
<th>Test statistic</th>
<th>(3 2 3)</th>
<th>(3 3 4)</th>
<th>(3 4 3)</th>
<th>(4 3 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>20</td>
<td>$F_0(I_p-1, 0)$</td>
<td>0.7812</td>
<td>0.794</td>
<td>0.7864</td>
<td>0.7806</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F_{S&amp;S1}$</td>
<td>0.236</td>
<td>0.8092</td>
<td>0.2502</td>
<td>0.7826</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F_{S&amp;S2}$</td>
<td>0.0908</td>
<td>0.7784</td>
<td>0.0964</td>
<td>0.7546</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>$F_0(I_p-1, 0)$</td>
<td>0.9844</td>
<td>0.987</td>
<td>0.9864</td>
<td>0.9808</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F_{S&amp;S1}$</td>
<td>0.5734</td>
<td>0.9836</td>
<td>0.579</td>
<td>0.9752</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F_{S&amp;S2}$</td>
<td>0.1484</td>
<td>0.9712</td>
<td>0.154</td>
<td>0.969</td>
</tr>
<tr>
<td>II</td>
<td>20</td>
<td>$F_0(I_p-1, 0)$</td>
<td>0.4224</td>
<td>0.5974</td>
<td>0.4258</td>
<td>0.6232</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F_{S&amp;S1}$</td>
<td>0.1916</td>
<td>0.5948</td>
<td>0.1948</td>
<td>0.5466</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F_{S&amp;S2}$</td>
<td>0.0364</td>
<td>0.4964</td>
<td>0.0354</td>
<td>0.5388</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>$F_0(I_p-1, 0)$</td>
<td>0.7702</td>
<td>0.9264</td>
<td>0.7702</td>
<td>0.9324</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F_{S&amp;S1}$</td>
<td>0.4038</td>
<td>0.9202</td>
<td>0.408</td>
<td>0.873</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F_{S&amp;S2}$</td>
<td>0.0564</td>
<td>0.8302</td>
<td>0.0512</td>
<td>0.876</td>
</tr>
</tbody>
</table>

* Nominal insignificant level $1 - \alpha = 0.95$. 
Table 4

95% simultaneous confidence intervals

<table>
<thead>
<tr>
<th>$\mu_i - \mu_j$</th>
<th>Scheffé type ($n_0 = 127$)</th>
<th>asymptotic ($n = 149$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_1 - \mu_2$</td>
<td>$[-0.248 \pm 0.675]$</td>
<td>$[-0.277 \pm 0.601]$</td>
</tr>
<tr>
<td>$\mu_1 - \mu_3$</td>
<td>$[-0.174 \pm 0.211]$</td>
<td>$[-0.167 \pm 0.197]$</td>
</tr>
<tr>
<td>$\mu_1 - \mu_4$</td>
<td>$[-0.360 \pm 0.450]$</td>
<td>$[-0.372 \pm 0.392]$</td>
</tr>
<tr>
<td>$\mu_1 - \mu_5$</td>
<td>$[-1.213 \pm 0.230]$</td>
<td>$[-1.200 \pm 0.216]$</td>
</tr>
<tr>
<td>$\mu_1 - \mu_6$</td>
<td>$[-1.491 \pm 0.504]$</td>
<td>$[-1.404 \pm 0.457]$</td>
</tr>
<tr>
<td>$\mu_2 - \mu_3$</td>
<td>$[0.074 \pm 0.696]$</td>
<td>$[0.110 \pm 0.613]$</td>
</tr>
<tr>
<td>$\mu_2 - \mu_4$</td>
<td>$[-0.113 \pm 0.789]$</td>
<td>$[-0.094 \pm 0.695]$</td>
</tr>
<tr>
<td>$\mu_2 - \mu_5$</td>
<td>$[-0.966 \pm 0.691]$</td>
<td>$[-0.922 \pm 0.614]$</td>
</tr>
<tr>
<td>$\mu_2 - \mu_6$</td>
<td>$[-1.244 \pm 0.835]$</td>
<td>$[-1.127 \pm 0.740]$</td>
</tr>
<tr>
<td>$\mu_3 - \mu_4$</td>
<td>$[-0.187 \pm 0.480]$</td>
<td>$[-0.204 \pm 0.411]$</td>
</tr>
<tr>
<td>$\mu_3 - \mu_5$</td>
<td>$[-1.039 \pm 0.240]$</td>
<td>$[-1.033 \pm 0.227]$</td>
</tr>
<tr>
<td>$\mu_3 - \mu_6$</td>
<td>$[-1.317 \pm 0.517]$</td>
<td>$[-1.237 \pm 0.466]$</td>
</tr>
<tr>
<td>$\mu_4 - \mu_5$</td>
<td>$[-0.853 \pm 0.475]$</td>
<td>$[-0.828 \pm 0.413]$</td>
</tr>
<tr>
<td>$\mu_4 - \mu_6$</td>
<td>$[-1.131 \pm 0.613]$</td>
<td>$[-1.033 \pm 0.559]$</td>
</tr>
<tr>
<td>$\mu_5 - \mu_6$</td>
<td>$[-0.278 \pm 0.533]$</td>
<td>$[-0.205 \pm 0.479]$</td>
</tr>
</tbody>
</table>

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