Chapter 376

Mixed Models Tests for the Slope Difference in a 3-Level Hierarchical Design with Fixed Slopes (Level-3 Randomization)

Introduction

This procedure calculates power and sample size for a three-level hierarchical mixed model which is randomized at the third level. The goal of the study is to compare two group slopes. If the group means are identical at the beginning of the study (which they often are in a randomized trial), testing the difference in slopes is the same as testing the difference in means at the end of the study. This is a test of the time-by-treatment interaction.

The study is assumed to be longitudinal in that the third level is some type of cluster (e.g., clinic or hospital), the second level is subjects nested within the third level, and the first level is a repeated measurement at equally spaced time points on the subjects. Ahn, Heo, and Zhang (2015) call this a *longitudinal cluster randomized design*.

The data are analyzed by considering the average trend of responses over time. These trends can be considered as fixed (this procedure) or random (a companion procedure).

Randomization

Different models are used depending on how subjects are assigned to the intervention (treatment) groups. This procedure assumes that all subjects (level-2 units) in a cluster (level-3 unit) are assigned to an intervention group at random. This is called *level-3 randomization*. A companion procedure analyzes the case when subjects are individually randomized to one of the two groups (*level-2 randomization*).

Fixed or Random

The subject-specific slopes of responses across the repeated measurements can be assumed to be fixed or random. In this fixed case, all subjects are assumed to share a common fixed slope with no variation. In the random case, the slopes are assumed to have a normal distribution with a modelled variance.

Technical Details

Our formulation comes from Ahn, Heo, and Zhang (2015), chapter 6, section 6.4.1.1, pages 201-203. The hierarchical mixed model used for the analysis is

$$Y_{ijk} = \beta_0 + \xi X_{ijk} + \tau T_{ijk} + \delta X_{ijk} T_{ijk} + u_i + u_{j(i)} + e_{ijk}$$

where

Y_{ijk} is the continuous response of the kth level-1 unit of the jth level-2 unit of the ith level-3 unit.

X_{ijk} is an indicator variable that is 1 if ijk^{th} unit is in group 1 and 0 if it is in group 2.

T_{ijk} is an integer that represents the time period. We assume that $T_{ijk} = T_k$ and that these time values increase from 0 (baseline measurement) to M – 1 (final measurement).

β_0 is the overall fixed intercept.

ξ is the intervention effect at baseline.

τ is the slope of the time effect.

δ is the treatment effect of interest. It models the difference between the two group slopes.

u_i is the level-3 random intercept effect for the ith level-3 unit. It is distributed as $N(0, \sigma_3^2)$.

$u_{j(i)}$ is the level-2 random intercept effect for the $j(i)^{th}$ level-2 unit. It is distributed as $N(0, \sigma_2^2)$.

e_{ijk} is a random error term which is distributed as $N(0, \sigma_e^2)$.

σ^2 is the variance of Y_{ijk}, where $\sigma^2 = \sigma_e^2 + \sigma_2^2 + \sigma_3^2$.

ρ is the correlation among level-1 units which are in a particular level-2 unit. For fixed models like this, $\rho = Corr(Y_{ijk}, Y_{ijk'}) = (\sigma_2^2 + \sigma_3^2)/\sigma^2$.

C_1 is the number of level-3 units (clusters) assigned to group 1.

C_2 is the number of level-3 units assigned to group 2.

K is the number of level-2 units (subjects) per level-3 unit.

M is the number of level-1 units per level-2 unit, i.e., the number of repeated measurements.

The test of significance of the $X_{ijk} T_{ijk}$ interaction term in the mixed model is the test statistic of interest. It tests the difference of the two slopes.

The power can be calculated using

$$Power = \Phi \left\{ \left| \frac{\delta}{\sigma} \right| \sqrt{\frac{C_2 K M \text{Var}(T)}{\left[f_3 (1 + \frac{1}{\lambda}) \right]}} - \Phi^{-1}(1 - \alpha/2) \right\}$$

where $\lambda = C_1/C_2$, $f_3 = 1 - \rho$, and $\text{Var}(T) = (M - 1)(M + 1)/12$.

Example 1 – Calculating Power

Suppose that a three-level hierarchical design is planned in which repeated measurements (level-1) will be taken on subjects (level-2) within hospitals (level-3). This analysis will calculate the power for detecting the difference in slopes of two interventions.

The following parameter settings are used for the power analysis: $\delta = 0.8$; $\sigma = 2.6$; $\rho = 0.1$; $K = 4$; $M = 4, 5$; $\alpha = 0.05$; and $C1 = C2 = 5, 10, 15, 20$.

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**
C1 (Level 3 Units Assigned to Group 1).........**5 10 15 20**
C2 (Level 3 Units Assigned to Group 2).........**C1**
K (Level 2 Units Per Level 3 Unit)..................**4**
M (Level 1 Units Per Level 2 Unit) **4 5**
Slope Input Type...**δ (Slope Difference)**
δ (Slope Difference)......................................**0.8**
σ (Standard Deviation)..................................**2.6**
ρ (Within Subject Correlation).......................**0.1**

Output

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

Numeric Reports

Numeric Results for a Three-Level Hierarchical Mixed Model
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Solve For: Power
Groups: 1 = Treatment, 2 = Control
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	Total Sample Size N	Number of Level 3 Units			Number of Level 2 Units per Level 3 Unit K	Number of Level 1 Units per Level 2 Unit M	Slope Difference δ	Standard Deviation σ	Within-Subject Correlation ρ	Alpha
Power		Group 1 C1	Group 2 C2	Total C						
0.6306	160	5	5	10	4	4	0.8	2.6	0.1	0.05
0.9003	200	5	5	10	4	5	0.8	2.6	0.1	0.05
0.9003	320	10	10	20	4	4	0.8	2.6	0.1	0.05
0.9957	400	10	10	20	4	5	0.8	2.6	0.1	0.05
0.9779	480	15	15	30	4	4	0.8	2.6	0.1	0.05
0.9999	600	15	15	30	4	5	0.8	2.6	0.1	0.05
0.9957	640	20	20	40	4	4	0.8	2.6	0.1	0.05
1.0000	800	20	20	40	4	5	0.8	2.6	0.1	0.05

Power   The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N   The total number of Level-1 units.
C1, C2, and C The number of Level-3 units assigned to groups 1, 2, and both, respectively.
K   The average number of Level-2 units per Level-3 unit.
M   The average number of Level-1 units per Level-2 unit.
δ   The difference in the two group slopes at which the power is calculated.
σ   The standard deviation of the Level-1 responses.
ρ   The correlation among Level-1 units in a particular Level-2 unit.
Alpha   The probability of rejecting a true null hypothesis.

Summary Statements
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A 2-group 3-level hierarchical design will have subjects (level-2 units) in clusters (level-3 units, e.g., classes, clinics, or hospitals), with random assignment of clusters to each of the 2 treatment arms (level-3 randomization), and with repeated measurements (level-1 units) on each subject (over time). This design will be used to test whether the outcome trends (slopes) of the two groups are different by testing whether the 2 group means are different ($\mu1 - \mu2$) at the final time point, using the appropriate mean difference term of the linear mixed-effects model, assuming fixed slopes, with a Type I error rate (α) of 0.05. The standard deviation of Yijk (σ), assuming a fixed-slope model, is assumed to be 2.6, where (fixed-slope) σ^2 is the sum of the error term variance, the level-2 random intercept variance, and the level-3 random intercept variance. The correlation coefficient of level-1 units (repeated measurements on a subject) is assumed to be 0.1. To detect a slope difference of 0.8, with 5 level-3 units (clusters) in Group 1 and 5 level-3 units in Group 2, with 4 level-2 units (subjects) obtained from each level-3 unit, and with 4 level-1 units (repeated measurements) obtained from each level-2 unit (subject) (for a grand total of 160 level-1 measurements), the power is 0.6306.
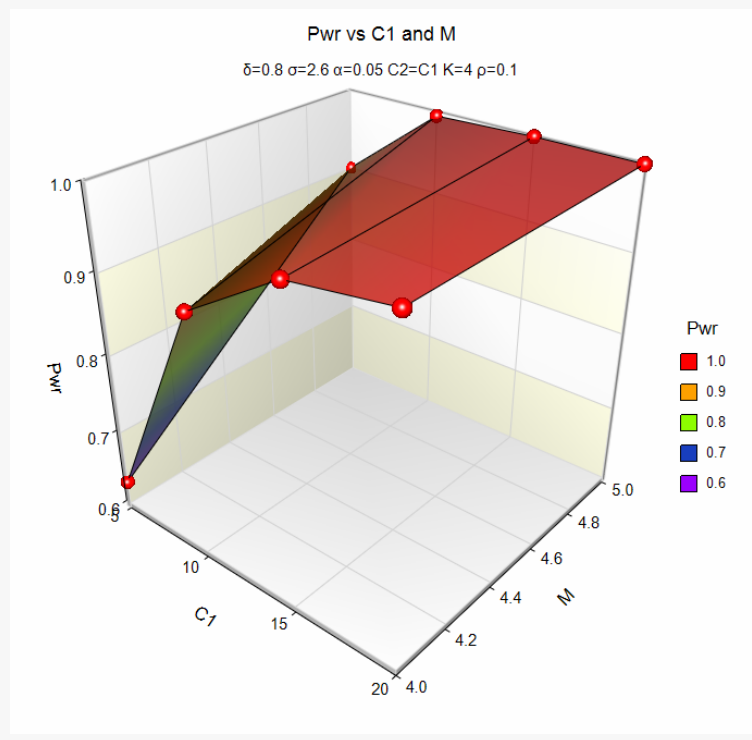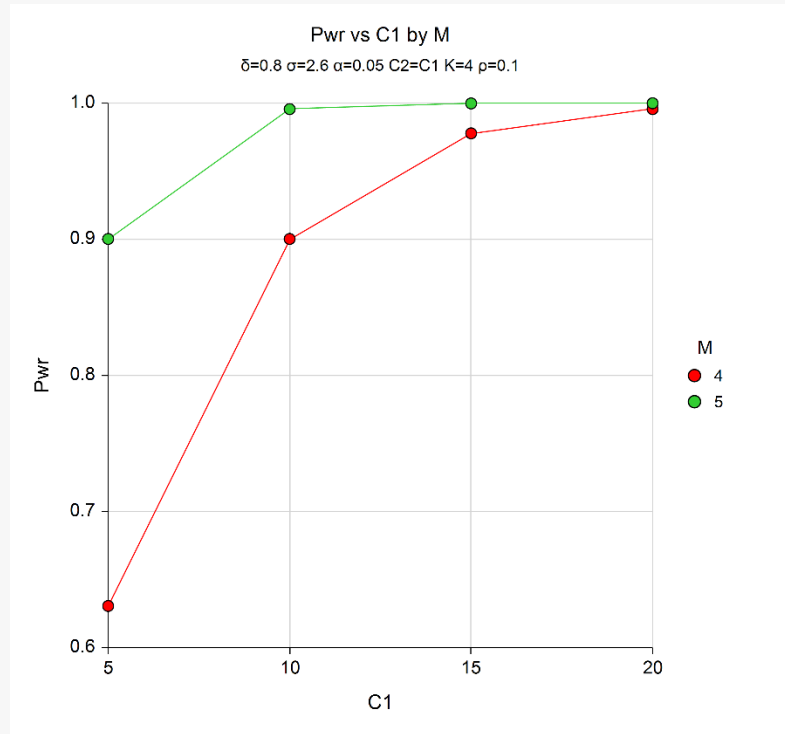───

References
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Ahn, C., Heo, M., and Zhang, S. 2015. Sample Size Calculations for Clustered and Longitudinal Outcomes in Clinical Research. CRC Press. New York.
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This report shows the power for each of the scenarios.

Plots Section

These plots show the power versus the level-3 count for the two values of M.

Example 2 – Calculating Sample Size (Number of Level 3 Units)

Continuing with the last example, suppose the researchers want to determine the number of clusters needed to achieve 90% power for the values of M.

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
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Solve For ....**C1 (Number Level 3 Units)**
Power...**0.90**
Alpha..**0.05**
C2 (Level 3 Units Assigned to Group 2).........**C1**
K (Level 2 Units Per Level 3 Unit).................**4**
M (Level 1 Units Per Level 2 Unit) **4 5**
Slope Input Type..**δ (Slope Difference)**
δ (Slope Difference).......................................**0.8**
σ (Standard Deviation)..................................**2.6**
ρ (Within Subject Correlation).......................**0.1**

Output

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

Numeric Results for a Three-Level Hierarchical Mixed Model
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Solve For: C1 (Number Level 3 Units in Group 1)
Groups: 1 = Treatment, 2 = Control
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	Total Sample Size	Number of Level 3 Units			Number of Level 2 Units per Level 3 Unit	Number of Level 1 Units per Level 2 Unit	Slope Difference	Standard Deviation	Within-Subject Correlation	
Power	N	Group 1 C1	Group 2 C2	Total C	K	M	δ	σ	ρ	Alpha
0.9003	320	10	10	20	4	4	0.8	2.6	0.1	0.05
0.9003	200	5	5	10	4	5	0.8	2.6	0.1	0.05

This report shows the power for each of the scenarios.

Example 3 – Validation using Ahn, Heo, and Zhang (2015)

Ahn, Heo, and Zhang (2015) page 204 provide a table in which several scenarios are reported. We will validate this procedure by the first row of the table. The following parameter settings were for the analysis: power = 0.80; δ = 0.3; σ = 4; ρ = 0.1; K = 8; M = 5; and α = 0.05. These settings resulted in a value of C2 (their $N_3^{(0)}$) of 32 and an attained power of 0.807.

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 ....**C1 (Number Level 3 Units)**
Power..**0.80**
Alpha...**0.05**
C2 (Level 3 Units Assigned to Group 2).........**C1**
K (Level 2 Units Per Level 3 Unit).................**8**
M (Level 1 Units Per Level 2 Unit) **5**
Slope Input Type...**δ (Slope Difference)**
δ (Slope Difference)......................................**0.3**
σ (Standard Deviation)..................................**4**
ρ (Within Subject Correlation).......................**0.1**

Output

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

Numeric Results for a Three-Level Hierarchical Mixed Model

Solve For: C1 (Number Level 3 Units in Group 1)
Groups: 1 = Treatment, 2 = Control

| | Total Sample Size | Number of Level 3 Units | | | Number of Level 2 Units per Level 3 Unit | Number of Level 1 Units per Level 2 Unit | Slope Difference | Standard Deviation | Within-Subject Correlation | |
| | | Group 1 | Group 2 | Total | | | | | | |
Power	N	C1	C2	C	K	M	δ	σ	ρ	Alpha
0.8074	2560	32	32	64	8	5	0.3	4	0.1	0.05

PASS calculates the same values of C2 and power: 32 and 0.807.