Chapter 532

GEE Tests for Multiple Means in a Cluster-Randomized Design

Introduction

This module calculates the power for testing for differences among the group means from **continuous**, correlated data from a cluster-randomized design that are analyzed using the GEE method.

GEE is different from mixed models in that it does not require the full specification of the joint distribution of the measurements, as long as the marginal mean model is correctly specified. Estimation consistency is achieved even if the correlation matrix is incorrect. For clustered designs such as those discussed here, GEE assumes a *compound symmetric* (CS) correlation structure.

The outcomes are averaged at the cluster level. The precision of the experiment is increased by increasing the number of subjects per cluster as well as the number of clusters.

Missing Values

This procedure allows you to specify the proportion of subjects that are missing by the end of the study.

Technical Details

Theory and Notation

Technical details are given in Ahn, Heo, and Zhang (2015), chapter 4, section 4.4.4, pages 116-119 and in Zhang and Ahn (2013).

Suppose we want to compare the means of G groups. Further suppose each of these groups consists of K_g (g = 1, ..., G) clusters for a total of K clusters. Each cluster provides outcomes for M subjects.

The mean of y_{gki} is modeled by

$$y_{gki} = \mu_g + \epsilon_{gki}$$

where

y_{gki} is the response from subject i in cluster k in group g, with variance σ^2,

r_g is the proportion of subjects in group g,

μ_g is group mean (g = 1, ..., G),

ϵ_{gki} is a zero-mean error term with variance σ^2.

In this procedure, the primary interest is to test $H_0: \mu_1 = \cdots = \mu_G$ against the alternative that at least one mean is different.

GEE is used to estimate and test hypotheses about these group means. H_0 is rejected with a type I error α if $\boldsymbol{B}'\boldsymbol{W}^{-\mathbf{1}}\boldsymbol{B} > \chi^2_{G-1,1-\alpha}$ where $\chi^2_{G-1,1-\alpha}$ is the 100(1 - α)th percentile of a chi-square distribution with G-1 degrees of freedom. The mean deviation vector $\boldsymbol{B}$ is given by

$$\boldsymbol{B} = \sqrt{K}(\hat{\mu}_1 - \hat{\mu}, \dots, \hat{\mu}_{G-1} - \hat{\mu})'$$

and $\boldsymbol{W}$ is a consistent estimate of the variance matrix based on the residuals.

Correlation Patterns

In a cluster-randomized design with K clusters, each consisting of M subjects, observations from a single cluster are correlated. The resulting correlation matrix is assumed to have a *compound symmetric* pattern with a common correlation coefficient ρ. That is, the correlation matrix within a cluster is

$$[\rho_{jj'}] = \begin{bmatrix} 1 & \rho & \rho & \rho & \cdots & \rho \\ \rho & 1 & \rho & \rho & \cdots & \rho \\ \rho & \rho & 1 & \rho & \cdots & \rho \\ \rho & \rho & \rho & 1 & \cdots & \rho \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \rho & \rho & \rho & \rho & \cdots & 1 \end{bmatrix}_{M \times M}$$

Missing Data

The problem of missing data occurs for several reasons. In these designs, it is assumed that the responses of some proportion, P, of the subjects will be missing.

Sample Size Calculations

The details of the calculation of sample size and power is given in Ahn, Heo, and Zhang (2015), Chapter 4. These are summarized here.

As explained above, GEE is used to estimate the regression coefficients. Under the alternative hypothesis, as K approaches infinity, the test statistic $U'\widehat{W}^{-1}U$ is approximately distributed as a noncentral chi-square random variable with G – 1 degrees of freedom and noncentrality parameter $U = K\boldsymbol{\eta}'\boldsymbol{W}^{-1}\boldsymbol{\eta}$, where

$$\boldsymbol{\eta}' = (\mu_1 - \bar{\mu}, \dots, \mu_{G-1} - \bar{\mu})$$

$$\bar{\mu} = \sum_{g=1}^{G} r_g \mu_g$$

$$\boldsymbol{\eta}'\boldsymbol{W}^{-1}\boldsymbol{\eta} = \frac{\overline{m}^2}{s}\left[\sum_{g=1}^{G-1} r_g \eta_g^2 + \frac{1}{r_G}\left(\sum_{g=1}^{G-1} r_g \eta_g\right)^2\right]$$

$$\overline{m} = (1-P)M$$

$$s = \sigma^2\big(M^2\rho + M(1-\rho)\big)(1-P)$$

Here, P is the proportion missing.

This noncentral distribution can be used to calculate the power using the following

$$Power = Pr\left(\chi'^2_{G-1}(U) > \chi^2_{G-1,1-\alpha}\right)$$

Using this power function, the sample size can be determined using a simple binary search.

Example 1 – Determining the Power

Researchers are planning a study comparing medications: a standard drug and two experimental drugs. The experimental drugs appear to have about the same impact. All patients within a cluster will receive the same drug. The clusters available for study will be randomly assigned to one of the three groups.

To begin, the researchers want to determine the power for Ki equal to 5, 10, and 15. They will assume an average cluster size of 10.

The researchers want to detect a difference represented by the group means 1, 2, and 3.

Similar studies have had a within-cluster standard deviation of 3. These studies also showed an autocorrelation between subjects within a cluster of between 0.2 and 0.5, so they want to try values those values. The test will be conducted at the 0.05 significance level. The subjects will be divided equally among the three groups.

At this stage of planning, the researchers want to ignore the possibility that some subjects will drop out.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	**Power**
Alpha	**0.05**
G (Number of Groups)	**3**
Group Allocation Input Type	**Equal (K1 = K2 = ⋯ = KG)**
Ki (Clusters Per Group)	**5 10 15**
M (Average Cluster Size)	**10**
μi's Input Type	**μ1, μ2, ..., μG**
μ1, μ2, ..., μG	**1 2 3**
σ (Standard Deviation)	**3**
ρ (Intracluster Correlation, ICC)	**0.2 0.5**
Missing Input Type	**Constant = 0**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Reports

Numeric Results

Solve For: Power
Number of Groups: 3

Power	Number of Subjects N	Number of Clusters K	Clusters per Group Ki	Average Cluster Size M	Group Means Values μi	Group Means SD σm	Standard Deviation σ	Effect Size σm / σ	ICC ρ	Alpha	Missing Proportion
0.4125	150	15	5	10	μi(1)	0.82	3	0.272	0.2	0.05	0
0.2275	150	15	5	10	μi(1)	0.82	3	0.272	0.5	0.05	0
0.7139	300	30	10	10	μi(1)	0.82	3	0.272	0.2	0.05	0
0.4191	300	30	10	10	μi(1)	0.82	3	0.272	0.5	0.05	0
0.8805	450	45	15	10	μi(1)	0.82	3	0.272	0.2	0.05	0
0.5886	450	45	15	10	μi(1)	0.82	3	0.272	0.5	0.05	0

Item	Values
μi(1)	1, 2, 3

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N	The total number of subjects in the study.
K	The total number of clusters in the study.
Ki	The number of clusters per group.
M	The average cluster size (number of subjects per cluster) used for all clusters.
μi	Group Means. Gives the name and number of the set containing the mean responses for each group.
σm	The standard deviation of the group means.
σ	The standard deviation of the responses within a cluster.
σm / σ	Effect Size. It is the ratio of σm and σ.
ρ	The intracluster correlation coefficient (ICC) used for all clusters. This is the correlation between any two subjects within a cluster.
Alpha	The probability of rejecting a true null hypothesis.
Missing Proportion	The proportion of each cluster that is assumed to be missing at the end of the study.

Summary Statements

A parallel, 3-group cluster-randomized design will be used to test whether any of the 3 means is different from the others. The comparison will be made using a generalized estimating equation (GEE) regression coefficient Chi-square test with 2 degrees of freedom, with a Type I error rate (α) of 0.05. The standard deviation of responses (σ, assumed to be constant across all clusters) is anticipated to be 3. The autocorrelation matrix of the responses within a cluster is assumed to be compound symmetric with an intraclass correlation coefficient (ICC) of 0.2. Missing values are assumed to occur completely at random (MCAR), and the anticipated proportion missing is 0. To detect the group means 1, 2, 3, or the corresponding effect size 0.272 (σm / σ, where σm is the standard deviation of the group means, 0.82), with a total of 15 clusters (allocated to the 3 groups as 5, 5, 5), with an average cluster size of 10 subjects per cluster (for a total sample size of 150 subjects), the power is 0.4125.

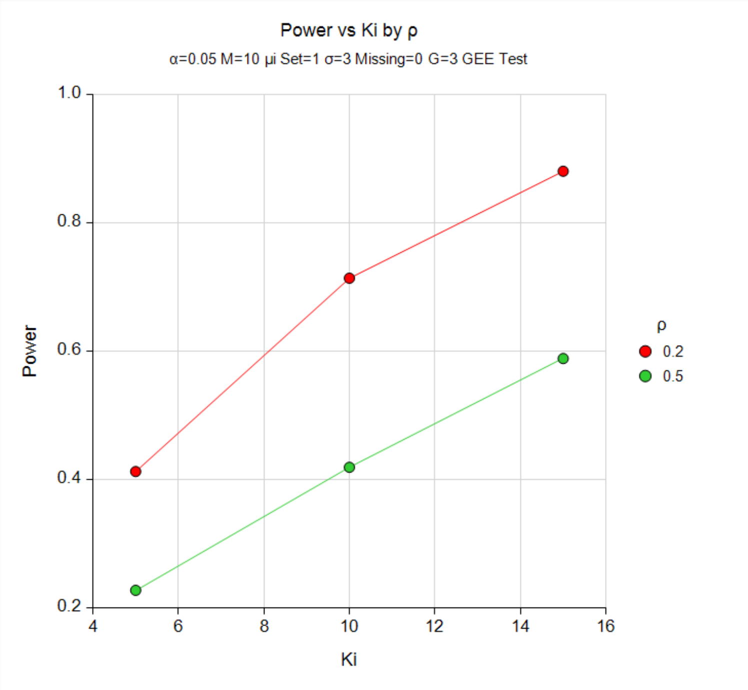
References

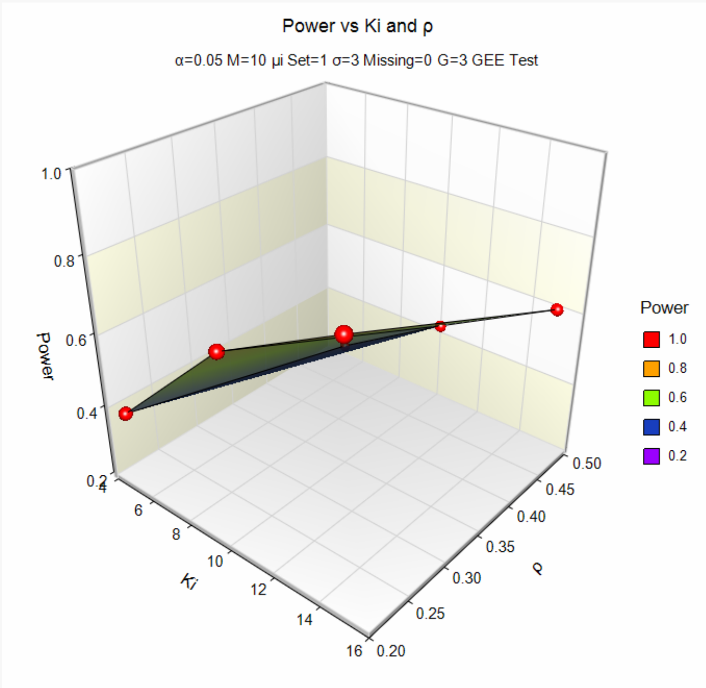
Ahn, C., Heo, M., and Zhang, S. 2015. Sample Size Calculations for Clustered and Longitudinal Outcomes in Clinical Research. CRC Press. New York. See pages 116-119.
Zhang, S. and Ahn, C. 2013. Sample Size Calculations for Comparing Time-Averaged Responses in K-Group Repeated-Measurement Studies. Computational Statistics and Data Analysis. Vol 58(1). Pages 283-291.

This report gives the power for various values of the other parameters. The definitions of each of the columns in the report are shown in the Report Definitions section. Note that the details of the μi set are shown below the table.

Plots Section

Plots





These charts show the relationship among the design parameters.

Example 2 – Determining the Power with Varying Cluster Counts

Continuing with Example 1, we want to give an example that stores the cluster counts on a spreadsheet. This allows us to compare various cluster count patterns.

This example will use all the settings of Example 1, except that various patterns of cluster counts across the three groups will be used. The following cluster count patterns are entered on the spreadsheet.

Eq	Add1	Add5
10	9	5
10	10	10
10	11	15

Note that we renamed column 1 from *C1* to *Eq*, column 2 from *C2* to *Add1*, and column 3 from *C3* to *Add5* by right clicking the column names and entering the new values.

Also note that each column sums to 30. That is, each column provides a pattern that results in a total cluster count of 30. However, the individual patterns are different. In the first column, the Ki's are all equal. In the second column, the Ki increase by 1. In the third column, the Ki increase by 5. This analysis is being run to determine the impact of unequal allocation.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For .... **Power**
Alpha.. **0.05**
G (Number of Groups) **3**
Group Allocation Input Type .... **Enter columns of Ki's**
Columns of Ki's **EQ-ADD5**
M (Average Cluster Size).............................. **10**
μi's Input Type .... **μ1, μ2, ..., μG**
μ1, μ2, ..., μG.. **1 2 3**
σ (Standard Deviation).................................. **3**
ρ (Intracluster Correlation, ICC).................... **0.2 0.5**
Missing Input Type.. **Constant = 0**

Input Spreadsheet Data

Row	Eq	Add1	Add5
1	10	9	5
2	10	10	10
3	10	11	15

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Reports

Numeric Results

Solve For: Power
Number of Groups: 3

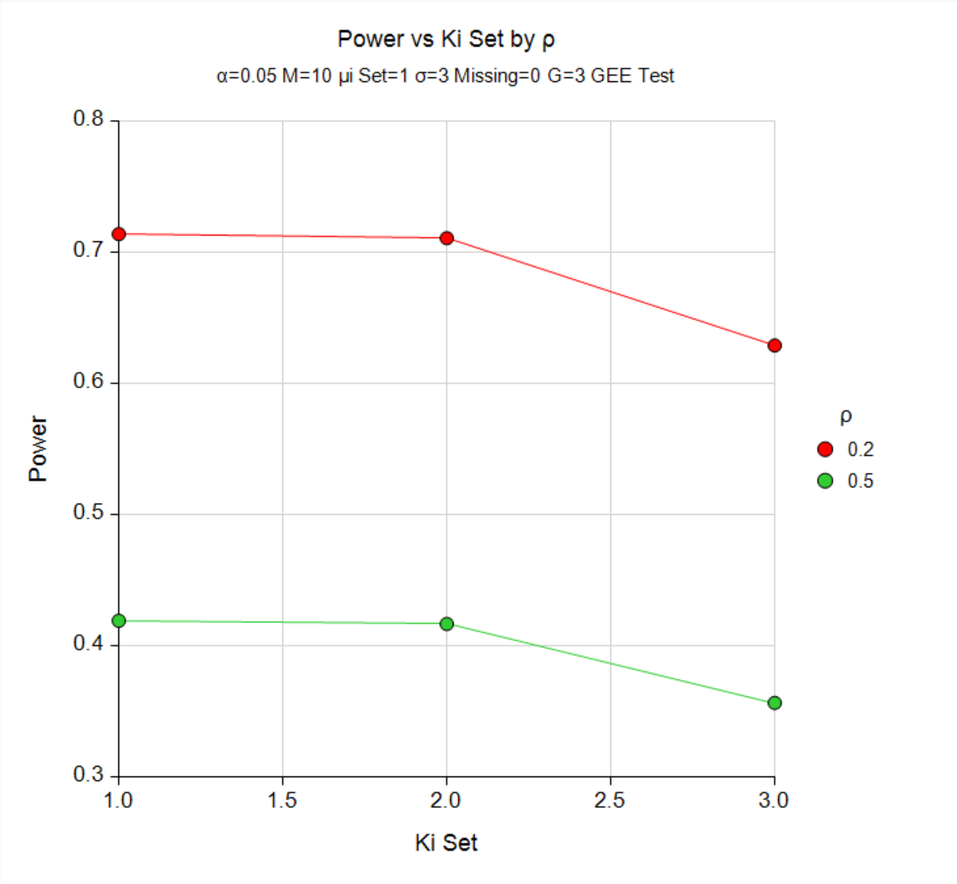
Power	Number of Subjects N	Number of Clusters K	Clusters per Group Ki	Average Cluster Size M	Group Means Values μi	Group Means SD σm	Standard Deviation σ	Effect Size σm / σ	ICC ρ	Alpha	Missing Proportion
0.7139	300	30	Eq(1)	10	μi(1)	0.82	3	0.272	0.2	0.05	0
0.4191	300	30	Eq(1)	10	μi(1)	0.82	3	0.272	0.5	0.05	0
0.7108	300	30	Add1(2)	10	μi(1)	0.82	3	0.272	0.2	0.05	0
0.4167	300	30	Add1(2)	10	μi(1)	0.82	3	0.272	0.5	0.05	0
0.6290	300	30	Add5(3)	10	μi(1)	0.82	3	0.272	0.2	0.05	0
0.3565	300	30	Add5(3)	10	μi(1)	0.82	3	0.272	0.5	0.05	0

Item	Values
Eq(1)	10, 10, 10
Add1(2)	9, 10, 11
Add5(3)	5, 10, 15
μi(1)	1, 2, 3

This report gives the power for various values of the other parameters. Note that the details of the Ki columns and the μi sets are shown in the Set footnote below the numeric results.

Plots Section

Plots



Notice that the horizontal axis of this plot is labelled *Ki Set* and that the values of the horizontal variable are 1, 2, and 3. These are the Set Numbers. Hence the Ki Sets are named Eq(1), Add1(2), and Add5(3). The number in parenthesis is the number that is plotted. We note that the pattern can make a big difference in power.

Example 3 – Validation of Sample Size Calculation using Zhang and Ahn (2013)

Zhang and Ahn (2013) presents an example which we will use to validate this procedure. Their example uses G = 4, m = 3, σ = 1.43178, ρ = 0.45, α = 0.05, power = 0.9, compound symmetry correlation pattern, group cluster counts of 25, 25, 25, 26 (K = 101), no missing data, and group means of 1.99, 1.99, 1.99, 1.0. The resulting power was 0.90.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 3** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For .... **Power**
Alpha.. **0.05**
G (Number of Groups) **4**
Group Allocation Input Type .... **Enter K1, K2, ..., KG**
K1, K2, ..., KG (List)...................................... **25 25 25 26**
M (Average Cluster Size).............................. **3**
μi's Input Type .... **μ1, μ2, ..., μG**
μ1, μ2, ..., μG.. **1.99 1.99 1.99 1**
σ (Standard Deviation).................................. **1.43178**
ρ (Intracluster Correlation, ICC).................... **0.45**
Missing Input Type.. **Constant = 0**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Solve For: Power
Number of Groups: 4

					Group Means						
Power	Number of Subjects N	Number of Clusters K	Clusters per Group Ki	Average Cluster Size M	Values μi	SD σm	Standard Deviation σ	Effect Size σm / σ	ICC ρ	Alpha	Missing Proportion
0.9086	303	101	Ki(1)	3	μi(1)	0.43	1.43	0.299	0.45	0.05	0

Item	Values
Ki(1)	25, 25, 25, 26
μi(1)	1.99, 1.99, 1.99, 1

The power of 0.9086 matches Zhang and Ahn (2013). Thus, the procedure is validated.