

Chapter 374

Mixed Models Tests for the Slope Difference in a 3-Level Hierarchical Design with Fixed Slopes (Level-2 Randomization)

Introduction

This procedure calculates power and sample size for a three-level hierarchical mixed model which is randomized at the second level. The goal of the study is to compare the 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 each subject (level-2 unit) is individually randomized to an intervention group. This is called *level-2 randomization*. A companion procedure analyzes the case of level-3 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 6.4.2, page 206-208. 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 k^{th} level-1 unit of the j^{th} level-2 unit of the i^{th} 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 i^{th} level-3 unit. It is distributed as $N(0, \sigma_3^2)$.
- $u_{j(i)}$ is the level-2 random intercept effect for the $j(i)^{\text{th}}$ 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, $\rho = \text{Corr}(Y_{ijk}, Y_{ijk'}) = (\sigma_2^2 + \sigma_3^2)/\sigma^2$.
- C is the number of level-2 units (subjects) per level-3 unit.
- K_1 is the number of level-2 units (clusters) assigned to group 1.
- K_2 is the number of level-2 units assigned to group 2.
- 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 is calculated using

$$\text{Power} = \Phi \left\{ \left| \frac{\delta}{\sigma} \right| \sqrt{\frac{K_2 C M \text{Var}(T)}{[f_3(1 + \frac{1}{\lambda})]}} - \Phi^{-1}(1 - \alpha/2) \right\}$$

where $\lambda = K_1/K_2$, $f_3 = 1 - \rho$, 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. Randomization will be at the subject (level-2) units.

The following parameter settings are used for the power analysis: $\delta = 0.5$; $\sigma = 2.6$; $\rho = 0.1$; $K1 = 4, 6$; $M = 4$; $\alpha = 0.05$; and $C = 4, 6$.

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
C (Level 3 Units).....	4 6
K1 (Level 2 Units Assigned to Group 1).....	5 10 15 20
K2 (Level 2 Units Assigned to Group 2).....	K1
M (Level 1 Units Per Level 2 Unit)	4
Slope Input Type.....	δ (Slope Difference)
δ (Slope Difference).....	0.5
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

Solve For: **Power**
 Groups: 1 = Treatment, 2 = Control

Power	Total Sample Size N	Number of Level 3 Units C	Number of Level 2 Units per Level 3 Unit		Number of Level 1 Units per Level 2 Unit M	Slope Difference δ	Standard Deviation σ	Within-Subject Correlation ρ	Alpha
			Group 1 K1	Group 2 K2					
0.2992	160	4	5	5	4	0.5	2.6	0.1	0.05
0.5268	320	4	10	10	4	0.5	2.6	0.1	0.05
0.6994	480	4	15	15	4	0.5	2.6	0.1	0.05
0.8177	640	4	20	20	4	0.5	2.6	0.1	0.05
0.4190	240	6	5	5	4	0.5	2.6	0.1	0.05
0.6994	480	6	10	10	4	0.5	2.6	0.1	0.05
0.8601	720	6	15	15	4	0.5	2.6	0.1	0.05
0.9396	960	6	20	20	4	0.5	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.
- C The number of Level-3 units.
- K1 and K2 The average number of Level-2 units per Level-3 unit assigned to groups 1 and 2, respectively.
- M The number of Level-1 units (repeated measurements) per Level-2 unit (subject).
- 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

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 subjects to each of the 2 treatment arms (level-2 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 ($\mu_1 - \mu_2$) 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 Y_{ijk} (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 0.5, with 4 level-3 units (clusters), and within each level-3 unit, level-2 sample sizes of 5 subjects in Group 1 and 5 subjects in Group 2, 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 0.2992.

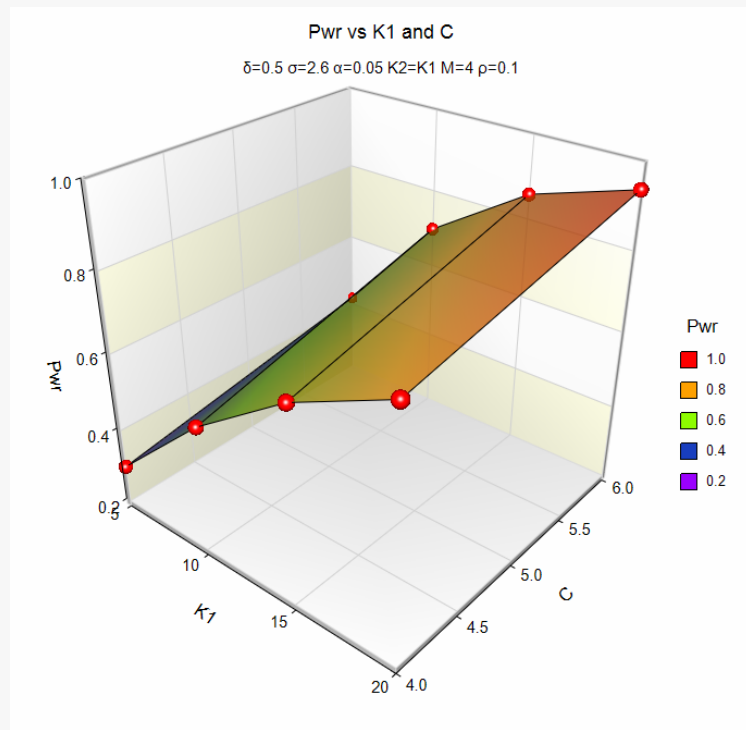
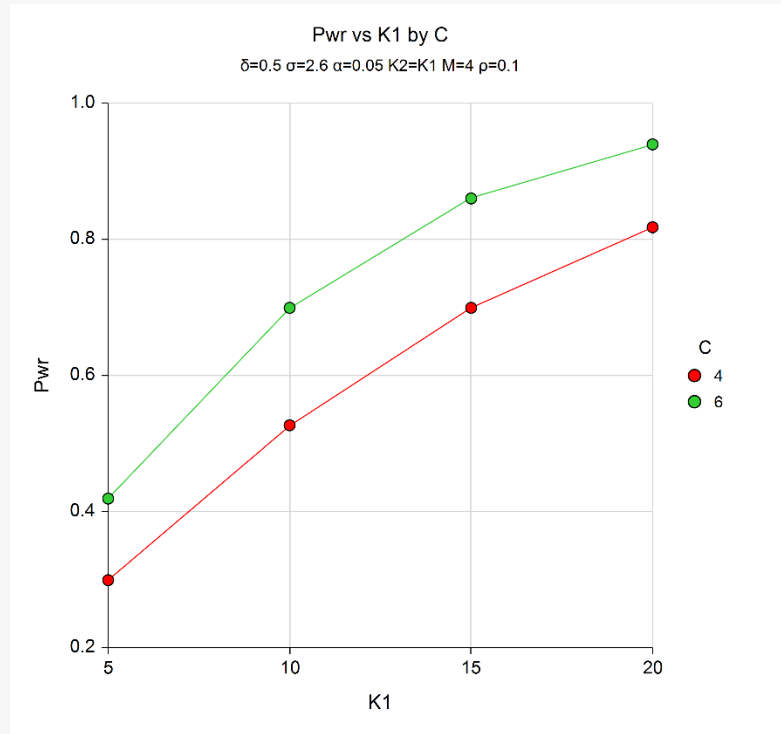
References

Ahn, C., Heo, M., and Zhang, S. 2015. Sample Size Calculations for Clustered and Longitudinal Outcomes in Clinical Research. CRC Press. New York.

This report shows the power for each of the scenarios.

Plots Section

Plots



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

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

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	
Solve For	K1 (Number Level 2 Units Per Level 3 Unit)
Power.....	0.90
Alpha.....	0.05
C (Level 3 Units).....	4 6
K2 (Level 2 Units Assigned to Group 2).....	K1
M (Level 1 Units Per Level 2 Unit)	4
Slope Input Type.....	δ (Slope Difference)
δ (Slope Difference).....	0.5
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										
Solve For: K1 (Number Level 2 Units Per Level 3 Unit)										
Groups: 1 = Treatment, 2 = Control										
Power	Total Sample Size N	Number of Level 3 Units C	Number of Level 2 Units per Level 3 Unit		Number of Level 1 Units per Level 2 Unit M	Slope Difference δ	Standard Deviation σ	Within-Subject Correlation ρ	Alpha	
			Group 1 K1	Group 2 K2						
0.9047	832	4	26	26	4	0.5	2.6	0.1	0.05	
0.9148	864	6	18	18	4	0.5	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. Actually, the table is for level-3 randomization. Following their instructions, we switch K and C to obtain results for level-2 randomization.

The following parameter settings were for the analysis: power = 0.80; $\delta = 0.3$; $\sigma = 4$; $\rho = 0.1$; $K_1 = 8$; $M = 5$; and $\alpha = 0.05$. These settings resulted in a value of C (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 **C (Number Level 3 Units)**
 Power..... **0.8**
 Alpha..... **0.05**
 K1 (Level 2 Units Assigned to Group 1)..... **8**
 K2 (Level 2 Units Assigned to Group 2)..... **K1**
 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: **C (Number Level 3 Units)**
 Groups: 1 = Treatment, 2 = Control

Power	Total Sample Size N	Number of Level 3 Units C	Number of Level 2 Units per Level 3 Unit		Number of Level 1 Units per Level 2 Unit M	Slope Difference δ	Standard Deviation σ	Within-Subject Correlation ρ	Alpha
			Group 1 K1	Group 2 K2					
0.8074	2560	32	8	8	5	0.3	4	0.1	0.05

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