



臺中榮民總醫院
Taichung Veterans General Hospital

相關樣本/配對資料的統計推論

醫學研究部 生統小組

陳俊朋

2023/06/06

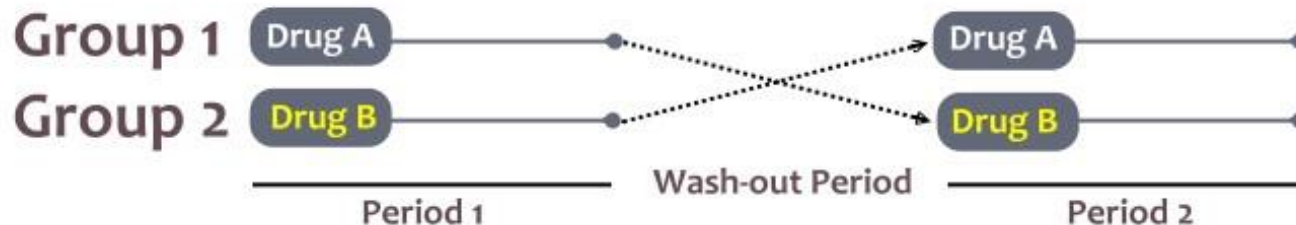


大綱

- 臨床試驗
- 重複測量相關統計方法
- Conditional Logistic Regression
- Cox regression

臨床試驗設計

- 平行設計(Parallel Trail)
 - 將研究對象隨機分派為治療組與對照組
 - 受試者接受單一種治療方式
- 交叉設計(Cross-over Trail)
 - 受試者在不同時間點接受不同治療
 - 受試者本身為自己的對照組
 - 較少的樣本數達到相同的檢定力



臨床試驗遺漏值問題

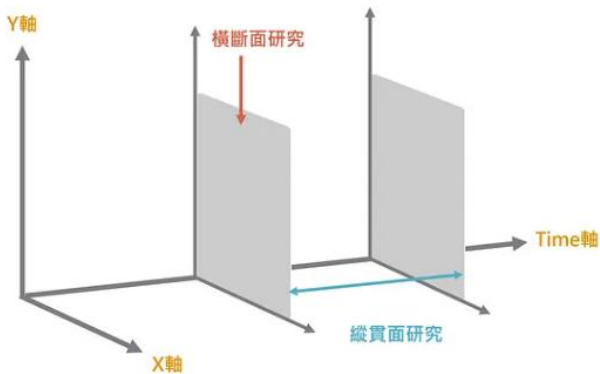
- 違反「意圖治療(intent to treat, ITT)」的定義(所有接受隨機分配的受試者皆應納入統計分析)，造成選擇偏差(selection bias)
- 排除因療效太好或太差而退出試驗的受試者，可能造成療效估計的偏差
- 樣本數減少，導致統計檢定力降低
- 中途退出試驗的病人對試驗藥物的順從性不佳
- 完整受試者群體(complete patient population)無法代表整個目標病人群體(target patient population)

臨床試驗遺漏值處理

- 單一插補法 (single imputation)
 - 將每位受試者缺失的資料給予一個合理的數值
- 多重插補法 (multiple imputation)
 - 將每位受試者缺失的資料給予多個合理的數值

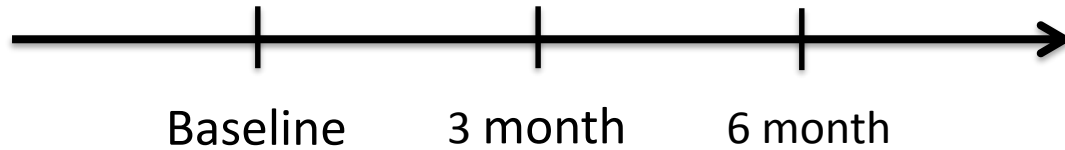
研究設計

| Cross-sectional | Longitudinal |
|------------------------------------------------------|-------------------------------------------------------------------|
| Single point in time | Period of time |
| Different samples | Same sample |
| Provides snapshot of society at a given point | Follows changes in participants over time |
| Compare many different variables at the same time | The difference between these studies is the timeline and variable |
| Cheaper | Expensive and require more resources |

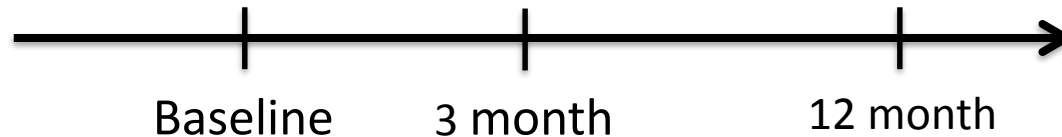


重複測量使用時機

- 相同受試者在不同時間點進行多次測量
 - 間隔時間相同



- 間隔時間不同



重複測量優缺點

- 優點
 - 需求樣本數較少
 - 不同時間點變化
 - 不同組別，隨著時間的變化
- 缺點
 - 資料完整性不佳
 - 個案須定期追蹤
 - 某些因素可能影響資料

重複測量統計

- 單組重複測量
 - 同一組內的個案，在多個時間點測量
- 多組重複測量
 - 將個案分組後，依照各組分類在多個時間點測量

重複測量統計

重複2次

- 類別變項
 - McNemar test (2*2 table)
 - McNemar-Bowker test (3*3 table)
- 連續變項
 - Paired t test
 - Wilcoxon signed-rank test
 - ANCOVA

重複3次以上

- 類別變項
 - Cochran's Q test
- 連續變項
 - Friedman test
 - Repeated measures ANOVA
 - Linear Mixed Model (LMM)
 - Generalized Estimating Equation (GEE)

重複測量建檔

- 寬資料

| no | Group | Sex | MMSE_1 | MMSE_2 | MMSE_3 |
|-----|-------|-----|--------|--------|--------|
| N01 | 0 | 0 | 30 | 28 | 30 |
| N02 | 0 | 1 | 11 | 15 | 14 |
| N03 | 0 | 1 | 26 | 28 | 26 |
| N04 | 0 | 0 | 22 | 21 | 22 |
| N05 | 0 | 0 | 27 | 26 | 25 |
| N06 | 0 | 0 | 21 | 20 | 21 |
| N07 | 0 | 0 | 28 | 27 | 28 |
| N08 | 0 | 1 | 23 | 22 | 23 |
| N09 | 0 | 1 | 14 | 13 | 12 |
| N10 | 0 | 1 | 20 | 19 | 20 |
| C01 | 1 | 0 | 11 | 12 | 10 |
| C02 | 1 | 0 | 13 | 18 | 12 |
| C03 | 1 | 0 | 26 | 29 | 25 |
| C04 | 1 | 0 | 21 | 19 | 20 |
| C05 | 1 | 1 | 27 | 25 | 26 |
| C06 | 1 | 1 | 19 | 13 | 18 |
| C07 | 1 | 1 | 28 | 30 | 27 |
| C08 | 1 | 1 | 15 | 18 | 14 |
| C09 | 1 | 0 | 10 | 12 | 9 |
| C10 | 1 | 0 | 13 | 17 | 12 |

- 長資料

| no | Group | Sex | visit | MMSE |
|-----|-------|-----|-------|------|
| N01 | 0 | 0 | 1 | 30 |
| N01 | 0 | 0 | 2 | 28 |
| N01 | 0 | 0 | 3 | 30 |
| N02 | 0 | 1 | 1 | 11 |
| N02 | 0 | 1 | 2 | 15 |
| N02 | 0 | 1 | 3 | 14 |
| N03 | 0 | 1 | 1 | 26 |
| N03 | 0 | 1 | 2 | 28 |
| N03 | 0 | 1 | 3 | 26 |
| N04 | 0 | 0 | 1 | 22 |
| N04 | 0 | 0 | 2 | 21 |
| N04 | 0 | 0 | 3 | 22 |
| N05 | 0 | 0 | 1 | 27 |
| N05 | 0 | 0 | 2 | 26 |
| N05 | 0 | 0 | 3 | 25 |

McNemar test

- 僅適用2*2 table
- 單組同一人前後測/兩種不同診斷工具

Table 4 Comparison of the ability of community surveillance in obtaining additional data on suicide compared with the hospital and police records

| | Non-case | Case | Test statistics |
|------------------------------------|------------------|------|------------------------------------------------|
| Community surveillance | 15 | 67 | Cochran's Q test 67.9 (p<0.01) |
| Hospital records | 69 | 13 | |
| Police records | 65 | 17 | |
| Post hoc McNemar's test statistics | | | |
| Community surveillance | Hospital records | | McNemar's χ^2 test 37.1 (p<0.01) |
| | Non-case | Case | |
| Non-case | 6 | 9 | |
| Case | 63 | 4 | |
| Community surveillance | Police records | | McNemar's χ^2 test 35.6 (p<0.01) |
| | Non-case | Case | |
| Non-case | 8 | 7 | |
| Case | 57 | 10 | |
| Hospital records | Police records | | McNemar's χ^2 test 0.67 (p=0.41) NS |
| | Non-case | Case | |
| Non-case | 55 | 14 | |
| Case | 10 | 3 | |

NS, Not significant.

McNemar-Bowker test

- 適用3*3 table以上
- 單組同一人前後測/兩種不同診斷工具

Table 2. 2016 FSS by 2019 FSS Among Undergraduates (n = 338)

| 2016 FSS ^a | 2019 FSS ^b | | | | Total |
|-----------------------|-----------------------|-----------|-----------|-----------|------------|
| | High | Marginal | Low | Very Low | |
| High | 106 (31.4) | 36 (10.7) | 38 (11.2) | 18 (5.3) | 198 (58.6) |
| Marginal | 21 (6.2) | 16 (4.7) | 16 (4.7) | 11 (3.3) | 64 (18.9) |
| Low | 9 (2.7) | 9 (2.7) | 9 (2.7) | 13 (3.8) | 40 (11.8) |
| Very low | 1 (0.3) | 1 (0.3) | 17 (5.0) | 17 (5.0) | 36 (10.6) |
| Total | 137 (40.4) | 62 (18.3) | 80 (23.6) | 59 (17.4) | 338 (100) |

FSS indicates food security status.

^aMeasured using the 10-item Food Security Survey Module; ^bMeasured using the 18-item Food Security Survey Module.

Note: Values displayed as n (% of total). Statistical test conducted is the McNemar-Bowker test ($\chi^2 = 47.878$, degrees of freedom = 6, $P < 0.001$) and paired samples Wilcoxon signed rank test ($P < 0.001$). Critical $P \leq 0.05$.

Cochran's Q test

- 單組的相同個案，用同一工具測量三次/不同工具(類別型資料屬於二分類)

Table 4 Comparison of the ability of community surveillance in obtaining additional data on suicide compared with the hospital and police records

| | Non-case | Case | Test statistics |
|------------------------|-----------------|-------------|--------------------------------------------|
| Community surveillance | 15 | 67 | Cochran's Q test 67.9 ($p < 0.01$) |
| Hospital records | 69 | 13 | |
| Police records | 65 | 17 | |

Paired t test

- 針對常態分布的連續數值或是大樣本的資料做平均值的比較
- 用於前後測比較，如2014與2016體重。

TABLE 1 | Demographic data of study participants in 2014 and 2016.

| | 2014 (n = 4,537) | | 2016 (n = 4,537) | | p-value |
|--------------------------------|------------------|---------|------------------|---------|--------------------|
| | n | % | n | % | |
| Age | 71.75 | ±5.93 | 73.75 | ±5.93 | – |
| Gender | | | | | 1.000 |
| Male | 2,207 | (48.6%) | 2,207 | (48.6%) | |
| Female | 2,330 | (51.4%) | 2,330 | (51.4%) | |
| Smoking | 309 | (6.8%) | 297 | (6.5%) | 0.119 |
| Drinking | 547 | (12.1%) | 581 | (12.8%) | 0.862 |
| Exercise | 3,237 | (71.3%) | 3,462 | (76.3%) | 0.930 |
| BMI | 24.49 | ±3.47 | 24.41 | ±3.42 | 0.004** |
| Height (cm) | 157.67 | ±8.15 | 157.59 | ±8.12 | 0.063 |
| Weight (kg) | 60.99 | ±10.38 | 60.78 | ±10.47 | <0.001** |
| Waist (cm) | 83.20 | ±9.72 | 84.59 | ±9.66 | <0.001** |
| SBP (mmHg) | 133.91 | ±18.19 | 134.63 | ±18.52 | 0.007** |
| DBP (mmHg) | 78.14 | ±10.91 | 77.21 | ±11.26 | <0.001** |
| Pulse pressure (mmHg) | 55.77 | ±13.82 | 57.42 | ±13.74 | <0.001** |
| Fasting plasma glucose (mg/dl) | 104.02 | ±21.92 | 104.89 | ±25.17 | 0.009** |
| Triglycerides (mg/dl) | 117.03 | ±66.71 | 114.85 | ±67.83 | 0.024* |
| HDL cholesterol (mg/dl) | 55.61 | ±15.66 | 55.60 | ±15.78 | 0.922 |

Wilcoxon signed-rank test

- 針對非常態分布的連續數值或小樣本，檢定兩組資料的中位數
- 用於前後測比較，術前和術後各部位角度數值

Table 2 Changes in pre- and postoperative radiographic parameters pre-operative and postoperative data

| | Pre-operative (n = 11) | | Postoperative (n = 11) | | p value |
|-------------------------------|------------------------|----------------|------------------------|----------------|---------|
| Local parameters | | | | | |
| Slip percentage | 60.0 | (53.0, 62.0) | 30.0 | (23.0, 36.0) | 0.003** |
| Dubousset's lumbosacral angle | 84.1 | (75.6, 92.3) | 97.9 | (92.5, 111.4) | 0.003** |
| Pelvic parameters | | | | | |
| Pelvic tilt | 24.2 | (22.2, 30.5) | 25.4 | (15.8, 30.4) | 0.131 |
| Pelvic incidence | 62.1 | (53.1, 80.8) | 64.9 | (52.1, 81.4) | 0.059 |
| Sacral slope | 32.3 | (30.4, 49.1) | 41.9 | (35.9, 52.2) | 0.091 |
| Spinal parameters | | | | | |
| LL | -49.4 | (-70.3, -34.7) | -57.7 | (-70.0, -47.1) | 0.013* |
| PI-LL mismatch | 16.0 | (10.0, 26.3) | 9.9 | (0.0, 19.0) | 0.021* |
| SVA (mm) | 36.9 | (18.3, 59.8) | 23.6 | (0.1, 54.1) | 0.213 |

Wilcoxon signed rank, median (IQR). * $P < 0.05$, ** $P < 0.01$

Abbreviations: LL Lumbar Lordosis; PI Pelvic Incidence.; SVA sagittal vertical axis

ANCOVA

- 常用在前後測的介入研究中
- 調整相關變項後，檢驗一個或多個自變量對依變項的差異

Table 3 Treatment effects in outcome measures^a

| Endpoints | Hydroxyurea | | Placebo | | Treatment effect, mean (SE) | 95% CI | p ^b |
|----------------------------------------|--------------|-----|--------------|-----|-----------------------------|---------------|----------------|
| | Mean (SE) | No. | Mean (SE) | No. | | | |
| Primary | | | | | | | |
| GMFM | 0.14 (0.57) | 37 | 2.02 (0.88) | 20 | -1.88 (1.00) | -3.89 to 0.13 | 0.11 |
| MMT | -0.58 (0.56) | 37 | -0.03 (0.98) | 20 | -0.55 (1.05) | -2.65 to 1.55 | 0.49 |
| Full-length mRNA (2 ^{-ΔΔCT}) | 3.62 (0.98) | 37 | 1.45 (0.50) | 20 | 2.17 (1.39) | -0.61 to 4.94 | 0.13 |
| Secondary | | | | | | | |
| MHFMS | 0.02 (0.03) | 26 | 0.04 (0.04) | 12 | -0.02 (0.05) | -0.12 to 0.07 | 0.35 |
| FVC | -0.21 (0.06) | 37 | -0.22 (0.12) | 20 | 0.01 (0.13) | -0.25 to 0.26 | 0.48 |

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; FVC = forced vital capacity; GMFM = Gross Motor Function Measure; MHFMS = Modified Hammersmith Functional Motor Scale; MMT = Manual Muscle Test; SMA = spinal muscular atrophy.

^a Measures after 18 months – baseline, last observation carried forward.

^b The *p* values were computed by ANCOVA with adjusted covariates of sex, age, SMA type, and walker or nonwalker.

Friedman test

- 相同個案，測量三次時間點(數值型資料)
- 整體顯著可再做事後檢定(Dunn-Bonferroni)

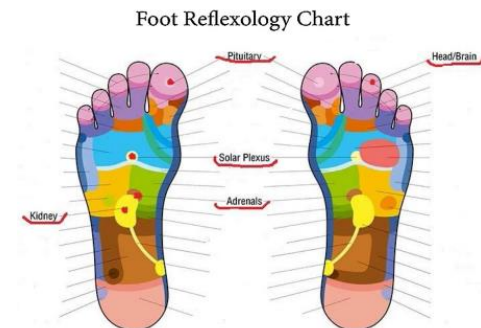


Table 3 – Comparison of median of duration of last night's sleep on the third, fourth, fifth and sixth days of hospitalization in two groups.

| Duration of last night's sleep | | Third day (before the intervention) | Fourth day (before the intervention) | Fifth day (before the intervention) | Sixth day (before the intervention) | Friedman statistic and p-value |
|-------------------------------------|--------|-------------------------------------------|--------------------------------------------|-------------------------------------------|-------------------------------------------|-----------------------------------|
| Intervention | Median | 4.5 (3–7.5) ^a | 6 (3–7.3) | 6 (3–7.5) | 8 (5.5–9.75) | $X^2=60.184$ $p<0.001$ |
| Control | Median | 4.5 (3–7.5) | 4.30 (3–7.3) | 4.5 (3–7.5) | 4.5 (3–7) | |
| Mann–Whitney U test and p-values | | Z=0.000 p=1.000 | Z=2.28 p=0.023 | Z=3.24 p<0.001 | Z=6.12 p<0.001 | |

^a (Min–Max).

Repeated measures ANOVA

- Outcome 為數值型資料且需符合常態分佈
- 寬資料，有一次資料missing則排除此個案

Table 2 The level of biochemical parameters at baseline, 6 months and 12 months between the two groups

| Items | groups | Cases (n) | Treatment time* | | | Repeated measures† | | |
|----------------|--------------|-----------|-----------------|--------------|--------------|-----------------------|----------------|-----------------|
| | | | Baseline | 6 months | 12 months | Interaction effect, P | Time effect, P | Group effect, P |
| Aβ40 (pg/mL) | Intervention | 105 | 27.78±20.80 | 26.88±20.81 | 28.62±20.79 | 0.468 | 0.027 | 0.480 |
| | Control | 105 | 33.46±24.06 | 32.43±24.00 | 33.22±23.20 | | | |
| Aβ42 (pg/mL) | Intervention | 105 | 34.39±21.71 | 32.33±21.70 | 30.50±21.69 | <0.001 | <0.001 | 0.987 |
| | Control | 105 | 33.28±21.26 | 33.76±21.24 | 33.19±20.51 | | | |
| PS1 (pg/mL) | Intervention | 105 | 48.78±44.39 | 48.89±44.39 | 48.89±44.39 | 0.951 | 0.727 | 0.272 |
| | Control | 105 | 44.51±37.92 | 44.63±37.92 | 44.74±37.65 | | | |
| PS2 (pg/mL) | Intervention | 105 | 10.43±19.02 | 10.57±19.02 | 10.69±19.03 | 0.142 | <0.001 | 0.133 |
| | Control | 105 | 11.01±17.44 | 11.17±17.44 | 11.55±17.53 | | | |
| PS1mRNA | Intervention | 105 | 28.85±2.59 | 30.19±2.61 | 29.77±2.59 | 0.040 | <0.001 | 0.070 |
| | Control | 105 | 28.89±2.58 | 30.41±2.58 | 29.86±2.60 | | | |
| PS2mRNA | Intervention | 105 | 4.00±0.43 | 4.34±0.53 | 4.17±0.53 | 0.121 | <0.001 | 0.409 |
| | Control | 105 | 4.18±0.39 | 4.60±0.61 | 4.34±0.38 | | | |
| APP | Intervention | 105 | 44.75±39.77 | 41.69±39.73 | 39.96±39.59 | <0.001 | <0.001 | <0.001 |
| | Control | 105 | 44.71±33.20 | 42.56±33.20 | 45.56±33.24 | | | |
| APPmRNA | Intervention | 105 | 32.59±1.53 | 30.28±1.50 | 27.96±1.54 | <0.001 | <0.001 | <0.001 |
| | Control | 105 | 32.41±1.41 | 31.44±1.47 | 31.55±1.38 | | | |
| BACE1 (µg/mL) | Intervention | 105 | 300.83±11.96 | 298.14±11.97 | 296.23±12.01 | <0.001 | <0.001 | <0.001 |
| | Control | 105 | 299.94±12.05 | 297.76±12.06 | 300.62±11.84 | | | |
| BACE1mRNA | Intervention | 105 | 27.59±1.29 | 25.29±1.55 | 23.48±1.91 | <0.001 | <0.001 | <0.001 |
| | Control | 105 | 27.24±1.32 | 26.09±1.31 | 27.82±1.27 | | | |
| 25-D (ng/mL) | Intervention | 105 | 18.82±2.91 | 20.90±3.12 | 22.77±3.41 | <0.001 | <0.001 | <0.001 |
| | Control | 105 | 19.44±2.81 | 19.18±2.81 | 19.08±2.84 | | | |
| 1,25-D (ng/mL) | Intervention | 105 | 30.37±2.60 | 31.79±2.57 | 33.61±2.77 | <0.001 | <0.001 | <0.001 |
| | Control | 105 | 30.22±2.67 | 29.01±2.67 | 30.71±2.64 | | | |

*Presented as mean±SD.

†P value for group (intervention vs control) derived from analysis of covariance adjusted for respective baseline value and for age, gender and education.

Aβ, amyloid beta; APP, Aβ protein precursor; BACE1, β-secretase 1; 25-D, 25-hydroxy vitamin D; 1,25-D, 1,25-dihydroxy vitamin; PS, presenilin.

Linear Mixed Model / Generalized Estimating Equation



- Linear Mixed Model
 - Outcome為數值型資料且需符合常態分佈
 - 資料型態為長資料，可容許遺漏值的存在
- GEE
 - 不需符合常態分佈假設，為半母數方法(semi-parametric)
 - Outcome可為連續、類別、順序或計數類型
 - 資料型態為長資料，可容許遺漏值的存在

GEE矩陣

- 獨立矩陣 (Independent)
- AR(1) 矩陣 (Auto-regressive first order)
- 可交換矩陣 (Exchangeable)
- 未結構化矩陣 (Unstructured)

獨立矩陣

| | t_1 | t_2 | t_3 | t_4 | t_5 |
|-------|-------|-------|-------|-------|-------|
| t_1 | — | | | | |
| t_2 | 0 | — | | | |
| t_3 | 0 | 0 | — | | |
| t_4 | 0 | 0 | 0 | — | |
| t_5 | 0 | 0 | 0 | 0 | — |

AR(1) 矩陣

| | t_1 | t_2 | t_3 | t_4 | t_5 |
|-------|----------|----------|----------|--------|-------|
| t_1 | — | | | | |
| t_2 | ρ | — | | | |
| t_3 | ρ^2 | ρ | — | | |
| t_4 | ρ^3 | ρ^2 | ρ | — | |
| t_5 | ρ^4 | ρ^3 | ρ^2 | ρ | — |

可交換矩陣

| | t_1 | t_2 | t_3 | t_4 | t_5 |
|-------|--------|--------|--------|--------|-------|
| t_1 | — | | | | |
| t_2 | ρ | — | | | |
| t_3 | ρ | ρ | — | | |
| t_4 | ρ | ρ | ρ | — | |
| t_5 | ρ | ρ | ρ | ρ | — |

未結構化矩陣

| | t_1 | t_2 | t_3 | t_4 | t_5 |
|-------|----------|----------|----------|-------------|-------|
| t_1 | — | | | | |
| t_2 | ρ_1 | — | | | |
| t_3 | ρ_2 | ρ_5 | — | | |
| t_4 | ρ_3 | ρ_6 | ρ_8 | — | |
| t_5 | ρ_4 | ρ_7 | ρ_9 | ρ_{10} | — |

GEE



Table 2 Adjusted odds ratio (OR) and 95% confidence interval (CI) of dementia, Alzheimer disease, and vascular dementia related to midlife BMI (results from generalized estimating equation models)

| Midlife BMI | No. of twins | All dementia | | | Alzheimer disease | | | Vascular dementia | | |
|--------------------|--------------|--------------|--------------------------|--------------------------|-------------------|--------------------------|--------------------------|-------------------|--------------------------|--------------------------|
| | | No. | OR (95% CI) ^a | OR (95% CI) ^b | No. | OR (95% CI) ^a | OR (95% CI) ^b | No. | OR (95% CI) ^a | OR (95% CI) ^b |
| Continuous | 8,534 | 464 | 1.09 (1.06-1.12) | 1.06 (1.03-1.10) | 232 | 1.09 (1.04-1.13) | 1.06 (1.01-1.10) | 74 | 1.14 (1.08-1.21) | 1.11 (1.04-1.19) |
| Categorical | | | | | | | | | | |
| <20 | 627 | 17 | 0.74 (0.44-1.25) | 0.79 (0.45-1.38) | 8 | 0.89 (0.64-1.23) | 0.66 (0.31-1.41) | 0 | — | — |
| 20-25 | 5,366 | 240 | 1 (Reference) | 1 (Reference) | 120 | 1 (Reference) | 1 (Reference) | 36 | 1 (Reference) | 1 (Reference) |
| >25 | 2,541 | 207 | 1.50 (1.22-1.84) | 1.80 (1.37-2.35) | 104 | 1.52 (1.15-2.02) | 1.98 (1.36-2.88) | 38 | 1.62 (1.01-2.59) | 1.35 (0.81-2.24) |
| 25-30 | 2,297 | 177 | 1.37 (1.11-1.70) | 1.71 (1.30-2.25) | 90 | 1.41 (1.05-1.89) | 1.91 (1.30-2.80) | 31 | 1.39 (0.85-2.29) | 1.17 (0.69-2.00) |
| >30 | 244 | 30 | 3.01 (1.95-4.64) | 3.88 (2.12-7.11) | 14 | 2.87 (1.57-5.26) | 3.43 (1.49-7.90) | 7 | 4.38 (1.89-10.14) | 3.50 (1.36-8.99) |

Abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio.

^a Adjusted for age, sex, and education.

^b Adjusted for age, sex, education, diabetes, hypertension, stroke, and heart disease.

| | A | B | C | D | E |
|----|-----|-------------|-------------|-------------|---|
| no | BMI | Diagnosis_1 | Diagnosis_2 | Diagnosis_3 | |
| 1 | 25 | 0 | 0 | 0 | |
| 2 | 30 | 0 | 0 | 1 | |
| 3 | 35 | 0 | 0 | 0 | |
| 4 | 18 | 0 | 0 | 0 | |
| 5 | 22 | 0 | 1 | 1 | |
| 6 | 19 | 0 | 0 | 1 | |
| 7 | 21 | 0 | 0 | 0 | |
| 8 | 33 | 0 | 1 | 1 | |
| 9 | 28 | 0 | 0 | 0 | |
| 10 | 35 | 0 | 0 | 1 | |

| Vascular risk factors, No. (%) | |
|--------------------------------|------------|
| Coronary heart disease | 63 (19.1) |
| Cardiac arrhythmia | 30 (9.1) |
| Cerebrovascular disease | 12 (3.6) |
| Hypertension | 217 (65.8) |
| Diabetes mellitus | 154 (46.7) |
| Obesity | 18 (5.5) |
| Smoking | 44 (13.3) |
| Physical inactivity | 121 (36.7) |



Table 2. Results of the generalized estimating equation analyzing the effect of 3-year MMSE changes in AD patients with and without APOE ε4 and different VRF indexes

| Variable | All AD patients (n = 330) | | AD patients with APOE ε4 (n = 129) | | AD patients without APOE ε4 (n = 201) | |
|-----------------------|---------------------------|----------------------|------------------------------------|----------------------|---------------------------------------|----------------------|
| | β (95% CI) | P value ^a | β (95% CI) | P value ^a | β (95% CI) | P value ^a |
| VRF groups | | | | | | |
| >3 VRFs | -1.16 (-2.1 to -0.21) | .02 | -1.99 (-3.62 to -0.36) | .02 | -0.59 (-1.7 to 0.52) | .3 |
| 3 VRFs | -0.36 (-1.24 to 0.51) | .42 | -1.2 (-2.8 to 0.4) | .14 | 0.11 (-0.9 to 1.1) | .83 |
| 2 VRFs | -0.15 (-0.92 to 0.61) | .69 | -0.51 (-1.8 to 0.78) | .44 | 0.27 (-0.64 to 1.18) | .56 |
| 1 VRF | -0.04 (-0.83 to 0.73) | .89 | -0.48 (-1.76 to 0.81) | .47 | 0.3 (-0.68 to 1.28) | .55 |
| 0 VRFs | Reference | | Reference | | Reference | |
| APOE ε4 | | | | | | |
| Carrier | -0.63 (-1.18 to -0.08) | .03 | | | | |
| Noncarrier | Reference | | | | | |
| Sex | | | | | | |
| Female | 0.35 (-0.15 to 0.85) | .17 | 0.64 (-0.21 to 1.5) | .14 | 0.19 (-0.42 to 0.79) | .55 |
| Male | Reference | | Reference | | Reference | |
| Age | -0.001 (-0.05 to 0.05) | .96 | 0.02 (-0.06 to 0.1) | .65 | -0.01 (-0.07 to 0.05) | .7 |
| Education | -0.01 (-0.07 to 0.04) | .66 | -0.06 (-0.15 to 0.03) | .2 | <0.001 (-0.07 to 0.07) | .99 |
| Disease duration | 0.001 (-0.004 to 0.01) | .76 | 0.005 (-0.003 to 0.01) | .2 | -0.001 (-0.008 to 0.005) | .72 |
| Baseline MMSE | 0.95 (0.9 to 0.99) | <.001 | 0.97 (0.9 to 1) | <.001 | 0.93 (0.87 to 1) | <.001 |
| Time | -1.17 (-1.4 to -1) | <.001 | -1.34 (-1.65 to -1.03) | <.001 | -1.08 (-1.3 to -0.86) | <.001 |
| Medication | -0.46 (-0.95 to 0.03) | .07 | -0.85 (-1.77 to 0.07) | .07 | -0.18 (-0.77 to 0.4) | .57 |
| Hospitalization rates | -0.24 (-0.66 to 0.17) | .25 | -0.6 (-1.2 to 0.004) | .05 | -0.18 (-0.71 to 0.34) | .49 |

Abbreviations: AD, Alzheimer disease; APOE, apolipoprotein E; CI, confidence interval; MMSE, Mini-Mental State Examination; NMDA, N-methyl-D-aspartate; VRF, vascular risk factor.

^aP values were adjusted for APOE ε4 carrier status (in all AD patients), sex, age, years of education, disease duration, baseline MMSE score, time, use of medication (acetylcholinesterase inhibitors or NMDA receptor antagonists), and hospitalization rates.

Logistic regression

Unconditional

- 用於非配對資料
- 依變項為二元、有順序或三組以上
- 高估結果

Conditional

- 用在配對病歷對照研究
- 針對配對資料分析的方法，如 1:n
- 利用條件式最大概似估計法估計

Conditional logistic regression

- 針對配對資料分析，用來分析兩組相關風險的統計方法
- 病例組及對照組最常見配對設計為1:1
- 用於分析有條件的二元變數與多個預測變數之間的關係

Table 3. Multivariable conditional logistic regression analysis of diagnosis and treatment of diabetes mellitus for out-of-hospital cardiac arrest incidence.

| | OHCA cases/ Community controls <i>n/n</i> | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) |
|-----------------------------|----------------------------------------------|---------------------------|--------------------------|
| Model1: DM diagnosis | | | |
| No | 1016 / 4684 | 1.00 | 1.00 |
| Yes | 370 / 860 | 2.04 (1.77–2.36) | 1.92 (1.65–2.24) |
| Model2: DM treatment | | | |
| No DM | 1016 / 4684 | 1.00 | 1.00 |
| DM and no treatment | 67 / 76 | 4.17 (2.97–5.84) | 4.17 (2.91–5.96) |
| Non-pharmacotherapy only | 11 / 13 | 4.04 (1.80–9.05) | 4.65 (2.00–10.84) |
| Oral hypoglycemic agent | 244 / 696 | 1.66 (1.41–1.96) | 1.55 (1.31–1.85) |
| Insulin | 48 / 75 | 3.04 (2.10–4.40) | 2.69 (1.82–3.96) |

OHCA: out-of-hospital cardiac arrest; DM: diabetes mellitus; OR: odds ratio; CI: confidence interval

*Adjusted for hypertension, smoking, alcohol, physical activity, sleeping hour, and body mass index.

Cox regression



- 評估多個變數對存活(Time to event)的影響
- 可使用類別/連續變數呈現危險因子，並估算出這些危險因子對outcome的影響

$$\log \frac{h(t)}{h_0(t)} = \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k$$

| Hazard ratio (HR) | Explanation |
|-------------------|----------------------------------------------|
| HR=1 | Two groups have the same survival experience |
| HR>1 | Survival is better in the control group |
| HR<1 | Survival is better in the treatment group |

Cox regression

| | Unadjusted | | | Adjusted* | | |
|----------------------------------------------------|------------|--------------|----------|-----------|---------------|----------|
| | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> |
| Aβ42, pg/ml | | | | | | |
| ≤16.8 | 1.00 | | | 1.00 | | |
| >16.8 | 11.71 | (1.45–94.64) | 0.021* | 16.84 | (1.88–150.45) | 0.011* |
| t-tau, pg/ml | | | | | | |
| ≤25.4 | 1.00 | | | 1.00 | | |
| >25.4 | 4.51 | (1.19–17.13) | 0.027* | 5.19 | (1.20–22.53) | 0.028* |
| Aβ42 × t-tau, pg²/ml² | | | | | | |
| ≤465.1 | 1.00 | | | 1.00 | | |
| >465.1 | 6.08 | (1.45–25.41) | 0.013* | 7.14 | (1.57–32.55) | 0.011* |
| Aβ42/t-tau | | | | | | |
| ≤0.63 | 1.00 | | | 1.00 | | |
| >0.63 | 0.28 | (0.08–1.07) | 0.063 | 0.29 | (0.07–1.17) | 0.083 |

Table 4. Cox regression analysis of predictors for cognitive decline in MCI. Abbreviations: HR, hazard ratio; CI, confidence interval. *Models were adjusted for age, gender, years of education, and APOE ε4 carrier status. **p* < 0.05.

SPSS操作步驟

Friedman test



- 同一組個案，測量三次時間點(數值型資料)
- 整體顯著可再做事後檢定(Dunn-Bonferroni)

| ID | Treatment | MMSE_Baseline | MMSE_3mo | MMSE_6mo |
|-----|-----------|---------------|----------|----------|
| A01 | 0 | 23 | 23 | 26 |
| A02 | 0 | 19 | 20 | 18 |
| A03 | 0 | 16 | 14 | 12 |
| A04 | 0 | 17 | 17 | 16 |
| A05 | 0 | 26 | 27 | 25 |
| A06 | 0 | 9 | 12 | . |
| A07 | 0 | 19 | 19 | . |
| A08 | 0 | 26 | 25 | 23 |
| A09 | 0 | 10 | 8 | 8 |
| A10 | 0 | 20 | 17 | 18 |
| A11 | 0 | 25 | 17 | 18 |
| A12 | 0 | 14 | 16 | 15 |
| A13 | 0 | 25 | 24 | . |
| A14 | 0 | 16 | 11 | . |
| A15 | 0 | 7 | 8 | . |

Friedman test 操作



分析 > 無母數檢定 > 歷史對話記錄 > K個相關樣本

SPSS menu path: Analyze > Nonparametric Tests > Legacy Dialogs > K Related Samples...

| | SE_6mo | Outcome | var | var | var |
|---------------------------|--------|---------|-----|-----|-----|
| Reports | | | | | |
| Descriptive Statistics | | | | | |
| Custom Tables | | | | | |
| Compare Means | | | | | |
| General Linear Model | 26 | 0 | | | |
| Generalized Linear Models | 18 | 0 | | | |
| Mixed Models | 12 | 1 | | | |
| Correlate | 16 | 0 | | | |
| Regression | 25 | 0 | | | |
| Loglinear | . | 1 | | | |
| Neural Networks | . | 0 | | | |
| Classify | 23 | 0 | | | |
| Dimension Reduction | 8 | 1 | | | |
| Scale | 18 | 0 | | | |
| Nonparametric Tests | | | | | |
| Forecasting | | | | | |
| Survival | | | | | |
| Multiple Response | | | | | |
| PS Matching | 18 | 0 | | | |
| Missing Value Analysis... | 21 | 0 | | | |
| Multiple Imputation | 13 | 0 | | | |
| Complex Samples | 16 | 0 | | | |
| Simulation... | 5 | 1 | | | |
| Quality Control | . | 0 | | | |
| ROC Curve... | . | 0 | | | |
| Ranfor Prediction | . | 0 | | | |
| | 23 | 0 | | | |

Tests for Several Related Samples dialog box

Test Variables:

- Treatment
- Outcome

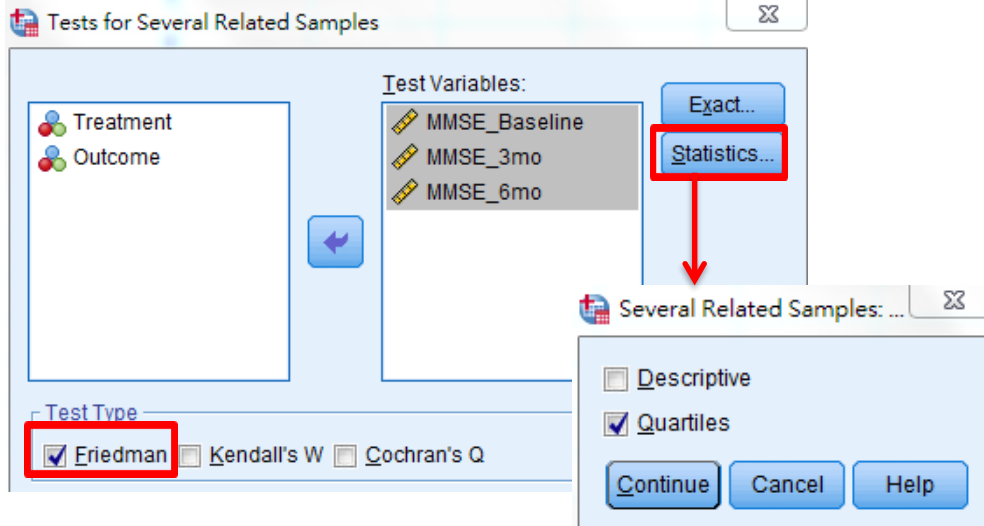
Test Variables list:

- MMSE_Baseline
- MMSE_3mo
- MMSE_6mo

Test Type:

- Friedman
- Kendall's W
- Cochran's Q

Friedman test output



→ NPar Tests

Descriptive Statistics

| | N | Percentiles | | |
|---------------|----|-------------|---------------|-------|
| | | 25th | 50th (Median) | 75th |
| MMSE_Baseline | 22 | 16.75 | 20.50 | 24.25 |
| MMSE_3mo | 22 | 16.00 | 18.00 | 23.00 |
| MMSE_6mo | 22 | 14.75 | 18.00 | 23.00 |

Friedman Test

Ranks

| | Mean Rank |
|---------------|-----------|
| MMSE_Baseline | 2.64 |
| MMSE_3mo | 1.86 |
| MMSE_6mo | 1.50 |

Test Statistics^a

| | |
|-------------|--------|
| N | 22 |
| Chi-Square | 16.506 |
| df | 2 |
| Asymp. Sig. | .000 |

a. Friedman Test

Table. (N=22)

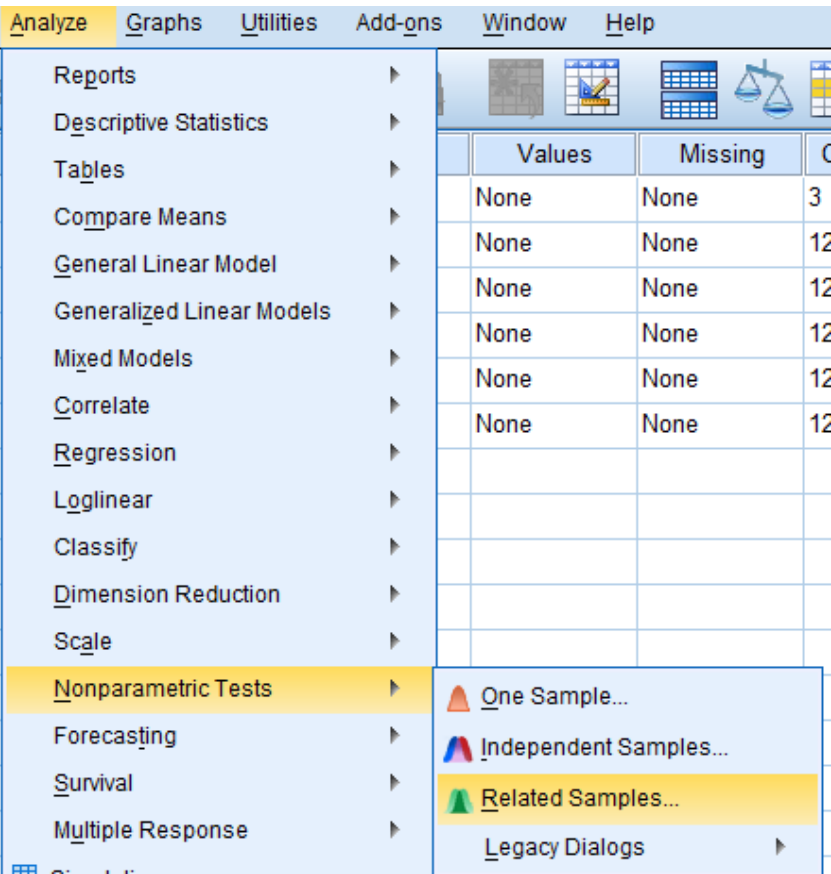
| | Baseline | 3 month | 6 month | <i>P value</i> |
|------|------------------|------------------|------------------|----------------|
| MMSE | 20.5 (16.8-24.3) | 18.0 (16.0-23.0) | 18.0 (14.8-23.0) | <0.001 |

Friedman test. Median (IQR)

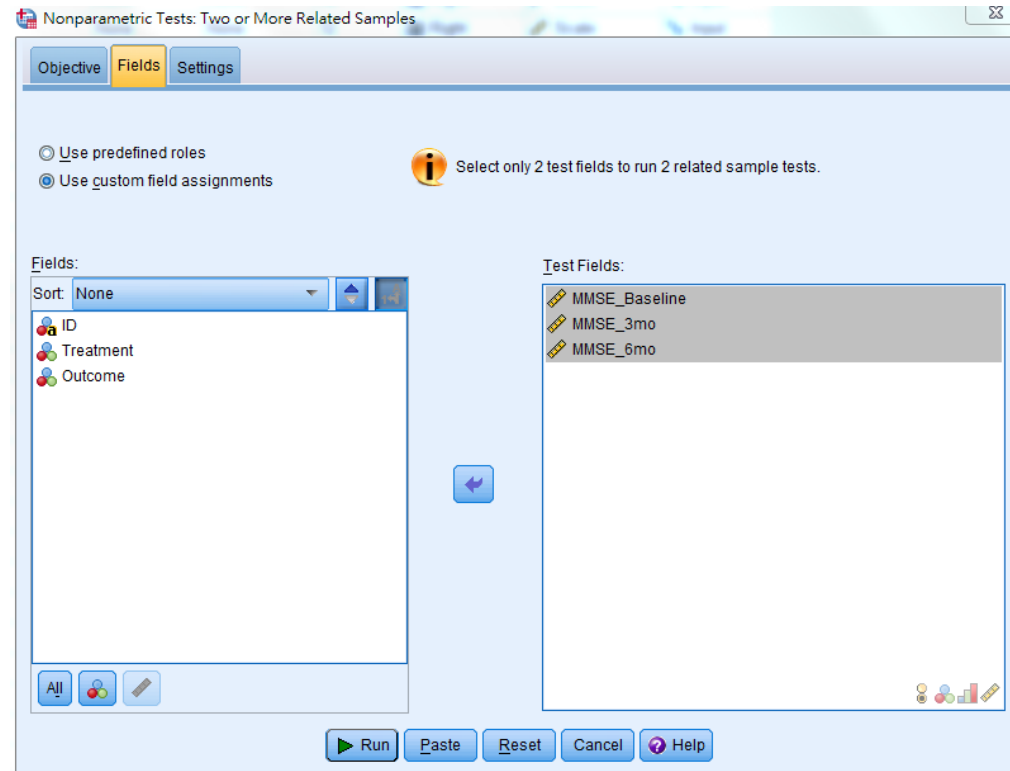
Friedman test (Post-hoc)

| Name | Type | Width | Decimals | Label | Values | Missing | Columns | Align | Measure |
|-------------|---------|-------|----------|-------|--------|---------|---------|-------|---------|
| ID | String | 3 | 0 | | None | None | 3 | Left | Nominal |
| Treatment | Numeric | 12 | 0 | | None | None | 12 | Right | Nominal |
| MMSE_Bas... | Numeric | 12 | 0 | | None | None | 12 | Right | Scale |
| MMSE_3mo | Numeric | 12 | 0 | | None | None | 12 | Right | Scale |
| MMSE_6mo | Numeric | 12 | 0 | | None | None | 12 | Right | Scale |

分析 > 無母數檢定 > 相關樣本



The image shows the SPSS Analyze menu with 'Nonparametric Tests' selected. The 'Related Samples...' option is highlighted. The 'Legacy Dialogs' sub-menu is also visible.



The image shows the 'Nonparametric Tests: Two or More Related Samples' dialog box. The 'Fields' tab is active, showing 'ID', 'Treatment', and 'Outcome' in the 'Fields:' list. The 'Test Fields:' list contains 'MMSE_Baseline', 'MMSE_3mo', and 'MMSE_6mo'. The 'Run' button is highlighted.

Friedman test (Post-hoc output)



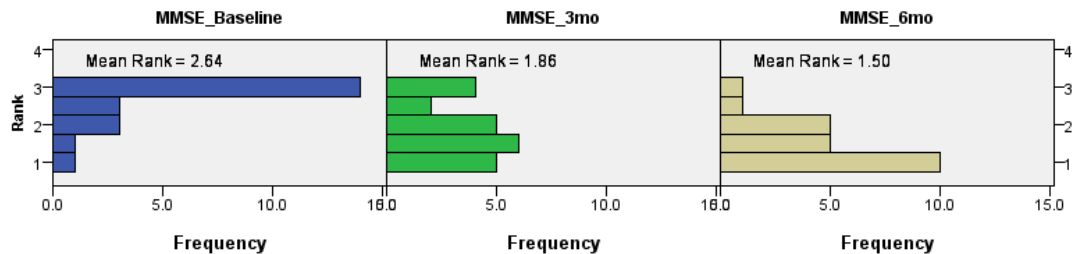
Hypothesis Test Summary

| Null Hypothesis | Test | Sig. | Decision |
|---------------------------------------------------------------------------|------------------------------------------------------------------|------|-----------------------------|
| 1 The distributions of MMSE_Baseline, MMSE_3mo and MMSE_6mo are the same. | Related-Samples Friedman's Two-Way Analysis of Variance by Ranks | .000 | Reject the null hypothesis. |

1

Asymptotic significances are displayed. The significance level is .05.

Related-Samples Friedman's Two-Way Analysis of Variance by Ranks



| | |
|--------------------------------|--------|
| Total N | 22 |
| Test Statistic | 16.506 |
| Degrees of Freedom | 2 |
| Asymptotic Sig. (2-sided test) | .000 |

2

| Sample1-Sample2 | Test Statistic | Std. Error | Std. Test Statistic | Sig. | Adj.Sig. |
|------------------------|----------------|------------|---------------------|------|----------|
| MMSE_6mo-MMSE_3mo | .364 | .302 | 1.206 | .228 | .683 |
| MMSE_6mo-MMSE_Baseline | 1.136 | .302 | 3.769 | .000 | .000 |
| MMSE_3mo-MMSE_Baseline | .773 | .302 | 2.563 | .010 | .031 |

3

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed. The significance level is .05.

st: Friedman Field(s): MMSE_Baseline, MMSE_3mo, MMSE_6mo(Test 1) View: Related Samples Test View

- Related Samples Test View
- Continuous Field Information
- Pairwise Comparisons

Cochran Q test



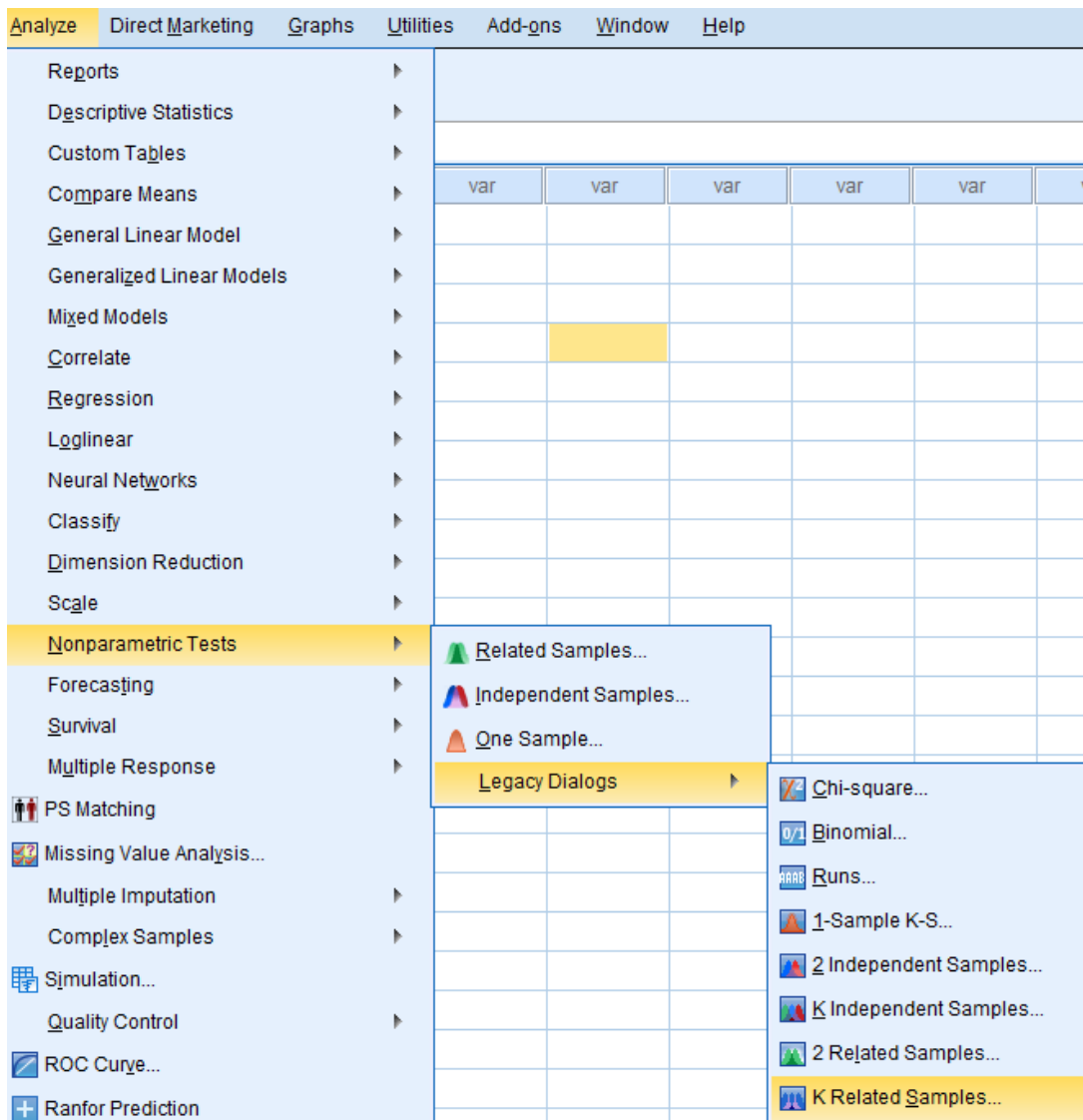
- 同一組個案，測量三次時間點(類別型資料--二分類)
- 0: 無抽菸; 1: 有抽菸

| id | test_1 | test_2 | test_3 |
|-----|--------|--------|--------|
| A01 | 0 | 1 | 1 |
| A02 | 0 | 1 | 1 |
| A03 | 1 | 1 | 1 |
| A04 | 1 | 0 | 1 |
| A05 | 0 | 0 | 0 |
| A06 | 1 | 1 | 1 |
| A07 | 1 | 1 | 1 |
| A08 | 1 | 0 | 1 |
| A09 | 1 | 1 | 1 |
| A10 | 0 | 0 | 1 |
| A11 | 1 | 1 | 1 |
| A12 | 1 | 1 | 1 |
| A13 | 1 | 0 | 1 |
| A14 | 1 | 0 | 0 |
| A15 | 0 | 0 | 1 |

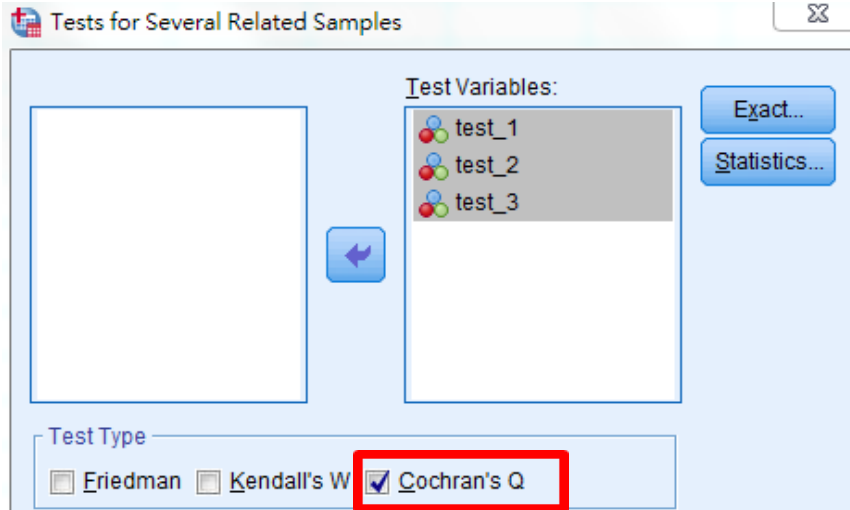
Cochran Q test 操作



分析 > 無母數檢定 > 歷史對話記錄 > K個相關樣本



Cochran Q test output



Cochran Test

Frequencies

| | Value | |
|--------|-------|----|
| | 0 | 1 |
| test_1 | 5 | 10 |
| test_2 | 7 | 8 |
| test_3 | 2 | 13 |

Test Statistics

| | |
|-------------|--------------------|
| N | 15 |
| Cochran's Q | 4.750 ^a |
| df | 2 |
| Asymp. Sig. | .093 |

a. 0 is treated as a success.

Table.

| | Test1 (n=15) | Test2 (n=15) | Test3 (n=15) | <i>p</i> value |
|---------|--------------|--------------|--------------|----------------|
| Smoking | | | | 0.093 |
| No | 5 (33.3%) | 7 (46.7%) | 2 (13.3%) | |
| Yes | 10 (66.7%) | 8 (53.3%) | 13 (86.7%) | |

Cochran Q test.

Repeated measures ANOVA

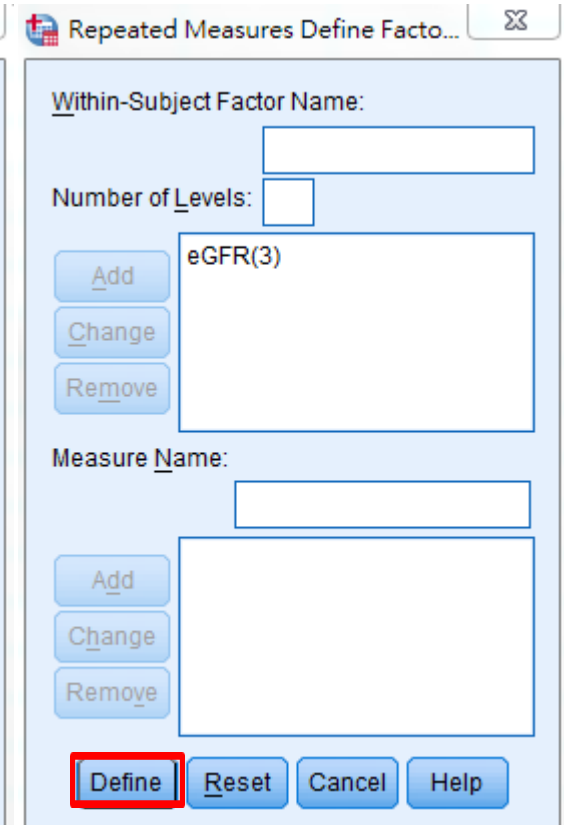
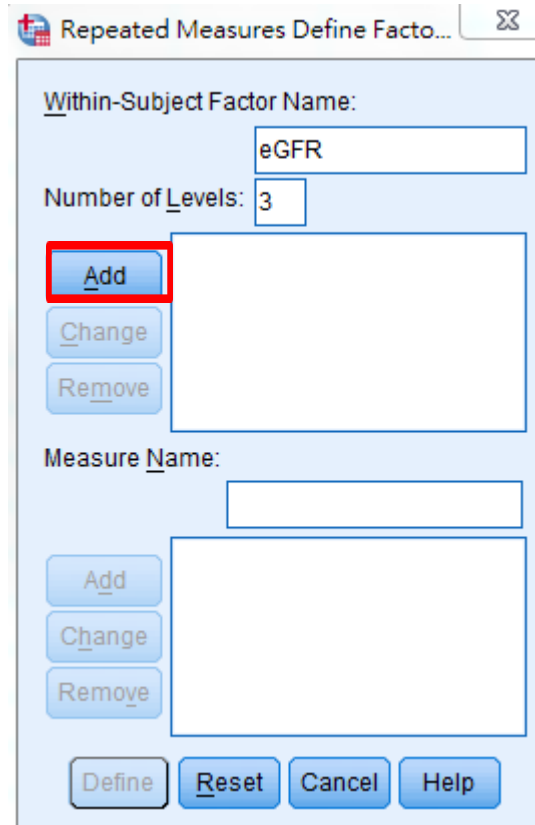
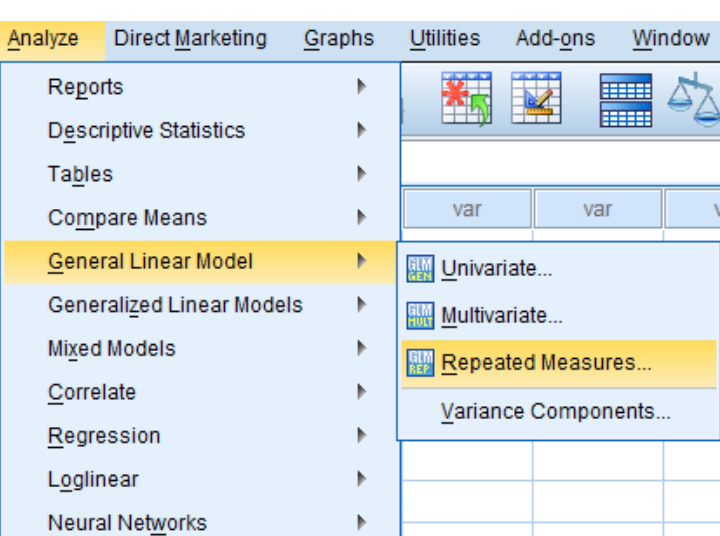


| Subject | eGFR_1 | eGFR_2 | eGFR_3 |
|---------|--------|--------|--------|
| 1.00 | 60.06 | 23.96 | 40.22 |
| 2.00 | 37.89 | 4.18 | 23.96 |
| 3.00 | 46.72 | 61.92 | 4.18 |
| 4.00 | 40.22 | 59.81 | 61.92 |
| 5.00 | 23.96 | 83.71 | 59.81 |
| 6.00 | 4.18 | 33.81 | 52.86 |
| 7.00 | 61.92 | 16.04 | 30.30 |
| 8.00 | 59.81 | 70.12 | 65.94 |
| 9.00 | 83.71 | 3.73 | 57.71 |
| 10.00 | 33.81 | 27.68 | 59.42 |
| 11.00 | 16.04 | 52.86 | 8.39 |
| 12.00 | 70.12 | 30.30 | 20.58 |
| 13.00 | 3.73 | 65.94 | 34.42 |
| 14.00 | 27.68 | 57.71 | 52.86 |
| 15.00 | 52.86 | 59.42 | 30.30 |

Repeated measures ANOVA操作



分析 > 一般線性模式 > 重複測量



Repeated measures ANOVA操作



Repeated Measures

Within-Subjects Variables (eGFR):

Subject
eGFR_1
eGFR_2
eGFR_3

Model...
Contrasts...
Plots...
Post Hoc...
Save...
Options...

Between-Subjects Factor(s):

Covariates:

OK Paste Reset Cancel Help

Repeated Measures

Within-Subjects Variables (eGFR):

Subject

Model...
Contrasts...
Plots...
Post Hoc...
Save...
Options...

Between-Subjects Factor(s):

類別變項

Covariates:

數值變項

OK Paste Reset Cancel Help

Repeated measures ANOVA操作



Repeated Measures: Options

Estimated Marginal Means

Factor(s) and Factor Interactions:

(OVERALL)
eGFR

Display Means for:
eGFR

Compare main effects

Confidence interval adjustment:
Bonferroni

Display

Descriptive statistics

Estimates of effect size

Observed power

Parameter estimates

SSCP matrices

Residual SSCP matrix

Transformation matrix

Homogeneity tests

Spread vs. level plot

Residual plot

Lack of fit

General estimable function

Significance level: .05 Confidence intervals are 95.0 %

Continue Cancel Help

Repeated Measures: Profile Plots

Factors:
eGFR

Horizontal Axis:
eGFR

Separate Lines:

Separate Plots:

Plots:

Add Change Remove

Continue Cancel Help

Repeated Measures: Profile Plots

Factors:
eGFR

Horizontal Axis:

Separate Lines:

Separate Plots:

Plots:
eGFR

Add Change Remove

Continue Cancel Help

Repeated measures ANOVA output



Descriptive Statistics

| | Mean | Std. Deviation | N |
|--------|---------|----------------|----|
| eGFR_1 | 42.1597 | 22.17652 | 30 |
| eGFR_2 | 38.6210 | 23.02831 | 30 |
| eGFR_3 | 24.1937 | 18.25126 | 30 |

Mauchly's Test of Sphericity^a

Measure: MEASURE_1

| Within Subjects Effect | Mauchly's W | Approx. Chi-Square | df | Sig. | Epsilon ^b | | |
|------------------------|-------------|--------------------|----|------|----------------------|-------------|-------------|
| | | | | | Greenhouse-Geisser | Huynh-Feldt | Lower-bound |
| eGFR | .885 | 3.413 | 2 | .182 | .897 | .952 | .500 |

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

$p > 0.05$ 代表資料符合球形假設

a. Design: Intercept

Within Subjects Design: eGFR

b. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

Tests of Within-Subjects Effects

Measure: MEASURE_1

| Source | | Type III Sum of Squares | df | Mean Square | F | Sig. |
|-------------|---------------------------|-------------------------|--------|-------------|-------|------|
| eGFR | Sphericity Assumed | 5434.473 | 2 | 2717.236 | 5.428 | .007 |
| | <u>Greenhouse-Geisser</u> | 5434.473 | 1.794 | 3029.031 | 5.428 | .009 |
| | Huynh-Feldt | 5434.473 | 1.905 | 2852.924 | 5.428 | .008 |
| | Lower-bound | 5434.473 | 1.000 | 5434.473 | 5.428 | .027 |
| Error(eGFR) | Sphericity Assumed | 29033.588 | 58 | 500.579 | | |
| | Greenhouse-Geisser | 29033.588 | 52.030 | 558.019 | | |
| | Huynh-Feldt | 29033.588 | 55.241 | 525.576 | | |
| | Lower-bound | 29033.588 | 29.000 | 1001.158 | | |

不符合球形假設

Repeated measures ANOVA output



Estimates

Measure: MEASURE_1

| eGFR | Mean | Std. Error | 95% Confidence Interval | |
|------|--------|------------|-------------------------|-------------|
| | | | Lower Bound | Upper Bound |
| 1 | 42.160 | 4.049 | 33.879 | 50.441 |
| 2 | 38.621 | 4.204 | 30.022 | 47.220 |
| 3 | 24.194 | 3.332 | 17.379 | 31.009 |

Pairwise Comparisons

Measure: MEASURE_1

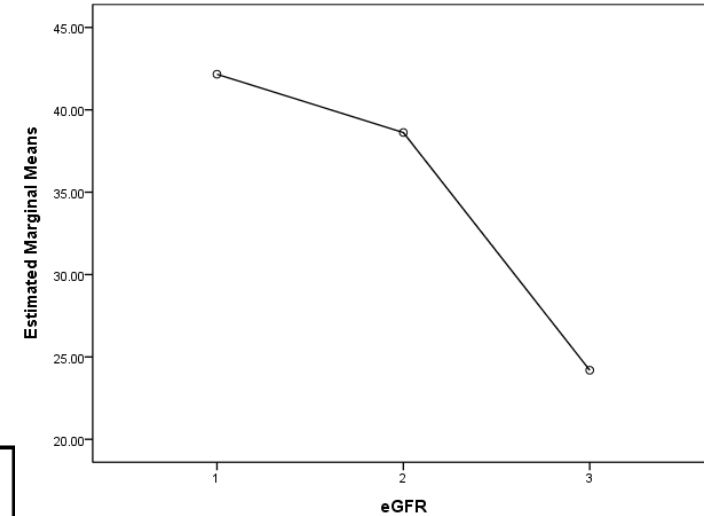
| (I) eGFR | (J) eGFR | Mean Difference (I-J) | Std. Error | Sig. ^b | 95% Confidence Interval for Difference ^b | |
|----------|----------|-----------------------|------------|-------------------|-----------------------------------------------------|-------------|
| | | | | | Lower Bound | Upper Bound |
| 1 | 2 | 3.539 | 6.652 | 1.000 | -13.363 | 20.441 |
| | 3 | 17.966* | 5.532 | .009 | 3.910 | 32.022 |
| 2 | 1 | -3.539 | 6.652 | 1.000 | -20.441 | 13.363 |
| | 3 | 14.427* | 5.026 | .023 | 1.656 | 27.199 |
| 3 | 1 | -17.966* | 5.532 | .009 | -32.022 | -3.910 |
| | 2 | -14.427* | 5.026 | .023 | -27.199 | -1.656 |

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

Estimated Marginal Means of MEASURE_1



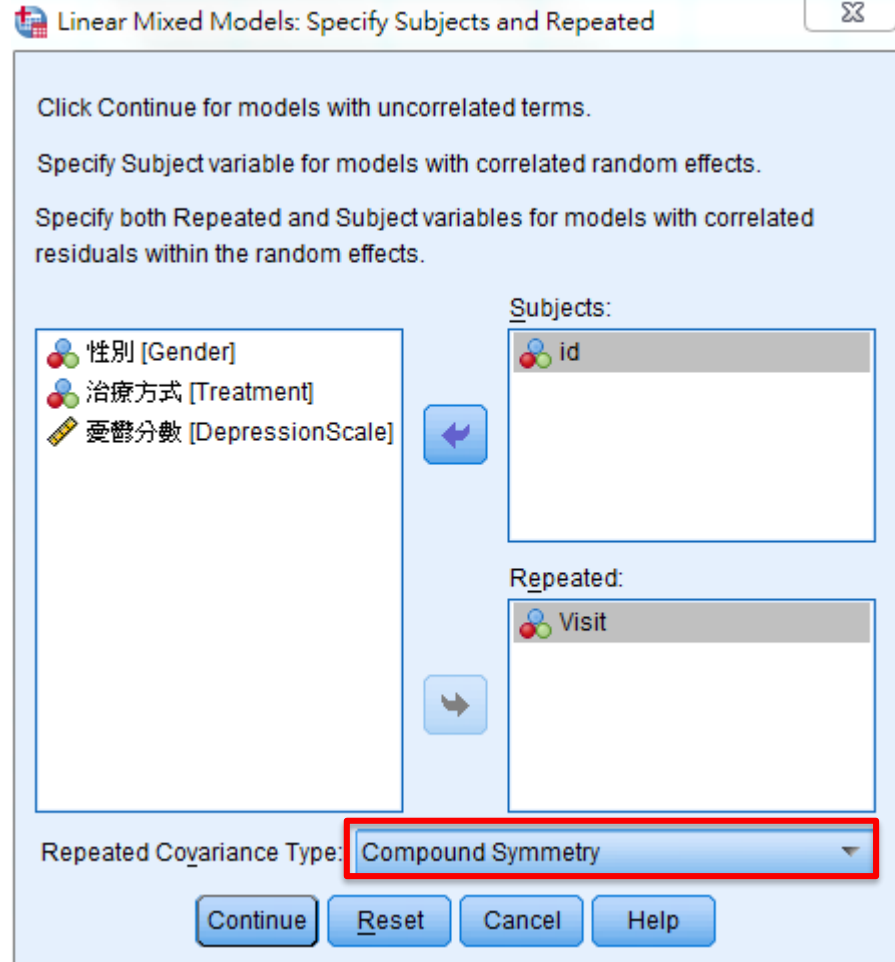
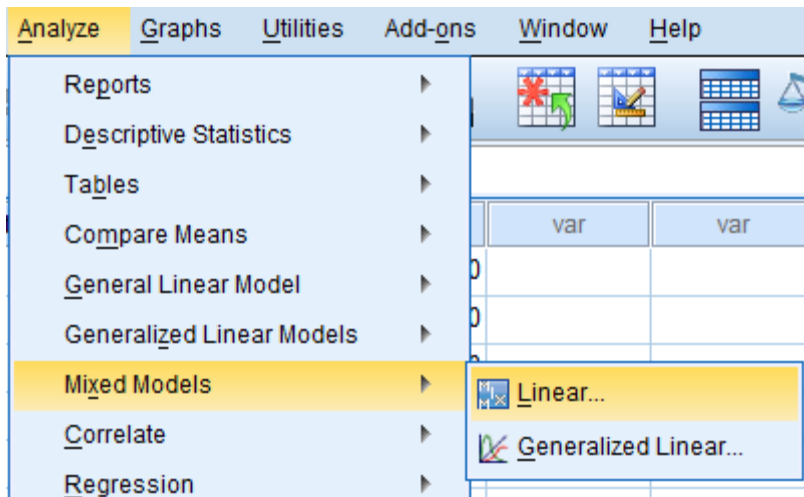
Mixed model



| id | Gender | Treatment | Visit | DepressionScale |
|----|--------|-----------|-------|-----------------|
| 1 | 2 | 1 | 1 | 4.0 |
| 1 | 2 | 1 | 2 | 32.0 |
| 1 | 2 | 1 | 3 | 13.0 |
| 1 | 2 | 1 | 4 | 19.0 |
| 1 | 2 | 1 | 5 | 11.0 |
| 2 | 2 | 1 | 1 | 29.0 |
| 2 | 2 | 1 | 2 | 14.0 |
| 2 | 2 | 1 | 3 | 8.0 |
| 2 | 2 | 1 | 4 | 5.0 |
| 2 | 2 | 1 | 5 | 4.0 |
| 3 | 1 | 1 | 1 | 19.0 |
| 3 | 1 | 1 | 2 | 27.0 |
| 3 | 1 | 1 | 3 | 9.0 |
| 3 | 1 | 1 | 4 | 15.0 |
| 3 | 1 | 1 | 5 | 9.0 |

Mixed model 操作

分析 > 混合模式 > 線性



重複共變異數類型:
複合對稱
(選取AIC及BIC最小)

Mixed model 操作



Linear Mixed Models

Dependent Variable: 憂鬱分數 [Depression...]

Factor(s): 性別 [Gender], 治療方式 [Treatment], Visit

Covariate(s): 數值變項

Residual Weight:

Fixed...
Random...
Estimation...
Statistics...
EM Means...
Save...

OK Paste Reset Cancel Help

Linear Mixed Models: Fixed Effects

Fixed Effects

Build terms Build nested terms

Factors and Covariates: Gender, Treatment, Visit

Model: Gender, Treatment, Visit, Treatment*Visit

Factorial

Include intercept Sum of squares: Type III

Continue Cancel Help

Linear Mixed Models: Statistics

Summary Statistics

Descriptive statistics

Case Processing Summary

Model Statistics

Parameter estimates

Tests for covariance parameters

Correlations of parameter estimates

Covariances of parameter estimates

Covariances of random effects

Covariances of residuals

Contrast coefficient matrix

Confidence interval: 95 %

Continue Cancel Help

Linear Mixed Models: EM Means

Estimated Marginal Means of Fitted Models

Factors(s) and Factor Interactions: (OVERALL), Gender, Treatment, Visit, Treatment*Visit

Display Means for: Gender, Treatment, Visit, Treatment*Visit

Compare main effects

Confidence Interval Adjustment: Bonferroni

Reference Category

Mixed model output



Information Criteria^a

Estimates of Fixed Effects^a

| | |
|--------------------------------------|---------|
| -2 Restricted Log Likelihood | 650.289 |
| Akaike's Information Criterion (AIC) | 654.289 |
| Hurvich and Tsai's Criterion (AICC) | 654.433 |
| Bozdogan's Criterion (CAIC) | 661.198 |
| Schwarz's Bayesian Criterion (BIC) | 659.198 |

| Parameter | Estimate | Std. Error | df | t | Sig. | 95% Confidence Interval | |
|---------------------------|----------------|------------|--------|-------|------|-------------------------|-------------|
| | | | | | | Lower Bound | Upper Bound |
| Intercept | 10.457603 | 3.313212 | 74.672 | 3.156 | .002 | 3.856871 | 17.058335 |
| [Gender=1] | 2.029279 | 2.351907 | 16.727 | .863 | .400 | -2.938983 | 6.997541 |
| [Gender=2] | 0 ^b | 0 | . | . | . | . | . |
| [Treatment=0] | 3.590407 | 4.499750 | 81.501 | .798 | .427 | -5.361851 | 12.542665 |
| [Treatment=1] | 0 ^b | 0 | . | . | . | . | . |
| [Visit=1] | 3.529088 | 3.898315 | 70.588 | .905 | .368 | -4.244717 | 11.302894 |
| [Visit=2] | 3.619997 | 3.898315 | 70.588 | .929 | .356 | -4.153808 | 11.393803 |
| [Visit=3] | -2.107276 | 3.898315 | 70.588 | -.541 | .591 | -9.881081 | 5.666530 |
| [Visit=4] | .165452 | 3.898315 | 70.588 | .042 | .966 | -7.608354 | 7.939257 |
| [Visit=5] | 0 ^b | 0 | . | . | . | . | . |
| [Visit=1] * [Treatment=0] | .076556 | 5.731167 | 70.319 | .013 | .989 | -11.352986 | 11.506098 |
| [Visit=2] * [Treatment=0] | 5.318980 | 5.731167 | 70.319 | .928 | .357 | -6.110562 | 16.748522 |
| [Visit=3] * [Treatment=0] | 6.490697 | 5.731167 | 70.319 | 1.133 | .261 | -4.938845 | 17.920239 |
| [Visit=4] * [Treatment=0] | -.782030 | 5.731167 | 70.319 | -.136 | .892 | -12.211572 | 10.647512 |
| [Visit=5] * [Treatment=0] | 0 ^b | 0 | . | . | . | . | . |
| [Visit=1] * [Treatment=1] | 0 ^b | 0 | . | . | . | . | . |
| [Visit=2] * [Treatment=1] | 0 ^b | 0 | . | . | . | . | . |
| [Visit=3] * [Treatment=1] | 0 ^b | 0 | . | . | . | . | . |
| [Visit=4] * [Treatment=1] | 0 ^b | 0 | . | . | . | . | . |
| [Visit=5] * [Treatment=1] | 0 ^b | 0 | . | . | . | . | . |

The information criteria are displayed in smaller-is-better form.

a. Dependent Variable: 憂鬱分數.

a. Dependent Variable: 憂鬱分數.

b. This parameter is set to zero because it is redundant.

Pairwise Comparisons^a

| (I) Visit | (J) Visit | Mean Difference (I-J) | Std. Error | df | Sig. ^b | 95% Confidence Interval for Difference ^b | |
|-----------|-----------|-----------------------|------------|--------|-------------------|-----------------------------------------------------|-------------|
| | | | | | | Lower Bound | Upper Bound |
| 1 | 2 | -2.712 | 2.741 | 68.882 | 1.000 | -10.662 | 5.238 |
| | 3 | 2.429 | 2.741 | 68.882 | 1.000 | -5.521 | 10.380 |
| | 4 | 3.793 | 2.741 | 68.882 | 1.000 | -4.157 | 11.743 |
| | 5 | 3.567 | 2.868 | 70.166 | 1.000 | -4.744 | 11.879 |
| 2 | 1 | 2.712 | 2.741 | 68.882 | 1.000 | -5.238 | 10.662 |
| | 3 | 5.141 | 2.741 | 68.882 | .649 | -2.809 | 13.092 |
| | 4 | 6.505 | 2.741 | 68.882 | .204 | -1.445 | 14.455 |
| | 5 | 6.279 | 2.868 | 70.166 | .319 | -2.032 | 14.591 |
| 3 | 1 | -2.429 | 2.741 | 68.882 | 1.000 | -10.380 | 5.521 |
| | 2 | -5.141 | 2.741 | 68.882 | .649 | -13.092 | 2.809 |
| | 4 | 1.364 | 2.741 | 68.882 | 1.000 | -6.587 | 9.314 |
| | 5 | 1.138 | 2.868 | 70.166 | 1.000 | -7.174 | 9.450 |
| 4 | 1 | -3.793 | 2.741 | 68.882 | 1.000 | -11.743 | 4.157 |
| | 2 | -6.505 | 2.741 | 68.882 | .204 | -14.455 | 1.445 |
| | 3 | -1.364 | 2.741 | 68.882 | 1.000 | -9.314 | 6.587 |
| | 5 | -.226 | 2.868 | 70.166 | 1.000 | -8.537 | 8.086 |
| 5 | 1 | -3.567 | 2.868 | 70.166 | 1.000 | -11.879 | 4.744 |
| | 2 | -6.279 | 2.868 | 70.166 | .319 | -14.591 | 2.032 |
| | 3 | -1.138 | 2.868 | 70.166 | 1.000 | -9.450 | 7.174 |
| | 4 | .226 | 2.868 | 70.166 | 1.000 | -8.086 | 8.537 |

Based on estimated marginal means

a. Dependent Variable: 憂鬱分數.

b. Adjustment for multiple comparisons: Bonferroni.

GEE/LMM-資料轉置處理



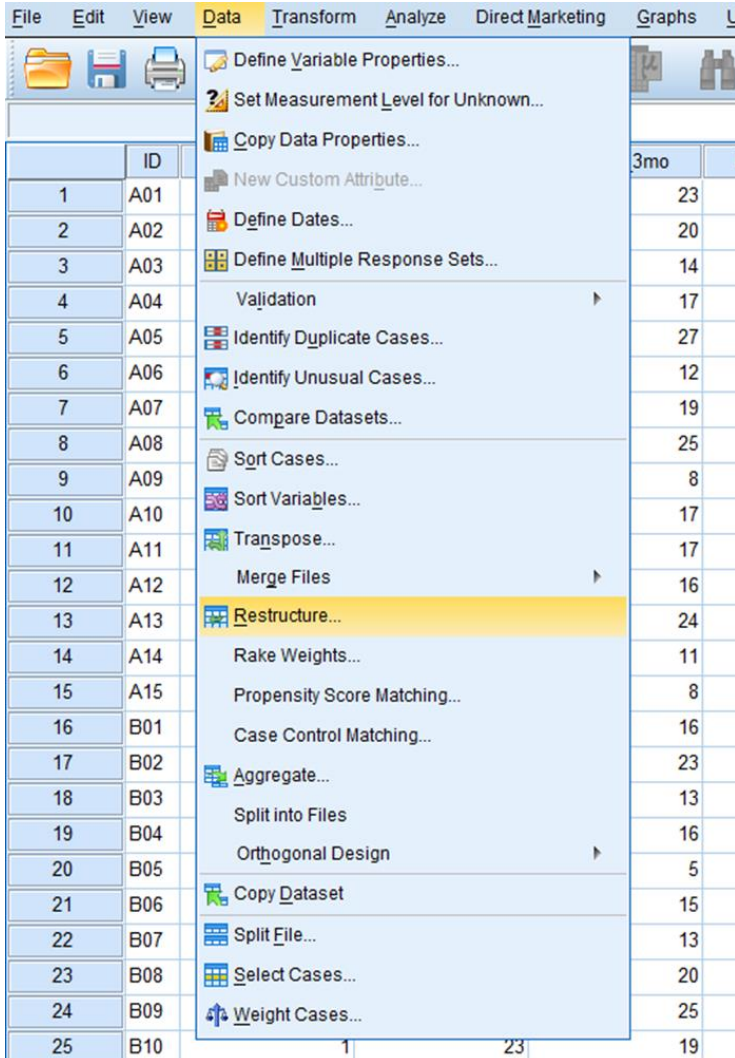
| No | Treatment | MMSE_Baseline | MMSE_3mo | MMSE_6mo |
|-----|-----------|---------------|----------|----------|
| A01 | 0 | 23 | 23 | 26 |
| A02 | 0 | 19 | 20 | 18 |
| A03 | 0 | 16 | 14 | 12 |
| A04 | 0 | 17 | 17 | 16 |
| A05 | 0 | 26 | 27 | 25 |
| A06 | 0 | 9 | 12 | . |
| A07 | 0 | 19 | 19 | . |
| A08 | 0 | 26 | 25 | 23 |
| A09 | 0 | 10 | 8 | 8 |
| A10 | 0 | 20 | 17 | 18 |

| id | No | Treatment | Times | MMSE |
|----|-----|-----------|-------|------|
| 1 | A01 | 0 | 1 | 23 |
| 1 | A01 | 0 | 2 | 23 |
| 1 | A01 | 0 | 3 | 26 |
| 2 | A02 | 0 | 1 | 19 |
| 2 | A02 | 0 | 2 | 20 |
| 2 | A02 | 0 | 3 | 18 |
| 3 | A03 | 0 | 1 | 16 |
| 3 | A03 | 0 | 2 | 14 |
| 3 | A03 | 0 | 3 | 12 |

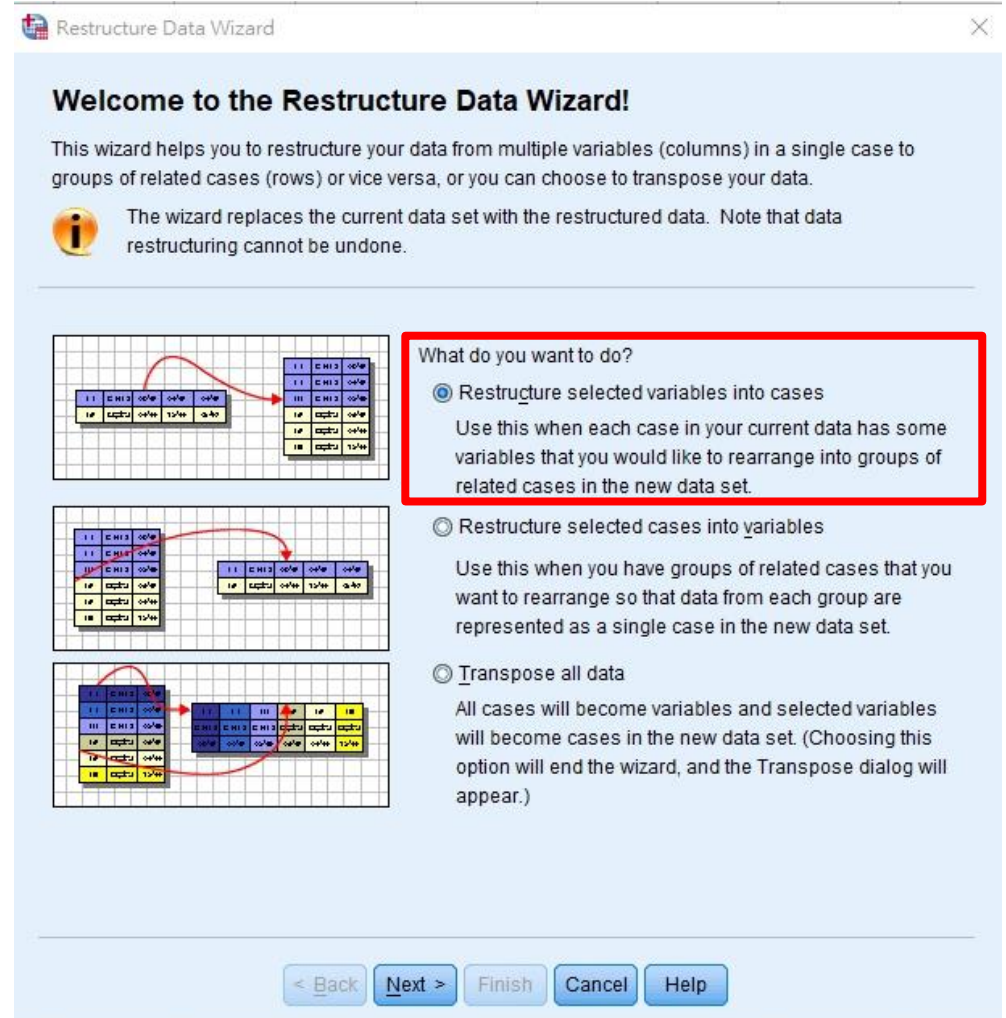


GEE/LMM-資料轉置處理

資料 > 重新架構



| ID | 3mo |
|----|-----|
| 1 | A01 |
| 2 | A02 |
| 3 | A03 |
| 4 | A04 |
| 5 | A05 |
| 6 | A06 |
| 7 | A07 |
| 8 | A08 |
| 9 | A09 |
| 10 | A10 |
| 11 | A11 |
| 12 | A12 |
| 13 | A13 |
| 14 | A14 |
| 15 | A15 |
| 16 | B01 |
| 17 | B02 |
| 18 | B03 |
| 19 | B04 |
| 20 | B05 |
| 21 | B06 |
| 22 | B07 |
| 23 | B08 |
| 24 | B09 |
| 25 | B10 |



Welcome to the Restructure Data Wizard!

This wizard helps you to restructure your data from multiple variables (columns) in a single case to groups of related cases (rows) or vice versa, or you can choose to transpose your data.

i The wizard replaces the current data set with the restructured data. Note that data restructuring cannot be undone.

What do you want to do?

- Restructure selected variables into cases
Use this when each case in your current data has some variables that you would like to rearrange into groups of related cases in the new data set.
- Restructure selected cases into variables
Use this when you have groups of related cases that you want to rearrange so that data from each group are represented as a single case in the new data set.
- Transpose all data
All cases will become variables and selected variables will become cases in the new data set. (Choosing this option will end the wizard, and the Transpose dialog will appear.)

< Back Next > Finish Cancel Help

GEE/LMM-資料轉置處理



Restructure Data Wizard - Step 2 of 7

Variables to Cases: Number of Variable Groups

You have chosen to restructure selected variables into groups of related cases in the new file.

A group of related variables, called a variable group, represents measurements on one variable.

For example, the variable may be width. If it is recorded in three separate measurements, each one representing a different point in time--w1, w2, and w3, then the data are arranged in a group of variables.

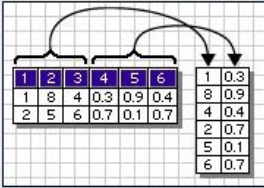
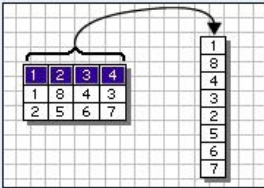
ⓘ If there is more than one variable in the file often it is also recorded in a variable group, for example height, recorded in h1, h2, and h3.

How many variable groups do you want to restructure?

One (for example, w1, w2, and w3)

More than one (for example, w1, w2, w3 and h1, h2, h3, etc.)

How Many?



< Back Next > Finish Cancel Help

Restructure Data Wizard - Step 3 of 7

Variables to Cases: Select Variables

For each variable group you have in the current data the restructured file will have one target variable.

In this step, choose how to identify case groups in the restructured data, and choose which variables belong with each target variable.

Optionally, you can also choose variables to copy to the new file as Fixed Variables.

Variables in the Current File:

- No
- Treatment
- MMSE_Baseline
- MMSE_3mo
- MMSE_6mo
- Outcome

Case Group Identification

Use case number

Name: Label...

Variables to be Transposed

Target Variable: MMSE

- MMSE_Baseline
- MMSE_3mo
- MMSE_6mo

Fixed Variable(s):

- No
- Treatment
- Outcome

1 2 3

< Back Next > Finish Cancel Help

GEE/LMM-資料轉置處理



Restructure Data Wizard - Step 4 of 7

Variables to Cases: Create Index Variables

In the current data, values for a variable group appear in a single case in multiple variables. For example, a single case contains the values for w1, w2, and w3.

In the new data, values for a variable group will appear in multiple cases in a single variable. For example, there will be three cases, one each for w1, w2, and w3.

An index is a new variable that identifies the group of new cases that was created from the original case. For example, an index named "w" would have the values 1, 2, and 3.

How many index variables do you want to create?

One
Use this when a variable group records the effects of a single factor, treatment or condition.

More than one How many?
Use this when a variable group records the effects of more than one factor, treatment or condition.

None
Use this if index information is stored in one of the sets of variables to be transposed.

| | | | |
|---|---|---|------|
| 1 | 1 | 1 | 0.07 |
| 1 | 1 | 2 | 0.11 |
| 1 | 1 | 3 | 0.05 |
| 2 | 1 | 1 | 0.08 |
| 2 | 1 | 2 | 0.04 |
| 2 | 1 | 3 | 0.06 |

| | | | | |
|---|---|---|---|------|
| 1 | 1 | 1 | 1 | 0.07 |
| 1 | 1 | 1 | 2 | 0.11 |
| 1 | 1 | 1 | 3 | 0.05 |
| 1 | 1 | 2 | 1 | 0.08 |
| 1 | 1 | 2 | 2 | 0.04 |
| 1 | 1 | 2 | 3 | 0.06 |

| | | | | |
|---|---|------|---|------|
| 1 | 1 | 0.08 | 2 | 0.07 |
| 2 | 1 | 0.11 | 2 | 0.11 |
| 3 | 1 | 0.07 | 2 | 0.05 |
| 4 | 1 | 0.06 | 2 | 0.08 |
| 5 | 1 | 0.09 | 2 | 0.04 |
| 6 | 1 | 0.02 | 2 | 0.06 |

< Back Next > Finish Cancel Help

Restructure Data Wizard - Step 5 of 7

Variables to Cases: Create One Index Variable

You have chosen to create one index variable. The variable's values can be sequential numbers or the names of variables in a group.

In the table you can specify the name and label for the index variable.

What kind of index values?

Sequential numbers
Index Values: 1, 2, 3

Variable names
Index Values: MMSE_Baseline, MMSE_3mo, MMSE_6mo

Edit the Index Variable Name and Label:

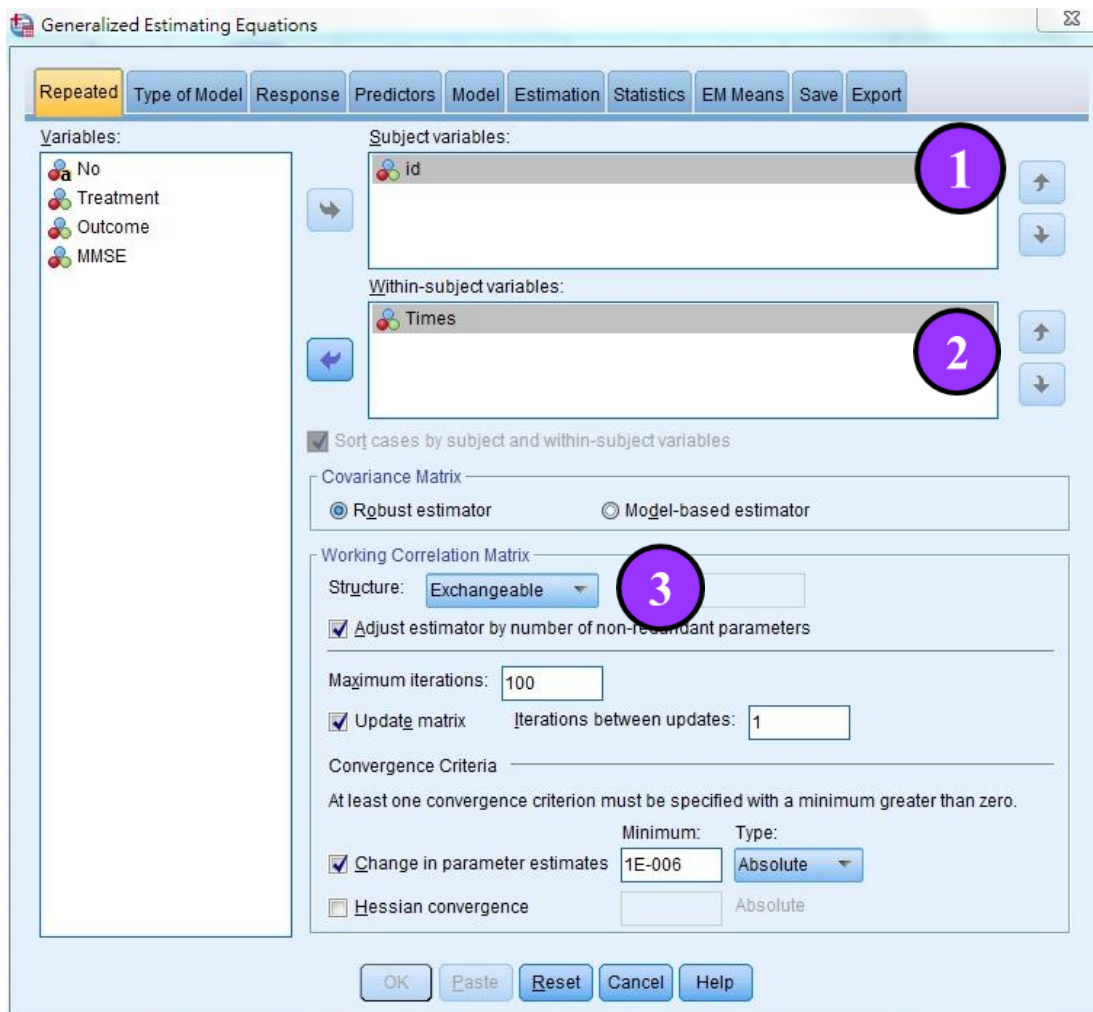
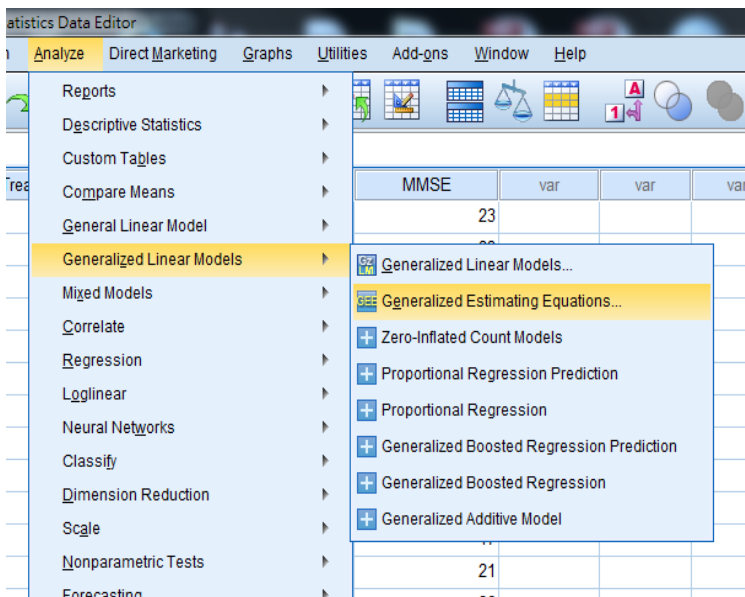
| | Name | Label | Levels | Index Values |
|---|-------|-------|--------|--------------|
| 1 | Times | | 3 | 1, 2, 3 |

< Back Next > Finish Cancel Help

GEE/LMM-分析操作



分析 > 廣義線性模型 > 廣義估計方程式(GEE)



GEE-分析操作



Generalized Estimating Equations

Repeated Type of Model Response Predictors Model Estimation Statistics EM Means Save Export

Choose one of the model types listed below or specify a custom combination of distribution and link function.

Scale Response

- Linear **Continuous outcome**
- Gamma with log link

Ordinal Response

- Ordinal logistic
- Ordinal probit

Counts

- Poisson loglinear
- Negative binomial with log link

Binary Response or Events/Trials Data

- Binary logistic **Binary outcome**
- Binary probit
- Interval censored survival

Mixture

- Tweedie with log link
- Tweedie with identity link

Custom

- Custom

Distribution: Normal Link function: Identity

Parameter

- Specify value
- Value: 1
- Estimate value

Power:

OK Paste Reset Cancel Help

GEE-分析操作



The image shows the 'Generalized Estimating Equations' dialog box in SPSS. The 'Response' tab is selected. On the left, a list of variables includes 'id', 'No', 'Treatment', 'Outcome', and 'Times'. On the right, the 'Dependent Variable' is set to 'MMSE', which is highlighted with a red box. Below this, the 'Type of Dependent Variable (Binomial Distribution Only)' section has 'Binary' selected. The 'Trials' section has 'Variable' selected, with an empty 'Trials Variable' field. The 'Scale Weight' section has an empty 'Scale Weight Variable' field. At the bottom, there are buttons for 'OK', 'Paste', 'Reset', 'Cancel', and 'Help'.

GEE-分析操作



Generalized Estimating Equations

Repeated Type of Model Response **Predictors** Model Estimation Statistics EM Means Save Export

Variables:
id
No
Outcome

Factors:
Treatment
Times

Options...

Covariates:

Offset
 Variable
Offset Variable:

 Fixed value
Value:

OK Paste Reset Cancel Help

Generalized Estimating Equations: Options

User-Missing Values
Specify how to treat cases with user-missing values on factors, subject variables, or within-subject variables.
 Exclude
 Include
Cases with user-missing values on the dependent variable, covariates, scale weight variable, or offset variable are always excluded.

Category Order for Factors
 Ascending
 Descending
 Use data order
The last unique category may be associated with a redundant parameter in the estimation algorithm.

Continue Cancel Help

數值小的當參考組

GEE-分析操作



Type>interaction

Specify Model Effects

Factors and Covariates:

- Treatment
- Times

Build Term(s)

Type: Interaction

Model:

- Treatment
- Times
- Treatment*Times

Number of Effects in Model: 3

Build Nested Term

Term:

By * (Within)

Add to Model Clear

Include intercept in model

OK Paste Reset Cancel Help

Generalized Estimating Equations

Model Effects

Analysis Type: Type III

Confidence Interval Level (%): 95

Chi-square Statistics

Wald

Generalized score

Log quasi-likelihood function: Full

Print

- Case processing summary
- Descriptive statistics
- Model information
- Goodness of fit statistics
- Model summary statistics
- Parameter estimates
- Include exponential parameter estimates
- Covariance matrix for parameter estimates
- Correlation matrix for parameter estimates
- Working correlation matrix
- Contrast coefficient (L) matrices
- General estimable functions
- Iteration history

Print Interval: 1

若為binary outcome需勾選

OK Paste Reset Cancel Help

GEE-分析操作



Generalized Estimating Equations

Repeated Type of Model Response Predictors Model Estimation Statistics **EM Means** Save Export

Factors and Interactions:

| M | Term |
|-------------------------------------|-----------------|
| <input checked="" type="checkbox"/> | Treatment |
| <input checked="" type="checkbox"/> | Times |
| <input checked="" type="checkbox"/> | Treatment*Times |

Display Means for:

| Term | Contrast | Reference Category |
|-----------------|----------|--------------------|
| Treatment | Pairwise | |
| Times | Pairwise | |
| Treatment*Times | Pairwise | |

Scale

Compute means for response
 Compute means for linear predictor

Adjustment for Multiple Comparisons:
Least significant difference

Display overall estimated mean

OK Paste Reset Cancel Help

GEE-Output



Model Information

| | |
|--------------------------------------|--------------|
| Dependent Variable | MMSE |
| Probability Distribution | Normal |
| Link Function | Identity |
| Subject Effect | 1 id |
| Within-Subject Effect | 1 Times |
| Working Correlation Matrix Structure | Exchangeable |

Categorical Variable Information

| | | | N | Percent |
|--------|-----------|----|--------|---------|
| Factor | Treatment | 1 | 42 | 51.2% |
| | | 0 | 40 | 48.8% |
| | Total | | 82 | 100.0% |
| | Times | 3 | 22 | 26.8% |
| 2 | | 30 | 36.6% | |
| 1 | | 30 | 36.6% | |
| Total | | 82 | 100.0% | |

Case Processing Summary

| | N | Percent |
|----------|----|---------|
| Included | 82 | 91.1% |
| Excluded | 8 | 8.9% |
| Total | 90 | 100.0% |

Continuous Variable Information

| | | N | Minimum | Maximum | Mean | Std. Deviation |
|--------------------|------|----|---------|---------|-------|----------------|
| Dependent Variable | MMSE | 82 | 5 | 27 | 18.45 | 5.444 |

Correlated Data Summary

| | | | |
|------------------------------------|-----------------------|-------|----|
| Number of Levels | Subject Effect | id | 30 |
| | Within-Subject Effect | Times | 3 |
| Number of Subjects | | | 30 |
| Number of Measurements per Subject | Minimum | | 2 |
| | Maximum | | 3 |
| Correlation Matrix Dimension | | | 3 |

Goodness of Fit^a

| | Value |
|-----------------------------------------------------------------------------------|----------|
| Quasi Likelihood under Independence Model Criterion (QIC) ^b | 2348.411 |
| Corrected Quasi Likelihood under Independence Model Criterion (QICC) ^b | 2348.971 |

Dependent Variable: MMSE
Model: (Intercept), Treatment, Times, Treatment * Times

a. Information criteria are in smaller-is-better form.

b. Computed using the full log quasi-likelihood function.

QIC/QICC數值
越小越好

GEE-Output



Parameter Estimates

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | |
|------------------------------|----------------|------------|------------------------------|--------|-----------------|----|------|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. |
| (Intercept) | 18.133 | 1.5602 | 15.075 | 21.191 | 135.073 | 1 | .000 |
| [Treatment=1] | 2.133 | 1.8698 | -1.531 | 5.798 | 1.302 | 1 | .254 |
| [Treatment=0] | 0 ^a | . | . | . | . | . | . |
| [Times=3] | -1.468 | .7448 | -2.928 | -.009 | 3.887 | 1 | .049 |
| [Times=2] | -.933 | .7022 | -2.310 | .443 | 1.767 | 1 | .184 |
| [Times=1] | 0 ^a | . | . | . | . | . | . |
| [Treatment=1] * [Times=3] | -1.424 | 1.0519 | -3.485 | .638 | 1.831 | 1 | .176 |
| [Treatment=1] * [Times=2] | -1.533 | 1.0299 | -3.552 | .485 | 2.216 | 1 | .137 |
| [Treatment=1] * [Times=1] | 0 ^a | . | . | . | . | . | . |
| [Treatment=0] * [Times=3] | 0 ^a | . | . | . | . | . | . |
| [Treatment=0] * [Times=2] | 0 ^a | . | . | . | . | . | . |
| [Treatment=0] * [Times=1] | 0 ^a | . | . | . | . | . | . |
| (Scale) | 30.557 | | | | | | |

6個月比Baseline的MMSE分數下降1.468分且有統計差異

Dependent Variable: MMSE

Model: (Intercept), Treatment, Times, Treatment * Times

a. Set to zero because this parameter is redundant.

GEE-Output



Estimates

| Times | Mean | Std. Error | 95% Wald Confidence Interval | |
|-------|-------|------------|------------------------------|-------|
| | | | Lower | Upper |
| 3 | 17.02 | 1.053 | 14.96 | 19.08 |
| 2 | 17.50 | .994 | 15.55 | 19.45 |
| 1 | 19.20 | .935 | 17.37 | 21.03 |

Pairwise Comparisons

| (I) Times | (J) Times | Mean Difference (I-J) | Std. Error | df | Sig. | 95% Wald Confidence Interval for Difference | |
|-----------|-----------|-----------------------|------------|----|------|---------------------------------------------|-------|
| | | | | | | Lower | Upper |
| 3 | 2 | -.48 | .380 | 1 | .207 | -1.23 | .26 |
| | 1 | -2.18 ^a | .526 | 1 | .000 | -3.21 | -1.15 |
| 2 | 3 | .48 | .380 | 1 | .207 | -.26 | 1.23 |
| | 1 | -1.70 ^a | .515 | 1 | .001 | -2.71 | -.69 |
| 1 | 3 | 2.18 ^a | .526 | 1 | .000 | 1.15 | 3.21 |
| | 2 | 1.70 ^a | .515 | 1 | .001 | .69 | 2.71 |

Pairwise comparisons of estimated marginal means based on the original scale of dependent variable MMSE

a. The mean difference is significant at the .05 level.

Overall Test Results

| Wald Chi-Square | df | Sig. |
|-----------------|----|------|
| 17.328 | 2 | .000 |

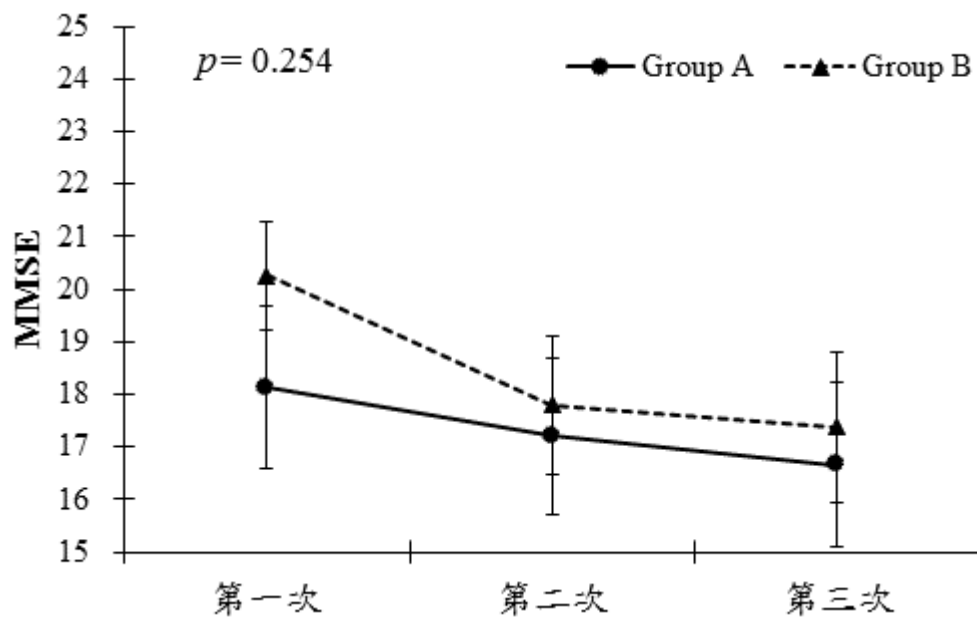
The Wald chi-square tests the effect of Times. This test is based on the linearly independent pairwise comparisons among the estimated marginal means.

GEE-Output



Estimates

| Treatment | Times | Mean | Std. Error | 95% Wald Confidence Interval | |
|-----------|-------|-------|------------|------------------------------|-------|
| | | | | Lower | Upper |
| 1 | 3 | 17.37 | 1.416 | 14.60 | 20.15 |
| | 2 | 17.80 | 1.324 | 15.21 | 20.39 |
| | 1 | 20.27 | 1.030 | 18.25 | 22.29 |
| 0 | 3 | 16.66 | 1.560 | 13.61 | 19.72 |
| | 2 | 17.20 | 1.482 | 14.29 | 20.11 |
| | 1 | 18.13 | 1.560 | 15.08 | 21.19 |



感謝您的聆聽！

Thank you!



相關樣本/配對資料的統計推論

