Analysis of ordinal longitudinal data

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Plan

1. Ordinal longitudinal data

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2. Analysis of longitudinal data - Marginal approach

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3. Global odds ratio as measure of association

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5. Application

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6. Conclusion

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Would you say that your health is: Excellent, Good, Poor

Ordinal longitudinal data - Example

524 patients, randomized into two treatment groups (RT or RT+PCV) and observed at 9 occassions time.

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$$\boldsymbol{\beta} = (\beta_{01}, ..., \beta_{0(K-1)}, \beta_{Time}, \beta_{Treat}, \beta_{Treat \times Time})'$$

Analysis of longitudinal data - Marginal approach

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- Gaussian outcome $\longrightarrow$ large class of linear models
- Non Gaussian outcome $\longrightarrow$ limited number of models, due to the lack of rich class of distributions

Analysis of longitudinal data - Marginal approach

Objective

- Describe the marginal expectation of the outcome variable as a function of the covariates while accounting for the correlation among the repeated observations for a given subject

Tools

- Gaussian outcome $\longrightarrow$ large class of linear models
- Non Gaussian outcome $\longrightarrow$ Complexity of the likelihood analysis

Analysis of longitudinal data - Marginal approach

Solution

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- Alternative to the likelihood-based analysis

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$$\downarrow$$

(Liang and Zeger, 1986)

Generalized estimating equations

GEE

Analysis of longitudinal data - GEE1

In GLM, score equation writes

$$S(\beta) = \sum_i \frac{\partial \mu_i}{\partial \beta} v_i^{-1}(y_i - \mu_i) = 0 \text{ , with } v_i = Var(Y_i)$$

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$$\begin{aligned} S(\beta) &= \sum_{i=1}^{N} \sum_{j=1}^{n_i} \frac{\partial \mu_{ij}}{\partial \beta} v_{ij}^{-1} (y_{ij} - \mu_{ij}) \\ &= \sum_{i=1}^{N} \frac{\partial \boldsymbol{\mu_i}'}{\boldsymbol{\beta}} V_i^{-1} (\boldsymbol{Y_i} - \boldsymbol{\mu_i}) = 0 \end{aligned}$$

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With $\boldsymbol{\mu_i} = E(\boldsymbol{Y_i})$ and $V_i = diag(v_{i1}, ..., v_{in_i})$

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With $\boldsymbol{\mu_i} = E(\boldsymbol{Y_i})$ and $V_i = diag(v_{i1}, ..., v_{in_i})$
$\rightarrow$ Independence estimating equation

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Let $R_i(\boldsymbol{\alpha})$ be a $n_i \times n_i$ symmetric matrix which fullfills the condition to be a correlation matrix , and let $\boldsymbol{\alpha}$ be an unknown vector which fully characterizes $R_i(\boldsymbol{\alpha})$.

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Define,

$$V_i = A_i^{1/2}(\boldsymbol{\beta}) R_i(\boldsymbol{\alpha}) A_i^{1/2}(\boldsymbol{\beta})$$

in which $A_i(\boldsymbol{\beta}) = diag\left\{v_{ij}(\mu_{ij}(\beta))\right\}$

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in which $A_i(\boldsymbol{\beta}) = diag\,\{v_{ij}(\mu_{ij}(\beta))\}$
$\rightarrow$ V_i is the 'working' covariance matrix of $\boldsymbol{Y_i}$ and is function of the parameter vectors $\boldsymbol{\beta}$ and $\boldsymbol{\alpha}$

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Using the new definition of V_i, consistent estimates of the model parameters, $\boldsymbol{\beta}$, can be obtained from the solution of the estimating equations

$$\sum_{i=1}^{N} D_i' V_i^{-1} (\boldsymbol{Y_i} - \boldsymbol{\mu_i}) = 0$$

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Large sample properties

As $N \to \infty$, $\sqrt{N}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}) \approx N(\mathbf{0}, I_0^{-1} I_1 I_0^{-1})$

$$\text{With } I_0 = \sum_{i=1}^{N} D_i' V_i^{-1} D_i$$

$$I_1 = \sum_{i=1}^{N} D_i' V_i^{-1} Var(\boldsymbol{Y_i}) V_i^{-1} D_i$$

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$I_0^{-1} I_1 I_0^{-1}$ is the so-called 'sandwich' estimator

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In practice, $Var(\boldsymbol{Y_i})$ is replaced by

$$[\boldsymbol{Y_i} - \boldsymbol{\mu_i}(\hat{\boldsymbol{\beta}})][\boldsymbol{Y_i} - \boldsymbol{\mu_i}(\hat{\boldsymbol{\beta}})]'$$

$\Rightarrow I_0^{-1} I_1 I_0^{-1}$: Robust estimator

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When $R_i(\boldsymbol{\alpha})$ is the true correlation matrix of the $\boldsymbol{Y_i}$'s,

$$Var(\hat{\boldsymbol{\beta}}) = I_0^{-1}$$

$\Rightarrow I_0^{-1}$: Naive estimator, model based estimator

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In practice, α is replaced by an estimate

Estimation of working correlation

Pearson residual to estimate $\boldsymbol{\alpha}$

Sensitive	$Corr(Y_{ij}, Y_{ik})$	Estimate
Independence	0	-
Exchangeable	$\boldsymbol{\alpha}$	$\hat{\boldsymbol{\alpha}} = \frac{1}{N}\sum_{i=1}^{N}\frac{1}{n_i(n_i-1)}\sum_{j\neq k} e_{ij}e_{ik}$
AR(1)	$\boldsymbol{\alpha}^t$	$\hat{\boldsymbol{\alpha}} = \frac{1}{N}\sum_{i=1}^{N}\frac{1}{n_i-1}\sum_{j\leq n_i-1} e_{ij}e_{i,j+1}$
Unstructured	$\boldsymbol{\alpha_{jk}}$	$\hat{\boldsymbol{\alpha_{jk}}} = \frac{1}{N}\sum_{i=1}^{N} e_{ij}e_{ik}$

$$e_{ij} = \frac{y_{ij} - \mu_{ij}}{\sqrt{v(\mu_{ij}}}$$

Fitting GEE1

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6. Update estimate for $\boldsymbol{\beta}$:

$$\hat{\boldsymbol{\beta}}^{(m+1)} = \hat{\boldsymbol{\beta}}^{(m)} - \left[\sum_{i=1}^{N} \frac{\partial \boldsymbol{\mu_i'}}{\partial \boldsymbol{\beta}} V_i^{-1} \frac{\partial \boldsymbol{\mu_i}}{\partial \boldsymbol{\beta}}\right]^{-1} \left[\sum_{i=1}^{N} \frac{\partial \boldsymbol{\mu_i'}}{\partial \boldsymbol{\beta}} V_i^{-1} (\boldsymbol{Y_i} - \boldsymbol{\mu_i})\right]^{-1}$$

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7. Iterate 2.- 5. until convergence.

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- Misspecification of working correlation matrix can affect the efficiency of $\hat{\beta}$
- Price to pay: correlation structure should not be interpreted

$\longrightarrow$ Solution : GEE2

Analysis of longitudinal data - GEE2

Scientific interest of GEE2 is on modeling

- the expectation of $\boldsymbol{Y}$ and
- the pairwise association of y_{ij} and y_{ik}

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- the expectation of $\boldsymbol{Y}$ and
- the pairwise association of y_{ij} and y_{ik}

Let γ_{jk} denotes the pairwise association and assume that $\boldsymbol{\gamma} = \boldsymbol{\gamma}(\boldsymbol{\alpha})$

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Let $\boldsymbol{\mu_i} = E[\boldsymbol{Y_i}]$ and $\boldsymbol{\eta_i} = E[\boldsymbol{\omega_i}]$.

Analysis of longitudinal data - GEE2

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Let $\boldsymbol{\mu_i} = E[\boldsymbol{Y_i}]$ and $\boldsymbol{\eta_i} = E[\boldsymbol{\omega_i}]$.

$\boldsymbol{\delta}$ can be estimated by solving the set of equations

$$\sum_{i=1}^{N} D_i V_i^{-1} f_i = 0$$

Analysis of longitudinal data - GEE2

$$\sum_{i=1}^{N} D_i V_i^{-1} f_i = 0 \rightarrow \text{ GEE2}$$

With $D_i = \begin{pmatrix} \frac{\partial \boldsymbol{\mu_i}}{\partial \boldsymbol{\beta}} & 0 \\ \frac{\partial \boldsymbol{\eta_i}}{\partial \boldsymbol{\beta}} & \frac{\partial \boldsymbol{\eta_i}}{\partial \boldsymbol{\alpha}} \end{pmatrix}$, $V_i = \begin{pmatrix} Var(\boldsymbol{Y_i}) & cov(\boldsymbol{Y_i}, \boldsymbol{\omega_i}) \\ cov(\boldsymbol{\omega_i}, \boldsymbol{Y_i}) & Var(\boldsymbol{\omega_i}) \end{pmatrix}$

and $f_i = \begin{pmatrix} \boldsymbol{Y_i} - \boldsymbol{\mu_i} \\ \boldsymbol{\omega_i} - \boldsymbol{\eta_i} \end{pmatrix}$

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and $f_i = \begin{pmatrix} \boldsymbol{Y_i} - \boldsymbol{\mu_i} \\ \boldsymbol{\omega_i} - \boldsymbol{\eta_i} \end{pmatrix}$

Consistency of $\hat{\boldsymbol{\delta}}$ depends on the correct specification of $E[\boldsymbol{Y_i}]$, and $\gamma(\boldsymbol{\alpha})$

Analysis of longitudinal data - GEE2

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Iterative weighted least squares formulation of Newton -Raphson process provides solution of GEE2 for $\boldsymbol{\delta}$

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and $f_i = \begin{pmatrix} \boldsymbol{Y_i} - \boldsymbol{\mu_i} \\ \boldsymbol{\omega_i} - \boldsymbol{\eta_i} \end{pmatrix}$

Alternative solution, changing GEE2 in two GEE1

Analysis of longitudinal data - GEE2

$$\sum_{i=1}^{N} D_i V_i^{-1} f_i = 0$$

$$\downarrow$$

$$\sum_{i=1}^{N} \frac{\partial \boldsymbol{\mu_i'}}{\partial \boldsymbol{\beta}} Var[\boldsymbol{Y_i}]^{-1}(\boldsymbol{Y_i} - \boldsymbol{\mu_i}) = 0$$

$$\sum_{i=1}^{N} \frac{\partial \boldsymbol{\eta_i'}}{\partial \boldsymbol{\alpha}} Var[\boldsymbol{\omega_i}]^{-1}(\boldsymbol{\omega_i} - \boldsymbol{\eta_i}) = 0$$

Global odds ratio as measure of association

Measure of association between pairs of outcomes:

- Continuous variable : correlation coefficient

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Global odds ratio is an extension of the simple odds ratio for a 2×2 contingency table

Global odds ratio as measure of association

Measure of association between pairs of outcomes:

- Continuous variable : correlation coefficient
- Binary variable : odds ratio (OR)
- Ordinal variable: Global odds ratio (GOR)

It can be defined as the odds ratio of a 2×2 table when adjacent rows and columns of a $K \times K$ contingency table ($K > 2$) are collapsed into a 2×2 table

Global odds ratio as measure of association

Measure of association between pairs of outcomes:

- Continuous variable : correlation coefficient
- Binary variable : odds ratio (OR)
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So, a $K \times K$ table has $(K-1)^2$ global odds ratios

Global odds ratio as measure of association - notation

For each subject i $(i = 1, ..., N)$ and at each time $t = 1, ..., n_i$, we have an ordinal outcome with K levels $Z_{it} = k$, $k = 1, ..., K$.

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Consider the ordinal outcomes of the subject i at the two time occasions s and t, Z_{is} and Z_{it}.

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Consider the ordinal outcomes of the subject i at the two time occasions s and t, Z_{is} and Z_{it}.

$$\gamma_{itk} = P[Z_{it} \leq k | X_{it} = x_{it}] \text{ and}$$

$$F_{ijk}(s,t) = P[Z_{is} \leq j, Z_{it} \leq k]$$

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$$\begin{bmatrix} P[Z_{is}=1, Z_{it}=1] & . \quad . \quad . & P[Z_{is}=1, Z_{it}=K] \\ . & . \quad . \quad . & . \\ . & . \quad . \quad . & . \\ . & . \quad . \quad . & . \\ P[Z_{is}=K, Z_{it}=1] & . \quad . \quad . & P[Z_{is}=K, Z_{it}=K] \end{bmatrix}$$

Global odds ratio as measure of association - definition

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Dichotomizing this contingency table at (j, k) leads to the following collapsed 2×2 contingency tables

Global odds ratio as measure of association - definition

$$\begin{bmatrix} P[Z_{is}=1,Z_{it}=1] & . \quad . \quad . & P[Z_{is}=1,Z_{it}=K] \\ . & . \quad . \quad . & . \\ . & . \quad . \quad . & . \\ . & . \quad . \quad . & . \\ P[Z_{is}=K,Z_{it}=1] & . \quad . \quad . & P[Z_{is}=K,Z_{it}=K] \end{bmatrix}$$

$$\downarrow$$

$$\begin{bmatrix} P[Z_{is} \le j, Z_{it} \le k] & P[Z_{is} \le j, Z_{it} \succ k] \\ P[Z_{is} \succ j, Z_{it} \le k] & P[Z_{is} \succ j, Z_{it} \succ k] \end{bmatrix}$$

Global odds ratio as measure of association - definition

$$\begin{bmatrix} P[Z_{is} \leq j, Z_{it} \leq k] & P[Z_{is} \leq j, Z_{it} \succ k] \\ P[Z_{is} \succ j, Z_{it} \leq k] & P[Z_{is} \succ j, Z_{it} \succ k] \end{bmatrix}$$

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The global odds ratio for subject i at occasion times s and t, at the cutpoint (j, k) is defined as

$$\Psi_{ijk}(s,t) = \frac{P[Z_{is} \le j, Z_{it} \le k] P[Z_{is} \succ j, Z_{it} \succ k]}{P[Z_{is} \le j, Z_{it} \succ k] P[Z_{is} \succ j, Z_{it} \le k]}$$

Global odds ratio as measure of association - definition

$$\begin{bmatrix} P[Z_{is} \leq j, Z_{it} \leq k] & P[Z_{is} \leq j, Z_{it} \succ k] \\ P[Z_{is} \succ j, Z_{it} \leq k] & P[Z_{is} \succ j, Z_{it} \succ k] \end{bmatrix}$$

Using definition of $F_{ijk}(s,t)$, γ_{isj} and γ_{itk}, the global odds ratio can be reexpressed as follow,

$$\Psi_{ijk}(s,t) = \frac{F_{ijk}(s,t)\{1 - \gamma_{isj} - \gamma_{itk} + F_{ijk}(s,t)\}}{\{\gamma_{isj} - F_{ijk}(s,t)\}\{\gamma_{itk} - F_{ijk}(s,t)\}}$$

Global odds ratio as measure of association - definition

$$\begin{bmatrix} P[Z_{is} \leq j, Z_{it} \leq k] & P[Z_{is} \leq j, Z_{it} \succ k] \\ P[Z_{is} \succ j, Z_{it} \leq k] & P[Z_{is} \succ j, Z_{it} \succ k] \end{bmatrix}$$

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So, $F_{ijk}(s,t)$ can be expressed in terms of $\Psi_{ijk}(s,t)$, γ_{isj} and γ_{itk}

Analysis of ordinal longitudinal data

Estimation of $\boldsymbol{\beta}$

Analysis of ordinal longitudinal data

Estimation of $\boldsymbol{\beta}$

Let $\boldsymbol{Y_i} = (\boldsymbol{Y'_{i1}}, \ldots, \boldsymbol{Y'_{in_i}})'$ with $\boldsymbol{Y_{it}} = (Y_{it1}, \ldots, Y_{it,(K-1)})'$ where

$$Y_{itk} = \begin{cases} 1 \text{ if } Z_{it} = k \\ 0 \text{ otherwise} \end{cases}$$

Analysis of ordinal longitudinal data

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$$Y_{itk} = \begin{cases} 1 \text{ if } Z_{it} = k \\ 0 \text{ otherwise} \end{cases}$$

Let $\boldsymbol{\pi_i} = (\boldsymbol{\pi'_{i1}}, ..., \boldsymbol{\pi'_{in_i}})$ with $\boldsymbol{\pi'_{it}} = (\pi_{it1}, .., \pi_{it,(K-1)})'$ where

$\pi_{itk} = E[Y_{itk}] = P[Y_{itk} = 1]$

Analysis of ordinal longitudinal data

First set of estimating equations,

$$\sum_{i=1}^{N} \boldsymbol{D_i'} V_i^{-1} (\boldsymbol{Y_i} - \boldsymbol{\pi_i}(\boldsymbol{\beta})) = 0$$

Analysis of ordinal longitudinal data

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with $\boldsymbol{D_i'} = d\boldsymbol{\pi_i}(\boldsymbol{\beta})/d\boldsymbol{\beta}$

Analysis of ordinal longitudinal data

First set of estimating equations,

$$\sum_{i=1}^{N} \boldsymbol{D_i'} V_i^{-1} (\boldsymbol{Y_i} - \boldsymbol{\pi_i}(\boldsymbol{\beta})) = 0$$

V_i is the 'working' covariance matrix of $\boldsymbol{Y_i}$

Analysis of ordinal longitudinal data

First set of estimating equations,

$$\sum_{i=1}^{N} \boldsymbol{D_i'} V_i^{-1}(\boldsymbol{Y_i} - \boldsymbol{\pi_i(\beta)}) = 0$$

$$\begin{bmatrix} V_{11i} & V_{12i} & . & . & . & V_{1n_i i} \\ . & . & . & . & . & . \\ . & . & . & . & . & . \\ V_{n_i 1i} & V_{n_i 2i} & . & . & . & V_{n_i n_i i} \end{bmatrix}$$

V_{tti} = covariance matrix at occassion time t for subject i

V_{sti} = covariance matrix at 2 $\neq$ occassions times for subject i

Analysis of ordinal longitudinal data

First set of estimating equations,

$$\sum_{i=1}^{N} \boldsymbol{D_i'} V_i^{-1} (\boldsymbol{Y_i} - \boldsymbol{\pi_i(\beta)}) = 0$$

$$\begin{bmatrix} V_{11i} & V_{12i} & . & . & . & V_{1n_ii} \\ . & . & . & . & . & . \\ . & . & . & . & . & . \\ V_{n_i1i} & V_{n_i2i} & . & . & . & V_{n_in_ii} \end{bmatrix}$$

$$Var(Y_{itj}) = P[Y_{itj} = 1](1 - P[Y_{itj} = 1])$$

$$Cov(Y_{isj}, Y_{itk}) = P[Y_{isj} = 1, Y_{itk} = 1] - P[Y_{isj} = 1]P[Y_{itk} = 1]$$

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$$Var(Y_{itj}) = P[Y_{itj} = 1](1 - P[Y_{itj} = 1])$$
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Estimation of α

Analysis of ordinal longitudinal data

Estimation of $\boldsymbol{\alpha}$

Let

$$\boldsymbol{\omega_i} = [\boldsymbol{\omega_i(1,2)'}, ..., \boldsymbol{\omega_i(s,t)'}, ..., \boldsymbol{\omega_i(n_i-1,n_i)'}]'$$

with

$$\boldsymbol{\omega_i(s,t)'} = (\omega_{i11}(s,t), \omega_{i12}(s,t), ..., \omega_{i1(K-1)}(s,t), \omega_{i21}(s,t), ..., \omega_{i(K-1)(K-1)}(s,t))'$$

where

$$\omega_{ijk}(s,t) = I[Y_{isj} = 1, Y_{itk} = 1] = Y_{isj}Y_{itk}$$

Analysis of ordinal longitudinal data

Estimation of $\boldsymbol{\alpha}$

Let

$$\boldsymbol{\eta_i} = [\boldsymbol{\eta_i(1,2)'}, ..., \boldsymbol{\eta_i(s,t)'}, ..., \boldsymbol{\eta_i(n_{i-1}, n_i)}]'$$

with

$$\boldsymbol{\eta_i(s,t)'} = (\eta_{i11}(s,t), \eta_{i12}(s,t), ..., \eta_{i1,(K-1)}(s,t), \eta_{i21}(s,t), ..., \eta_{i,(K-1),(K-1)}(s,t))'$$

where

$$\eta_{ijk}(s,t) = E[\omega_{ijk}(s,t)] = E[Y_{isj}Y_{itk}] = P[Y_{isj} = 1, Y_{itk} = 1]$$

Analysis of ordinal longitudinal data

Estimation of $\boldsymbol{\alpha}$

Let

$$\boldsymbol{\eta_i} = [\boldsymbol{\eta_i(1,2)'}, ..., \boldsymbol{\eta_i(s,t)'}, ..., \boldsymbol{\eta_i(n_{i-1}, n_i)}]'$$

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where

$$\eta_{ijk}(s,t) = E[\omega_{ijk}(s,t)] = E[Y_{isj}Y_{itk}] = P[Y_{isj} = 1, Y_{itk} = 1]$$

Analysis of ordinal longitudinal data

Second set of estimating equations,

$$\sum_{i=1}^{N} \boldsymbol{C_i'} W_i^{-1} (\boldsymbol{\omega_i} - \boldsymbol{\eta_i(\alpha, \beta)}) = 0$$

Analysis of ordinal longitudinal data

Second set of estimating equations,

$$\sum_{i=1}^{N} \boldsymbol{C_i'} W_i^{-1} (\boldsymbol{\omega_i} - \boldsymbol{\eta_i}(\boldsymbol{\alpha}, \boldsymbol{\beta})) = 0$$

with $\boldsymbol{C_i'} = \frac{\partial \boldsymbol{\eta_i}(\boldsymbol{\alpha})}{\partial \alpha}$

Analysis of ordinal longitudinal data

Second set of estimating equations,

$$\sum_{i=1}^{N} \boldsymbol{C_i'} W_i^{-1} (\boldsymbol{\omega_i} - \boldsymbol{\eta_i}(\boldsymbol{\alpha}, \boldsymbol{\beta})) = 0$$

W_i is the 'working' covariance matrix of $\boldsymbol{\omega_i}$

Analysis of ordinal longitudinal data

Second set of estimating equations,

$$\sum_{i=1}^{N} \boldsymbol{C_i'} W_i^{-1}(\boldsymbol{\omega_i} - \boldsymbol{\eta_i}(\boldsymbol{\alpha}, \boldsymbol{\beta})) = 0$$

$$W_i = \begin{bmatrix} W_{i12} & 0 & . & . & . & 0 \\ 0 & W_{i23} & . & . & . & 0 \\ . & . & . & . & . & . \\ . & . & . & . & . & . \\ 0 & 0 & . & . & . & W_{i,(n_i-1),n_i} \end{bmatrix} \text{ for } i = 1, ..., N$$

where W_{ist} $(s = 1, ..., n_i$ and $t = 2, ..., n_i; s < t)$ is a $(K-1)^2 \times (K-1)^2$ matrix that need to be specified.

Analysis of ordinal longitudinal data

Second set of estimating equations,

$$\sum_{i=1}^{N} \boldsymbol{C_i'} W_i^{-1} (\boldsymbol{\omega_i} - \boldsymbol{\eta_i}(\boldsymbol{\alpha}, \boldsymbol{\beta})) = 0$$

$$W_i = \begin{bmatrix} W_{i12} & 0 & . & . & . & 0 \\ 0 & W_{i23} & . & . & . & 0 \\ . & . & . & . & . & . \\ . & . & . & . & . & . \\ 0 & 0 & . & . & . & W_{i,(n_i-1),n_i} \end{bmatrix} \text{ for } i = 1, ..., N$$

$$Var(\omega_{ijk}(s,t)) = P[Y_{isj} = 1, Y_{itk} = 1][1 - P[Y_{isj} = 1, Y_{itk} = 1]]$$

$$Cov[\omega_{ijk}(s,t), \omega_{iuv}(s,t)] = -P[Y_{isj} = 1, Y_{itk} = 1]P[Y_{isu} = 1, Y_{itv} = 1] \text{ for } j \neq u \text{ and } k \neq v$$

Analysis of ordinal longitudinal data

In conclusion, the estimation of $(\boldsymbol{\beta}, \boldsymbol{\alpha})$ is obtained from

$$\sum_{i=1}^{N} \boldsymbol{D_i'} V_i^{-1} (\boldsymbol{Y_i} - \boldsymbol{\pi_i(\beta)}) = 0$$

$$\sum_{i=1}^{N} \boldsymbol{C_i'} W_i^{-1} (\boldsymbol{\omega_i} - \boldsymbol{\eta_i(\alpha, \beta)}) = 0$$

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But where is the global odds ratio?

Analysis of ordinal longitudinal data

$$\Psi_{ijk}(s,t) = \frac{F_{ijk}(s,t)\{1 - \gamma_{isj} - \gamma_{itk} + F_{ijk}(s,t)\}}{\{\gamma_{isj} - F_{ijk}(s,t)\}\{\gamma_{itk} - F_{ijk}(s,t)\}}$$

Analysis of ordinal longitudinal data

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Using this definition, $F_{ijk}(s,t) = P[Z_{is} \leq j, Z_{it} \leq k]$ can be expressed in terms of $\Psi_{ijk}(s,t)$, γ_{isj} and γ_{itk}

Analysis of ordinal longitudinal data

$$\Psi_{ijk}(s,t) = \frac{F_{ijk}(s,t)\{1 - \gamma_{isj} - \gamma_{itk} + F_{ijk}(s,t)\}}{\{\gamma_{isj} - F_{ijk}(s,t)\}\{\gamma_{itk} - F_{ijk}(s,t)\}}$$

Using this definition, $F_{ijk}(s,t) = P[Z_{is} \leq j, Z_{it} \leq k]$ can be expressed in terms of $\Psi_{ijk}(s,t)$, γ_{isj} and γ_{itk}

$$P[Y_{isj} = 1, Y_{itk} = 1] = F_{ijk}(s,t) - F_{ij,k-1}(s,t) - F_{i,j-1,k}(s,t) + F_{i,j-1,k-1}(s,t)$$

Then, $P[Y_{isj} = 1, Y_{itk} = 1]$ is function of $\Psi_{ijk}(s,t)$, γ_{isj} and γ_{itk}

Analysis of ordinal longitudinal data

$$\sum_{i=1}^{N} \boldsymbol{D_i'} V_i^{-1} (\boldsymbol{Y_i} - \boldsymbol{\pi_i}(\boldsymbol{\beta})) = 0$$

$$\sum_{i=1}^{N} \boldsymbol{C_i'} W_i^{-1} (\boldsymbol{\omega_i} - \boldsymbol{\eta_i}(\boldsymbol{\alpha}, \boldsymbol{\beta})) = 0$$

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How to solve this set of equations?

Analysis of ordinal longitudinal data

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How to solve this set of equations?

$\longrightarrow$ Fisher-scoring type algorithm

Analysis of ordinal longitudinal data

A Fisher-scoring type algorithm may be used to obtain $(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\alpha}})$

$$\hat{\boldsymbol{\beta}}^{(m+1)} = \hat{\boldsymbol{\beta}}^{(m)} - \left[\sum_{i=1}^{N} \hat{\boldsymbol{D}}_{\boldsymbol{i}}' \hat{V_i}^{-1} \hat{\boldsymbol{D}}_{\boldsymbol{i}}'\right]^{-1} \left[\sum_{i=1}^{N} \hat{\boldsymbol{D}}_{\boldsymbol{i}}' \hat{V_i}^{-1} (\boldsymbol{Y_i} - \boldsymbol{\pi_i}(\boldsymbol{\beta}))\right]^{-1}$$

and

$$\hat{\boldsymbol{\alpha}}^{(m+1)} = \hat{\boldsymbol{\alpha}}^{(m)} - \left[\sum_{i=1}^{N} \hat{\boldsymbol{C}}_{\boldsymbol{i}}' \hat{W_i}^{-1} \hat{\boldsymbol{C}}_{\boldsymbol{i}}'\right]^{-1} \left[\sum_{i=1}^{N} \hat{\boldsymbol{C}}_{\boldsymbol{i}}' \hat{W_i}^{-1} \left(\boldsymbol{\omega_i} - \boldsymbol{\eta_i}(\hat{\boldsymbol{\beta}}^{(\boldsymbol{m+1})}, \hat{\boldsymbol{\alpha}}^{(\boldsymbol{m})})\right)\right]^{-1}$$

Large sample properties

As $N \to \infty$, $N^{1/2}[(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta})', (\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha})'] \approx N(\mathbf{0}, V_{\boldsymbol{\beta},\boldsymbol{\alpha}})$, with

$$V_{\boldsymbol{\beta},\boldsymbol{\alpha}} = \begin{bmatrix} B_{11}^{-1} & 0 \\ B_{21} & B_{22}^{-1} \end{bmatrix} \begin{bmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{12}' & \Sigma_{22} \end{bmatrix} \begin{bmatrix} B_{11}^{-1} & B_{21}' \\ 0 & B_{22}^{-1} \end{bmatrix}$$

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Where

$$\begin{aligned} B_{11} &= N^{-1} \sum_{i=1}^{N} \boldsymbol{D_i'} V_i^{-1} \boldsymbol{D_i'} \\ B_{22} &= N^{-1} \sum_{i=1}^{N} \boldsymbol{C_i'} W_i^{-1} \boldsymbol{C_i'} \\ B_{12} &= B_{22}^{-1} \left\{ N^{-1} \sum_{i=1}^{N} \boldsymbol{C_i'} W_i^{-1} (-d\boldsymbol{w_i}/d\beta) \right\} B_{11}^{-1} \end{aligned}$$

Large sample properties

As $N \to \infty$, $N^{1/2}[(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta})', (\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha})'] \approx N(\mathbf{0}, V_{\boldsymbol{\beta},\boldsymbol{\alpha}})$, with

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Where

$$\begin{aligned} \Sigma_{11} &= N^{-1} \sum_{i=1}^{N} \boldsymbol{D_i'} V_i^{-1} \{Var(\boldsymbol{Y_i})\} V_i^{-1} \boldsymbol{D_i} \\ \Sigma_{22} &= N^{-1} \sum_{i=1}^{N} \boldsymbol{C_i'} W_i^{-1} \{Var(\boldsymbol{\omega_i})\} W_i^{-1} \boldsymbol{C_i} \\ \Sigma_{12} &= N^{-1} \sum_{i=1}^{N} \boldsymbol{D_i'} V_i^{-1} \{Cov(\boldsymbol{Y_i}, \boldsymbol{\omega_i})\} W_i^{-1} \boldsymbol{C_i} \end{aligned}$$

Large sample properties

The 'robust' asymptotic covariance matrix of $N^{1/2}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta})$ is

$$V_\beta = \left(B_{11}^{-1}\Sigma_{11}B_{11}^{-1}\right)$$

Large sample properties

The ’robust’ asymptotic covariance matrix of $N^{1/2}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta})$ is

$$V_\beta = \left(B_{11}^{-1}\Sigma_{11}B_{11}^{-1}\right)$$

The ’robust’ asymptotic covariance matrix of $N^{1/2}(\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha})$ is

$$V_\alpha = \left(B_{21}\Sigma_{11}B_{21}' + B_{22}^{-1}\Sigma_{12}'B_{21}' + B_{21}\Sigma_{12}B_{22}^{-1} + B_{22}^{-1}\Sigma_{22}B_{22}^{-1}\right)$$

Large sample properties

The 'naive' asymptotic covariance matrix of $N^{1/2}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta})$ is

$$V_\beta = B_{11}^{-1}$$

Large sample properties

The 'naive' asymptotic covariance matrix of $N^{1/2}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta})$ is

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The 'naive' asymptotic covariance matrix of $N^{1/2}(\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha})$ is

$$V_\alpha = \left(B_{21}\Sigma_{11}B_{21}' + B_{22}^{-1}\Sigma_{12}'B_{21}' + B_{21}\Sigma_{12}B_{22}^{-1} + B_{22}^{-1}\right)$$

Application - GEE2 - Visual impairment

Data from the Wisconsin Epidemiologic Study of Diabetic

$N = 720$ patients
Y= Severity of diabetic retinopathy (none, mild, moderate, proliferative)
$\boldsymbol{X}$= (Gender (0=male, 1=female), Dose of insulin (/day))

Application - GEE2 - Visual impairment

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Association between eyes		
Covariates	Estimates (SD)	P-value
int	0.60	
Gender	-0.861 (0.35)	*0.01*
(0=male, 1=female)		
Dose of insulin	-0.807 (0.335)	*0.02*

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Gender and dose of insulin per day were significantly related to the association between eyes

Application - GEE2 - Visual impairment

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int	0.60	
Gender (0=male, 1=female)	-0.861 (0.35)	*0.01*
Dose of insulin	-0.807 (0.335)	*0.02*

Males and subjects who take fewer doses of insulin per day have greater association between eyes than their counterparts

Further perspectives

Application to longitudinal analysis of quality of life data:

Further perspectives

Application to longitudinal analysis of quality of life data:

- Continuous VS. Categorical VS. Ordinal

Further perspectives

Application to longitudinal analysis of quality of life data:

- Continuous VS. Categorical VS. Ordinal

What happens when ordinal variable is treated as continuous or categorical?

Further perspectives

Application to longitudinal analysis of quality of life data:

- Continuous VS. Categorical VS. Ordinal

- Treatment of missing values

Further perspectives

Application to longitudinal analysis of quality of life data:

- Continuous VS. Categorical VS. Ordinal
- Treatment of missing values

Longitudinal analysis or competing risk?

- Administrative reasons, patient’s refusal, ...missing not planned
- Death, data no more collected after disease progression,...

Further perspectives

Application to longitudinal analysis of quality of life data:

- Continuous VS. Categorical VS. Ordinal
- Treatment of missing values

Longitudinal analysis or competing risk?

- Administrative reasons, patient's refusal, ...missing not planned
- Death, data no more collected after disease progression,...

In some situations, patients are not able to go until the last planned timepoint. Are the assumptions of models treating missing data still valid?

Further perspectives

Application to longitudinal analysis of quality of life data:

- Continuous VS. Categorical VS. Ordinal
- Treatment of missing values

Longitudinal analysis or competing risk?

- Administrative reasons, patient's refusal, ...missing not planned
- Death, data no more collected after disease progression,...

$\rightarrow$ Theory of competing risk

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Thank you for your attention